STATISTICAL ANALYSIS PLAN (Version 1.05)

Protocol Title:	A randomised controlled trial of the beta-blocker carvedilol versus placebo to reduce cardiovascular morbidity and mortality in high-risk patients receiving dialysis. A feasibility study (Version 5.0)
Short title:	BLOCADE: the **B**eta-blocker to **LO**wer **CA**rdiovascular **D**ialysis **E**vents Feasibility Study
Protocol Date:	8 March 2012
Trial Registration:	Australian New Zealand Clinical Trials Registry number ACTRN12609000174280

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DOCUMENT HISTORY

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V1.05	Page 9, Section 3.2.2, last paragraph: changed font to Times New Roman 12 point. Page 15, Section 6.3.1, 3rd line: substituted identity for logit as the link function.	21 July 2014

APPROVALS

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PREFACE

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for the Australasian Kidney Trials Network (AKTN) protocol 08.01, a study designed to assess the feasibility of conducting a large randomised trial to determine whether the beta-blocker carvedilol reduces cardiovascular and all-cause mortality in patients receiving dialysis.

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.(1) All work planned and reported for this SAP will follow national and international guidelines for statistical practice (2-5).

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

This SAP was written by a statistician and clinical investigators who were blinded to treatment allocation and treatment-related study results and will remain so until the central database is locked and the final data are extracted for analysis. To ensure blinding, treatment allocations are stored in a separate location accessible only by an un-blinded AKTN statistician.

The following documents were reviewed when preparing this SAP:

- Clinical Research Protocol for AKTN Trial Number 08.01 (6).
- Case report forms (CRFs) for AKTN Trial Number 08.01.
- Data Safety Monitoring Board (DSMB) Terms of Reference for AKTN Trial Number 08.01(7).
- ICH Guidance on Statistical Principles for Clinical Trials (1).
- ICH Guidance on Structure and Content of Clinical Study Reports (8).

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

ABBREVIATIONS

ABBREVIATION	DEFINITION
ADR	Adverse Drug Reaction
AKTN	Australasian Kidney Trials Network
DSMB	Data and Safety Monitoring Board
ESKD	End-Stage Kidney Disease
FSR	Final Statistical Report
HD	Haemodialysis
ICH	International Conference on Harmonisation
IDH	Intradialytic hypotension
ITT	Intention-To-Treat
IVRS	Interactive Voice Response System
PD	Peritoneal Dialysis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TMC	Trial Management Committee

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1. INTRODUCTION

1.1 Background

Cardiovascular disease is a major cause of morbidity and mortality in patients receiving dialysis (9, 10). However, current therapeutic strategies rely on extrapolation from randomised controlled trials conducted in people without end-stage kidney disease (ESKD). The increasing evidence of benefit from beta-blockers in randomised controlled trials in the general population may lead to more patients with end-stage kidney disease being prescribed beta-blockers, despite the absence of evidence for their use in this group, making future recruitment for a trial such as this more difficult. Thus, the present time is considered a window of opportunity in which to study this question.

There is insufficient data on the tolerability of carvedilol in the ESKD population and a feasibility study is a key step in performing a large trial. In addition to information on tolerability, a feasibility study will provide logistical data and data relevant to sample size estimation that will help plan the study.

1.2 Study synopsis

The BLOCADE trial is a feasibility study for a large multi-centre, randomised, placebo-controlled trial of the effectiveness of the beta-blocker carvedilol to reduce cardiovascular morbidity and mortality in high-risk patients receiving dialysis. The multi-centre feasibility study had a six week active run-in period during which all participants received carvedilol. After the run-in period participants who tolerated carvedilol were randomised 1:1 to receive carvedilol (experimental intervention) or placebo (control intervention).

The BLOCADE feasibility study began recruiting patients on 16 May 2011 and stopped recruiting on 28 February 2013 due to slow recruitment and lack of funds to continue recruiting participants. In total, 88 participants from 11 sites were consented into the study. Of these, 72 participants from 9 sites entered the run-in phase and 49 participants from 8 sites were randomised. The final end-of-study visit was conducted in June 2014. The central database is expected to be available for analysis by the end of June 2014.

