Request for CHMP Qualification Opinion
Acceptance of GFR Slope as a Validated Surrogate Endpoint for Chronic Kidney Disease Progression in Clinical Trials for Standard Marketing Authorization and Indication Extension Approvals

Initial Qualification Procedure – Discussion on List of Issues

Feb 7, 2023

Agenda

- Introductions
- Brief background and timeline
- Key results
- Replies to list of issues
- Discussion

Attendees

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Hiddo Heerspink PharmD PhD Groningen, Netherlands, *Clinical Trials Recruiting Core*

Tom Greene PhD, University of Utah, Salt Lake City, UT, *Statistical Core*

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Ed Vonesh PhD, Vonesh Statistical Consulting LLC, *Statistical core*

Ben Haaland PhD, University of Utah, *Statistical core*

Willem Collier PhD, University of Utah, *Statistical core*

Brief background

- The CKD Epidemiology Collaboration (CKD-EPI) (co-applicant with the National Kidney Foundation [NKF]), was formed in 2003 to evaluate one potential surrogate endpoint in CKD (proteinuria), as well as other key challenges in CKD epidemiology at the time.
- A central challenge recognized then and continues to today is that lack of treatments for CKD, in part because the clinical endpoint can only be measured after a long duration of disease or in populations with rapidly progressive disease
- CKD-EPI has conducted investigations over the past two decades to evaluate candidate surrogates including albuminuria, time to GFR decline and GFR slope

