Statistical Considerations

Investigator Meeting

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit | Hull and East Yorkshire Hospitals NHS Trust | NHS

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Sample Size Considerations

- Based on the primary outcome
- Primary outcome is the renal function at 3 years
  - Measured using the MDRD 4-variable eGFR (Continuous outcome)
- Power (usually 80% or 90%)
  - We have chosen 80% power
- Data for sample size
  - Ahmed AK et al. The impact of stopping inhibitors of the renin–angiotensin system in patients with advances chronic kidney disease
- What MCID we want to detect

Sample Size Considerations

- 1 Observation study provided data on eGFR in patients with advanced CKD

eGFR (ml/min)	12 months before ACEi/ARB stopped	When ACEi/ARB was stopped	12 months after ACEi/ARB was stopped
Mean ± Std.Err [Std.Dev]	22.9 ± 1.4 [10.1]	16.38 ± 1 [7.2]	26.6 ± 2.2 **[15.9]**

- The largest standard deviation (15.9) chosen
- A MCID of **5 ml/min** between the two groups was chosen
- With 80% power, alpha=0.05 and allowing for 20% attrition gives a total sample size of 410 participants (205 per arm)
- Sample size based on a 2-sample T-Test
- Sample size assumptions to be monitored by DMEC

Primary Outcome analysis

- The primary outcome is eGFR at 3 years
- Linear regression model adjusting for all minimisation covariates
- Data for eGFR collected every 3 months
- Multilevel mixed-effects linear regression analysis, including treatment by time cross-term across the entire 3 years of follow-up
- Results will be presented as mean difference in eGFR with 95% CI
- Longitudinal plots of mean changes from baseline over time by treatment group for visual inspection

Primary Outcome analysis

Primary endpoint (adjusted analyses using ANCOVA)

eGFR score (3 years)	Coefficient	Standard Error	95% CI	P-value
Continue treatment	-	-	-	-
STOP treatment				
Baseline eGFR				
Minimisation variables + other(s)				
Constant				

The interpretation of the coefficient for the STOP treatment arm is the mean difference in eGFR at 3 years compared to CONTINUE treatment arm, after adjusting for all other covariates in the model

Secondary Outcomes

Continuous Outcomes

- Blood pressure between groups
- Cystatin-C levels between groups
- Participant physical function (measured using the 6-minute walk test)
- Urine protein excretion between group
- Haemoglobin concentration between groups
- ESA dose between groups

Time to event outcomes

- Time taken to reach ESRD or need for renal replacement therapy

Quality of life (QOL) outcomes

- Participant QOL and wellbeing (measured using KDQOL-SF v.1.3 questionnaire)

Secondary Outcomes

Safety data & Categorical outcomes

- Hospitalisation rates from any cause
- Cardiovascular events
  - heart failure, hypertension, myocardial infarction, stroke
- Adverse events
- Mortality rates
- N of participants starting renal replacement therapy or sustaining a >50% decline in eGFR

Secondary Outcomes analyses

- **Continuous Endpoints**
  - Analysed in the same manner as the primary endpoint
- **Categorical (Dichotomous endpoints)**
  - Proportions and percentages will be compared between arms using Chi-squared test
  - Relative risks and 95% CI's will be calculated
  - Logistic regression may be used to adjust for any covariates
- **Time to event data**
  - Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons
  - Log-rank test and Cox proportional hazard model will be used
  - Treatment effects will be expressed as hazard ratios with 95% CI's

Subgroup analyses

- Several a priori subgroup analyses are planned:
  - Diabetes (Type 1 diabetes, Type 2 diabetes, non-diabetic)
  - BP as mean arterial pressure (<100, ≥100)
  - Age (<65 years, ≥65 years)
  - Proteinuria (PCR<100, ≥100)
  - eGFR (<15 ml/min, ≥15 ml/min)

- These analyses will be treated as hypothesis-generating

- Subgroup analysis will employ a test of interaction

- All analyses will be conducted using intention to treat (i.e. analysing in the group to which the subject was randomised)

- Full statistical analysis plan to describe all analysis in detail

Data Monitoring Committee

- It comprises of 3 people:
  - Dr John Firth (Chair) – Consultant Nephrologist
  - Dr Paul Kalra – Cardiologist
  - Mrs Merryn Voysey – Independent Statistician

- Their role will be to review:
  - study progress (i.e. recruitment rates, form return rates, baseline data)
  - sample size assumptions
  - outcome efficacy
  - mainly all of the safety data

- DMC will meet annually but can meet more regularly (i.e. every 4-6 months) if the DMC wishes to

Data Monitoring Committee

- DMC make recommendations to the Trial Steering Committee

- Possible recommendations include:
  - No action needed, trial continues as planned
  - Early stopping due, for example, to clear benefit or harm of treatment, futility, or external evidence

- Any recommendations on stopping the trial early will be based on a balance between safety, efficacy and any external evidence

- A DMEC charter outlining the terms of reference (including information on stopping rules) is agreed with the DMEC

Questions?