1.3 Sub-studies

The BLOCADE feasibility trial has two sub-studies: the home blood pressure sub-study and the 24 hour ambulatory blood pressure monitoring sub-study. Statistical analyses for these sub-studies are not described in this SAP.

2. STUDY OBJECTIVES

2.1 Primary objectives

The primary objective is to determine the feasibility and to inform the design of a larger clinical end-point study by measuring factors relevant to three aspects of planning a larger study:

1) Tolerability of carvedilol
2) Sample size for a clinical end-point study
3) Logistics of a larger study

2.2 Secondary objectives

Secondary objectives are to examine the effect of therapy with carvedilol compared to placebo on change in B-type natriuretic peptide (BNP) and change in quality of life. In addition, baseline BNP as a predictor of response to carvedilol will be assessed, where response is defined as failure to complete the run-in phase for any reason.

2.3 Tertiary (exploratory) objectives

Exploratory objectives include assessment of intradialytic hypotension during run-in and in response to random allocation to treatment.

3. STUDY DESIGN ISSUES

3.1 Overview

The BLOCADE trial is a phase III, randomised, double-blind, placebo-controlled, parallel group feasibility study with a six week open-label active run-in phase during which all participants received carvedilol up to a maximum dose of 6.25 mg twice daily. Participants who tolerated this dose for at least two weeks prior to the randomisation visit were randomised to carvedilol or placebo. After randomisation, participants were up-titrated to a maximum dose of 25 mg twice daily of carvedilol or placebo over a period of six weeks (plus another 4 weeks if needed), then followed for 12 months before being down-titrated off study drug over a period of four weeks.

3.2 Study population

The population of interest is patients receiving either haemodialysis (HD) or peritoneal dialysis (PD) at hospitals in Australia and New Zealand.

3.2.1 Inclusion criteria

Patients were eligible for inclusion in the trial if <u>all</u> of the following criteria were met:

1) The person was willing to participate and had signed the Participant Information and Consent Form
2) The person had end-stage kidney disease and was receiving either haemodialysis or peritoneal dialysis
3) At the time of signing the consent form, the person met the following:
   i) Age $\geq$50 years, OR
   ii) Age $\geq$18 years with diabetes, OR
   iii) Age $\geq$18 years and has clinical features of cardiovascular disease (myocardial infarction or ischaemic heart disease, ischaemic stroke or peripheral arterial disease)

as determined by the site investigator and defined in the **Appendix** (**Section 13.2**) of the BLOCADE Trial Protocol (6).

4) The treating nephrologist agreed the person could participate in the BLOCADE Feasibility Study

3.2.2 Exclusion criteria

Patients were excluded from the study if <u>any one</u> of the following conditions was met:

1) Scheduled for live donor transplant within six months.
2) Experienced a cardiovascular event in the previous 3 months. Cardiovascular events include: myocardial infarction, admission for unstable angina, coronary revascularisation procedure, peripheral arterial revascularisation procedure or stroke.
3) Definite contra-indication to beta-blockers, such as:
    a) 2nd or 3rd degree atrioventricular block unless treated with a permanent pacemaker
    b) sick sinus syndrome unless treated with a permanent pacemaker
    c) clinically significant reversible bronchospasm
    d) previous intolerance to beta-blockers
    e) other contra-indication
4) Currently taking a **beta-blocker**, **verapamil**, **diltiazem** or **moxonidine** and the treating nephrologist does not wish to stop these medications in order to enter the trial.
5) Considered by the treating nephrologist to be clinically or haemodynamically unstable for the study.
6) Unstable target weight (defined by a change of <u>≥</u>2.0kg in target base weight over the preceding month).
7) Severe hepatic dysfunction (transaminases <u>≥</u>3x higher than the upper normal limit) on the most recent liver function tests (if performed within 3 months).
8) Already involved in a clinical trial where the intervention being trialled is likely to confound the outcome of this trial.
9) Considered by the treating physician to have a life expectancy of less than 12 months.
10) Inability to provide consent or follow study instructions due to psychological illness or other condition.
11) Pregnant or planning to be pregnant during the trial period.