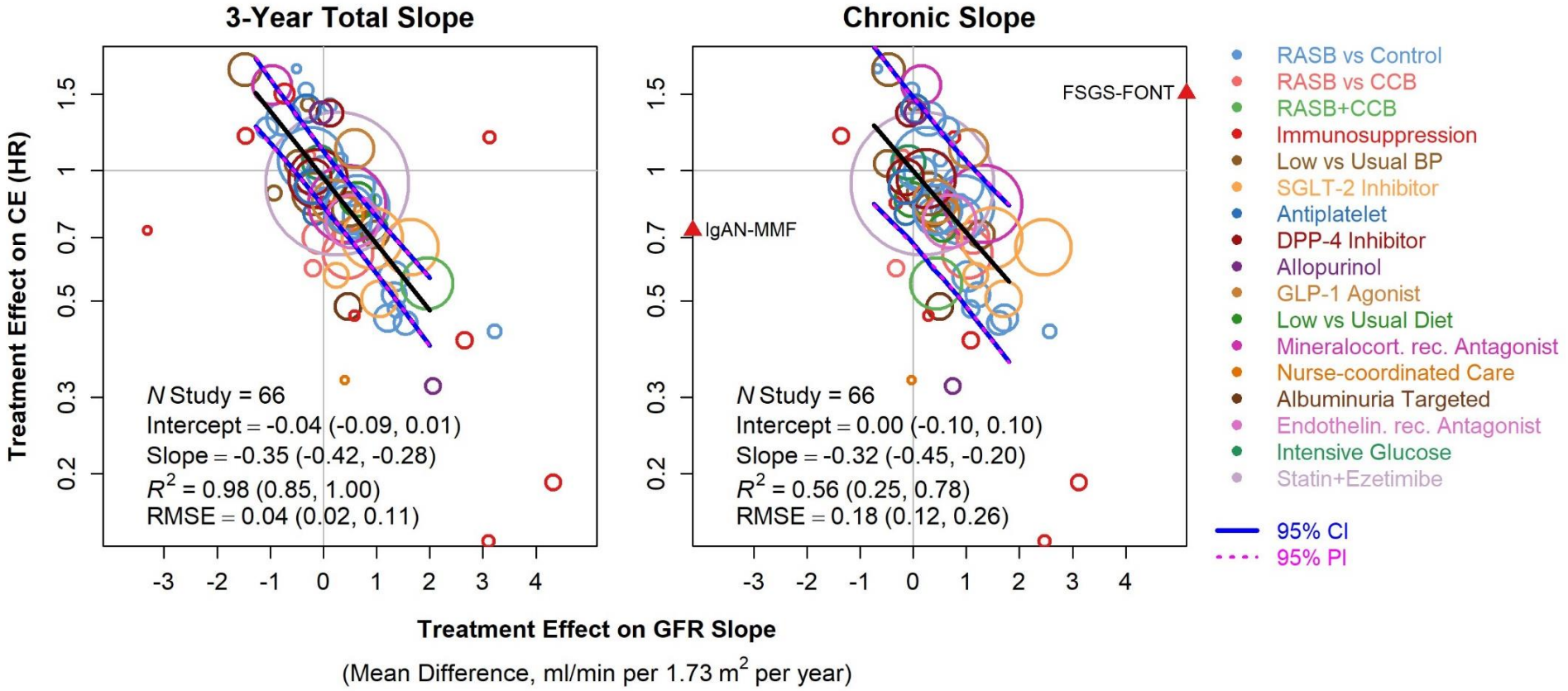
Timeline

2018 March 18	NKF FDA EMA Scientific Workshop presenting first evidence for GFR slope as valid surrogate endpoint (Inker et al JASN 2019)
2021 March	Decision to submit to EMA qualification procedure with inclusion of recent well powered trials conducted in a more diverse set of populations and interventions
2021 May 21	Drs. Inker and Heerspink discussion with EMA regarding submission of qualification opinion
2022 August 25	Submission of qualification document
2022 December 12	EMA response received
2023 January 30	Response document submitted

Outline

- Review of main finding
- Replies to issues raised
  - Study populations and context of use: Question 1 and 2
  - Endpoints: Question 5
  - GFR slope: Question 7, 10, 11, 12
  - Estimand: Question 13
  - Study design: Question 9
- Summary
- Backup : Question 3, 4, 6, 8, 9d-e, 14

Figure 9: Trial-level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint



Key results

1. Very strong associations between treatment effects on total slope computed over 3 years and treatment effects on the clinical endpoint, consistent across subgroups based on disease, GFR, ACR
2. Moderate associations between treatment effects on chronic slope and treatment effects on the clinical endpoint, with less consistency across subgroups based on disease, GFR, ACR

Question 1

1. Please provide clarification on the definition of the four populations included in the target population (CKD, diabetes, glomerular disease, CVD).

   - Our response document includes the definition of these groups
   - The diabetes group both diabetic kidney disease and studies of diabetes, not selected for DKD
   - The CVD group includes those at high risk for CVD and those with heart failure
   - Of note, all studies met our criteria for number of kidney clinical events and thus as a population were at high risk for CKD progression

Question 1

a. Please clarify whether the studies summarized in the subgroup 'diabetes' only comprised patients with diabetic kidney disease or whether patients with GFR >90ml/min/1.73 m^2 were also included.

b. It should be clarified which entities were summarized under the group label 'CVD', and which proportion of patients in each of the 7 studies had GFR >90ml/min/1.73 m^2 at baseline.

- In our view, GFR > 90 is not the sole key parameter since CKD is defined by both GFR and ACR, and many patients with GFR > 90 will have substantial progression as in the case of diabetes or PKD.
- We provide information on the proportion with GFR > 90 and with GFR > 90 and ACR < 30
- In the studies of diabetes not selected for DKD, and in the CVD studies
  - The proportion with GFR > 90 and ACR < 30 ranges from 0 to ~ 40% (generally about 20%)
  - This proportion did not correlate strongly with the rate of CKD progression in the overall study

Question 1c: Exclude subjects with normal renal function at baseline. Results should be discussed considering the proposed context of use, which also apparently intends to include primary prevention of kidney disease.

- We were not able to do these analyses as we did not have access to all individual studies at this time
- We agree with EMA that is important to ensure that the trial level associations are robust by disease severity.
- The data we did present showed robustness of trial level analyses across GFR, ACR and populations. Results were consistent with
  - Restriction of the analysis to participants with ACR > 30
  - Removal of CVD studies*, which are the studies with greatest proportion of GFR > 90*
  - Subgroups based on mean level of GFR and rate of progression on the chronic arm
- For the purpose of supporting validity of GFR slope, we support use of the broad set of studies and participants as the greater heterogeneity of studies is essential to provide the strongest evidence to support GFR slope as a surrogate endpoint.

