PARASOL

Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis

Interim Meeting
June 8-9, 2024

Analysis Chapters

Description of analysis populations (1/11)

UoM Master Dataset: Populations
- All, Incident, Prevalent

Description of populations
- Baseline + follow up characteristics
  - Incudes details on number of values, median, etc
- Venn diagram of population

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Evaluation of **Intermediate-term change in eGFR-based endpoints** (2/11)

UoM Master Dataset: Populations
- All, incident, prevalent

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, media, etc
- Note: Populations may differ depending on analysis specific eligibility criteria
  - If so, comparison of included/excluded groups

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

eGFR endpoints (24, 36 & 48 months post-index)
- Mixed effects linear regression models with participant-specific intercepts and slopes
- Polynomial functions of time from index
- MMRM

Select eGFR endpoint(s) to apply in association analyses

Association of **Intermediate-term change in eGFR endpoints** vs. **KF endpoints** (3/11)

UoM Master Dataset: Populations
- All, incident, prevalent
- Selected sub-groups
  - Peds, adults, CKD12, CKD345, genetic FSGS, UPCR >=1.5 g/g - <3.5 g/g, UPCR >=3.5 g/g, nephrotic, non-nephrotic

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, median, etc

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

eGFR endpoint(s)
- Selected from Chapter 2
- 24, 36 & 48 months

vs.

KF endpoint(s)
- KF +/- 50% decline in eGFR

Application of **intermediate-term change in eGFR-based endpoints** as primary endpoint in phase 3 trial: Sample size and treatment effect requirements (4/11)

UoM Master Dataset: Populations
- All, incident, prevalent
- **Selected sub-groups**
  - Base on chapter 3 findings

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, median, etc
- Comparison of eGFR decline of populations and sub-groups over trial period (ie representing control group)

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

eGFR endpoint(s)
- Selected from Chapter 2
- **Sample size and treatment effect requirements based on standard phase 3 assumptions**

Evaluating **early-term change in proteinuria** vs. **intermediate-term change in eGFR & KF endpoints:** Accelerated approval pathway (5/11)

UoM Master Dataset: Populations
- All, incident, prevalent

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, median, etc

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

Proteinuria endpoint(s)
- 0-12 month time window
- Last proteinuria value, TW-Proteinuria
- % change, Classical CR/PR, FPR, Thresholds

vs.

eGFR endpoint(s)
- Selected from Chapter 2
- 24, 30 & 36 months

vs.

KF endpoint(s)
- KF +/- 50% decline in eGFR

Note: Inform on endpoints to apply in sub-group analyses (Chapter 6)

Sub-group analyses of **early-term change in proteinuria** vs. **intermediate-term change in eGFR & KF endpoints:** Accelerated approval pathway (6/11)

UoM Master Dataset: Populations
- Selected sub-groups (based on chapter 5 findings)
  - Peds, adults, CKD12, CKD345, genetic FSGS, UPCR >=1.5 g/g - <3.5 g/g, UPCR >=3.5 g/g, nephrotic, non-nephrotic

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, median, etc

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

Proteinuria endpoint(s)
- Selected from Chapter 5
- 0-12 months

vs.

eGFR endpoint(s)
- Selected from Chapter 5

KF endpoint(s)
- KF +/- 50% decline in eGFR

Describing quantitative models for **early-term change in proteinuria** vs. **intermediate-term eGFR change:** Accelerated approval pathway (7/11)

UoM Master Dataset: Populations
- Selected populations & sub-groups (based on chapter 5 & 6 findings)

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, median, etc

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

Proteinuria endpoint(s)
- Selected from Chapter 5
- 0-12 months

vs.

eGFR endpoint(s)
- Selected from Chapter 5
- 24, 36 & 48 months

Evaluating **intermediate-term change in proteinuria** vs. **KF endpoints:** Traditional approval pathway (8/11)

UoM Master Dataset: Populations
- All, incident, prevalent

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, median, etc

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

Proteinuria endpoint(s)
- 6-24 months
- Last proteinuria value, TW-Proteinuria
- % change, Classical CR/PR, FPR, Thresholds

vs.

eGFR endpoint(s)
- Selected from Chapter 2
- 24 & 36 months

vs.

KF endpoint(s)
- KF +/- 50% decline in eGFR

Note: Inform on endpoints to apply in sub-group analyses (Chapter 9)

Sub-group analyses of **intermediate-term change in proteinuria** vs. **KF endpoints:**

Traditional approval pathway (9/11)

UoM Master Dataset: Populations
- Selected sub-groups (based on chapter 8 findings)
  - Peds, adults, CKD12, CKD345, genetic FSGS, UPCR >=1.5 g/g - <3.5 g/g, UPCR >=3.5 g/g, nephrotic, non-nephrotic

Description of analysis populations
- Baseline + follow-up characteristics
  - Incudes details on number of values, median, etc

Validation & external populations
- Repeat analyses conducted on UoM master dataset

Analyses

Proteinuria endpoint(s)
- 6-24 months
- Last proteinuria value, TW-Proteinuria
- % change, Classical CR/PR, FPR, Thresholds

vs.

eGFR endpoint(s)
- Selected from Chapter 2
- 24 & 36 months

vs.

KF endpoint(s)
- KF +/- 50% decline in eGFR

Sensitivity analyses (10/11)

UPCR vs UACR

- Selected outputs comparing UPCR vs UACR data OR outputs excluding UACR data (if >25% of all proteinuria data)
  - Compare baseline and follow-up characteristics

Rich vs poor follow-up data

- Selected outputs comparing data stratified on richness of proteinuria and eGFR data
  - Compare baseline and follow-up characteristics

Winsorizing of eGFR

- Selected outputs comparing application of winsorizing of eGFR values >120 vs no winsorizing

Death in long-term outcomes endpoint

- Selected outputs that include death in long term outcomes (KF +/- 50% decline in eGFR)

Additional sub-group analyses

- Biopsy data-driven subgroups
- Medication data-driven subgroups
- Diagnosis – level of evidence sub-grouping

Meta-analyses (11/11)

- **To be** thought through