The eligibility criteria were more restrictive at the start of the trial. In an attempt to improve recruitment, protocol amendments on 8 March 2012 removed one inclusion criterion (The person has been receiving dialysis for more than 3 months but less than 36 months at the time of signing the consent form) and one exclusion criterion (Aged 75 or older at the time of signing the consent form).

3.3. Sample size

The planned sample size was 150 patients to enter the run-in phase. This number was based on a confidence interval approach for estimating the proportion of patients who would tolerate carvedilol during the run-in phase. Assuming a tolerability of 70%, 150 patients would give 95% confidence limits of 62.5% and 77.5%. Due to slow recruitment and diminished funds, recruitment was prematurely stopped after 88 participants had been

consented into the study. Of these, 72 entered the run-in phase (48% of the target sample size).

3.4 Treatment allocation

Participants who tolerated a twice daily 6.25 mg dose of carvedilol by the end of the run-in phase were randomised 1:1 to one of the two treatment groups. Randomisation was conducted using an interactive voice response system (IVRS). The IVRS randomised patients by an adaptive allocation algorithm designed to minimise study site and dialysis modality (haemodialysis or peritoneal dialysis) imbalance within the two treatment groups.

3.5 Treatment blinding and allocation concealment

Investigators and participants were blinded to randomised treatment assignment. Performing randomisation using an IVRS provided by the National Health and Medical Research Council Clinical Trials Centre in Sydney, Australia, ensured concealment of treatment allocation from site staff, who were responsible for performing the EQ5D, recording IDH over specific times and reporting SAEs. The three clinical end-point adjudicators adjudicated possible cardiovascular events during the course of the study and were also unaware of treatment assignment. Biochemistry staff in contracted laboratories who will perform outcome assessments such as measurement of BNP and other markers will be blinded to the treatment allocations.

3.6 Schedule of assessments

STUDY PHASE	BA	RUN-IN*			RA	TITRATION*					FOLLOW-UP*				END OF STUDY*		
		R0	R2	R4		T2	T4	T6	T8^	T10^	F3	F6	F9	F12	E2	E4	E6#
Assessment:																	
History	X																
Examination	X																
Height	X																
Heart Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ABPM (optional)	X											X					
IDH			X			X	X				X	X					
Home BP (optional)	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dry weight	X	X			X						X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X										X			X			
ECHO		X															
BNP		X										X		X			
Laboratory studies		X			X							X		X			
Quality of Life (EQ5D)	X											X		X			
Serious Adverse Events & Adverse Drug Reactions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BA=Baseline assessment, R0-R4 (weeks)=Run-in phase, RA=Randomisation visit, T2-T10 (weeks)=Titration phase, F3-F12 (months)=Follow-up phase, E2-E6 (weeks)=End of Study. *Visit Windows: Run-in = ±4 days; Titration = ±4 days; Follow-up = ±1 week; End of Study = ±4 days. ^Only if required. #Study Coordinator will contact participant by telephone 1 month after complete cessation of study drug to ascertain vital status and determine if adverse events occurred during this period.All assessments were to be conducted before a patient commenced their dialysis session. For haemodialysis patients, assessments were to be conducted after their "short break".

4. STUDY OUTCOME VARIABLES

4.1 Primary outcomes

A range of outcome measures were considered primary in order to assess the feasibility of a clinical end-point study with carvedilol as the intervention. These were:

1) Tolerability

    a. The proportion of participants who finish the run-in phase on a twice daily dose of carvedilol of at least 6.25 mg. Participants who enter run-in but do not take any study medication will be counted among those who fail to finish run-in. Those who do not finish the run-in phase as defined above will be classified as a carvedilol-related failure or a failure for other reasons.
    b. The proportion of participants randomised to carvedilol (placebo) that drop out due to any adverse event attributable to the study product.
    c. The incidence of major adverse events of symptomatic hypotension and symptomatic bradycardia in participants randomised to carvedilol (placebo).

2) Sample size

    a. The proportion of participants randomised to carvedilol (placebo) that cease study medication for any reason.
    b. The Proportion of participants randomised to carvedilol (placebo) that are thought to require beta-blocker therapy after randomisation.
    c. The proportion of participants who withdraw consent to participate in the study after randomisation.
    d. Overall post-randomisation rate of the proposed composite primary outcome for the clinical end-point study (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, resuscitated cardiac arrest).
    e. Overall post-randomisation rate of proposed secondary outcomes for the clinical end-point study (all-cause mortality, the composite primary outcome plus hospital admission for cardiovascular disease, total days in hospital, total days in hospital where cardiovascular disease is the main reason for admission).

3) Logistics

    a. Recruitment rate (number per month)
    b. The proportion of screened patients eligible for run-in.
    c. The proportion of participants eligible for run-in who enter run-in.
    d. The proportion of participants randomised to carvedilol (placebo) that are on a dose of 25 mg twice daily at each titration and follow-up visit.

4.2 Secondary outcomes

Carvedilol and placebo will be compared on the following outcomes:

1) Change from baseline in B-type natriuretic peptide (BNP)
2) Change from baseline in health-related quality of life (measured by EQ5D)

In addition, baseline BNP levels will be used to predict tolerance (yes, no) of a 6.25 mg dose of carvedilol during the run-in phase.

4.3 Tertiary outcomes

Outcomes for exploratory analyses are:

1) The proportion of participants who consented to participate in and completed the home blood pressure and twenty-four hour ambulatory blood pressure sub-studies.
2) Intra-dialytic hypotension (no, yes), defined as a fall in systolic blood pressure of at least 20 mm Hg during or post dialysis relative to pre-dialysis associated with symptoms of hypotension (nausea/vomiting, cramps/pain in legs, dizzy/light headed, syncope/pre-syncope/loss of consciousness, chest or abdominal pain, other symptom) and requiring treatment for hypotension (head-low position, modification of ultrafiltration rate or target, infusion of any type of intravenous fluid specifically to treat hypotension, other treatment for hypotension).

4.4 Serious adverse events and adverse drug reactions

Categories of serious adverse events (SAEs) and adverse drug reactions (ADRs) are:

1) SAEs classified according to World Health Organisation (WHO) categories (death, life-threatening, initial or prolonged hospitalisation, persistent or significant disability/incapacity, congenital anomaly, important medical event)
2) SAEs classified according to body system (cardiovascular, respiratory, gastrointestinal, dialysis complication, neurological, psychological, endocrine, pregnancy, haematology, skin, other)
3) SAE relationship to study medication (none, unlikely, possible, probable)
4) ADR severity (mild, moderate, severe, life-threatening)
5) ADR relationship to study medication (possible, probable)

5. SEQUENCE OF PLANNED ANALYSES

5.1 Interim analyses

SAEs and measures of study conduct and implementation by treatment group have been monitored on a regular basis by a Data and Safety Monitoring Board (DSMB). Only DSMB members and statisticians compiling closed-session reports for DSMB meetings have had access to un-blinded interim data and results. As this is a feasibility study, no interim efficacy analyses were planned or conducted.

5.2 Final analyses and reporting

All final planned analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the final end-of-study visit E6 and the database has been cleaned and locked. A blinded data review will be conducted by members of the Trial Management Committee (TMC) prior to locking the trial database. Treatment allocations will not be un-blinded and no un-blinded analyses will commence until this SAP has been

reviewed by the TMC and approved by the Chair of the TMC, the Director of the Australasian Kidney Trials Network (AKTN), and the Trial Statistician. Results from the final analyses will be reviewed by the TMC prior to completion of the FSR and subsequent manuscripts. Any post-hoc exploratory analyses performed to provide support for planned analyses but not identified in this SAP will be documented and reported in appendices to the FSR and clearly identified as unplanned analyses in the text of the FSR.

5.3 Changes to statistical information in the trial protocol

This SAP does not contain any important changes to statistical information given in the final version of the trial protocol (6).

6. STATISTICAL ANALYSES

6.1 Trial profile

All patients who provided informed consent will be accounted for in the FSR. A CONSORT-style flow diagram will illustrate patient progression through the trial from initial screening for eligibility to completion of the final post-randomisation outcome assessments. Reasons for study withdrawal and major protocol deviations and violations will be documented.

6.2 Patient characteristics and baseline comparisons

Demographic and other baseline characteristics will be summarised for participants who entered the run-in phase and by assigned treatment group for those who completed run-in and were randomised to carvedilol or placebo. Categorical variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator, which will be less than the number of patients assigned to the treatment group, will be reported either in the body or a footnote in the summary table. Continuous variables will be summarised by mean and standard deviation as well as quartiles.

The following baseline demographic and clinical characteristics will be presented: gender, age, ethnic origin (Caucasian, ATSI, Maori/Pacific Islander, Asian, Other, Unknown), height, weight, BMI, obesity (BMI <30, BMI ≥30), heart rate, blood pressure (systolic and diastolic), smoking status (never, former, current), primary cause of renal disease (diabetic nephropathy, hypertension/vascular, glomerulonephritis, reflux nephropathy, polycystic kidney disease, other, unknown), failing renal transplant (no, yes), dialysis treatment regimen (APD, CAPD, HD), diabetes mellitus (no, yes), hypertension (no, yes), ischaemic heart disease (no, yes), cardiac failure (no, yes), cerebrovascular disease (no, yes), peripheral arterial disease (no, yes), chronic lung disease (no, yes), quality of life, BNP, and a range of echocardiographic imagining measurements, including left ventricular end diastolic volume, left ventricular end diastolic dimension, left ventricular end systolic volume, left ventricular end systolic dimension, ejection fraction, stroke volume, left atrial size, E/A ratio, E/A duration, E/E' ratio, and global longitudinal strain.

6.3 Analysis of primary outcomes

6.3.1 Tolerability

Binomial proportions and 95% confidence intervals for the proportion of participants who completed run-in will be estimated using an intercept-only Generalised Linear Model from the binomial family with identity link function. Binomial proportions and 95% confidence intervals for randomised participants who drop out from carvedilol and placebo will be estimated using the same statistical model. Incidence rates for major adverse events (symptomatic hypotension and symptomatic bradycardia) in the randomised carvedilol and placebo groups will be estimated using intercept-only Poisson regression models.

6.3.2 Sample size

Except for the proposed clinical endpoints, all proportions and 95% confidence intervals will be estimated as described above for tolerability outcome variables. Due to the small number of adjudicated clinical events, only counts will be presented for the proposed clinical outcomes.

6.3.3 Logistics

Recruitment rate will be represented graphically by plotting monthly recruitment and cumulative recruitment numbers at each month of active recruitment. Proportions and 95% confidence intervals for screened patients eligible for run-in and eligible patients who entered run-in will be estimated as described above for tolerability outcome variables. Proportions randomised to carvedilol and placebo on a 25 mg dose during each titration and follow-up visit will be separately analysed for each treatment group using a mixed-effects logistic regression model with study visit as a fixed effect in the model and participant identifier as a random effect. Proportions on each dose of study drug (6.25 mg, 12.5 mg, 25 mg) by treatment group across titration and follow-up visits will be described.

6.4 Analysis of secondary outcomes

All randomised participants with outcome data will be analysed according to the Intention-to-Treat (ITT) principle. The full analysis set will exclude randomised participants who withdrew from the study before any follow-up data on BNP or EQ5D was collected. BNP and EQ5D will be separately analysed using a linear mixed model with treatment group and baseline measurements as fixed effects and participant identifier and study visit as random effects. If there is insufficient data to reliably estimate random effects, the BNP and EQ5D data will be analysed using analysis of covariance (ANCOVA). Separate analyses will be performed on data from the 6 and 12 month visits. In all analyses, the effect of intervention group on outcome will be adjusted for baseline measurements. In addition, a logistic regression model will be used to predict successful completion of run-in (no, yes) from baseline BNP measurements.

6.5 Analysis of safety outcomes

SAEs and ADRs that occurred during run-in will be summarised as number (percent). Post-randomisation SAE and ADR categories will be cross-tabulated with treatment group and summarised as number (percent).

6.6 Exploratory analyses

6.6.1 Sub-study participation

The number (percentage) of participants who consented to participate in and who completed the home blood pressure sub-study. Number (percentage) of participants who consented to participate in and who completed the twenty-four hour ambulatory blood pressure sub-study.

6.6.2 Intradialytic hypotension

The incidence rate of intradialytic hypotension during run-in will be estimated using an intercept-only Poisson regression model. A Poisson regression model with treatment group as a covariate will be used to compare incidence rates for intradialytic hypotension in the randomised carvedilol and placebo groups.

7. REPORTING CONVENTIONS

7.1 General reporting conventions

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

All titles will be centred on a page. The first title line will be the number of the table, figure, or data listing. The second (and if required, third) line will be the description of the table, figure, or data listing. The ICH numbering convention will be used for all TLFs (8).

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

7.2 Statistical summary conventions

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

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

8. TABLES, LISTINGS, AND FIGURES

This section lists the planned tables, listings and figures for the BLOCADE trial. Templates for all planned tables are in a separate document titled BLOCADE SAP Tables, Listings and Figures.

8.1 Planned tables

The following are planned summary tables:

Table 1. Reasons screened patients were not consented into the study
Table 2. Enrolment by study centre
Table 3. Stratification variables by treatment group for randomised participants
Table 4. Withdrawals, protocol deviations and violations during run-in
Table 5. Withdrawals, protocol deviations and violations by treatment group
Table 6. Demographic and clinical baseline characteristics for participants who entered run-in, overall and by successful completion of run-in (yes, no) [Table note indicating 16 consented participants did not enter run-in]
Table 7. Demographic and clinical baseline characteristics by final run-in dose for all participants who entered run-in
Table 8. Demographic and clinical baseline characteristics by treatment group for randomised participants
Table 9. Number (percent) for primary outcomes of feasibility, sample size and logistics
Table 10. Number of proposed primary and secondary outcomes for large clinical endpoint study
Table 11. Intradialytic hypotensive episodes per dialysis session during run-in
Table 12. Intradialytic hypotensive episodes per dialysis session overall and by treatment group for randomised participants
Table 13. Number (percentage) of dialysis sessions during which an intradialytic hypotensive event occurred during run-in
Table 14. Number (percentage) of dialysis sessions during which an intradialytic hypotensive episode occurred overall and by treatment group for randomised participants
Table 15. SAEs and ADRs during run-in, overall and by successful completion of run-in (yes, no)
Table 16. SAEs and ADRs by treatment group for randomised participants

8.2 Planned listings

The following are planned data and patient listings:

Listing 1. Reasons consented participants (n=16) did not enter run-in
Listing 2. Deaths and life threatening events during run-in
Listing 3. Post-randomisation deaths and life threatening
Listing 4. Reasons for patients withdrawing from the study
Listing 5. Medication compliance problems requiring patient to come off trial

8.3 Planned figures

The following are planned summary figures:

Figure 1. Monthly and cumulative enrolment
Figure 2. Flowchart of patient progression through the study
Figure 3. Proportions of participants on each dose of study drug (6.25 mg, 12.5 mg, 25 mg) by treatment group across titration and follow-up visits
Figure 4. BNP over time (baseline, F6, F12) by treatment group for randomised participants
Figure 5. EQ5D over time (baseline, F6, F12) by treatment group for randomised participants

9. REFERENCES

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