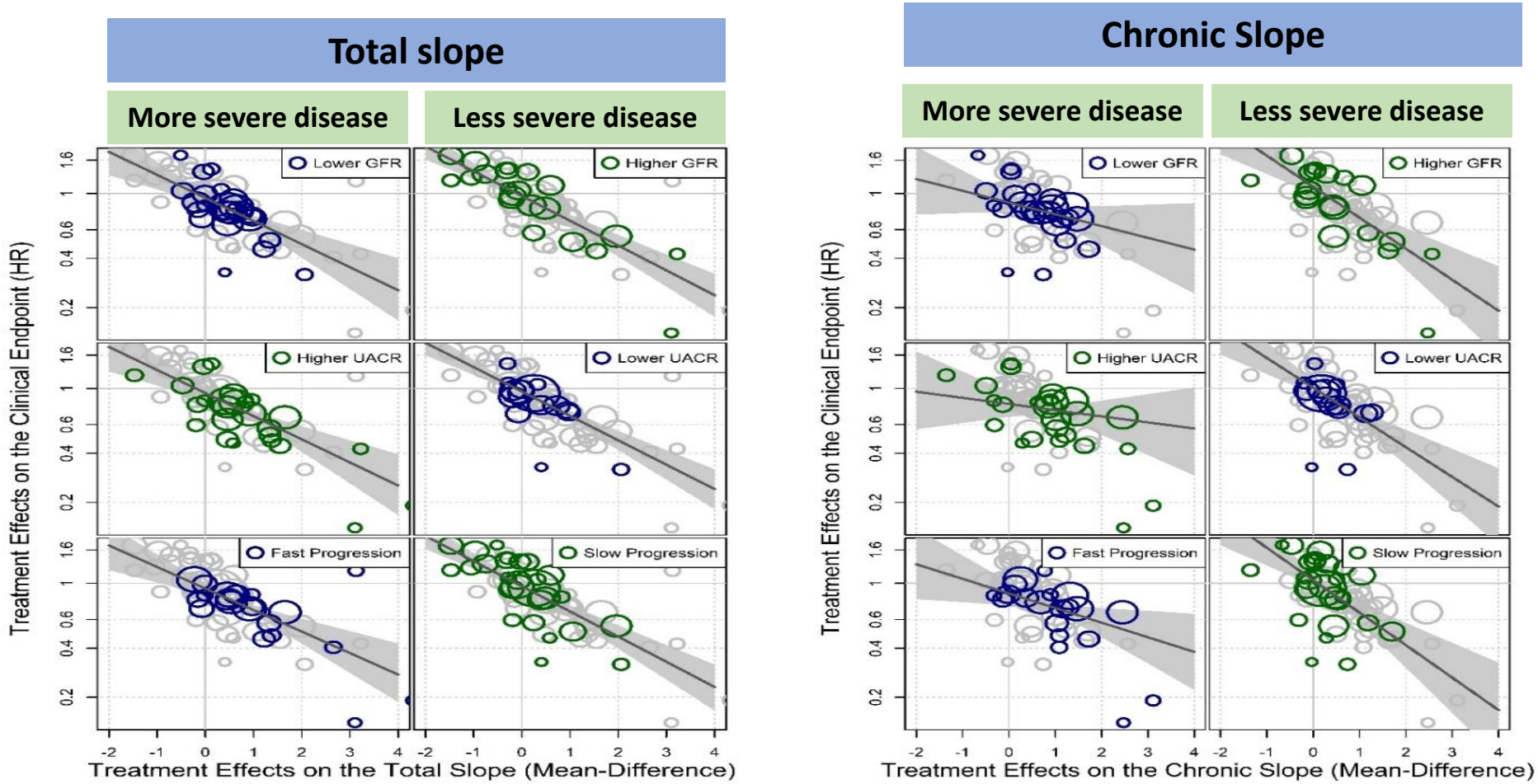
Question 1c: Exclude subjects with normal renal function at baseline. Results should be discussed considering the proposed context of use, which also apparently intends to include primary prevention of kidney disease.

- For context of use
  - We had not been proposing GFR slope to be used to study primary prevention of CKD.
  - For use of GFR slope, the study population would have to be estimated a priori to have sufficient progression to power an analysis for GFR slope
  - We propose a revised context of use:
    - **General setting**: The proposed novel method, GFR slope, is intended to be used as a validated surrogate endpoint for CKD progression in clinical trials for standard marketing authorization and indication extension approvals.
    - **Target population**: Broad population of patients with CKD or at risk for progressive CKD, including early and late disease across cause of CKD

Question 2: Please discuss subgroup analyses results, e.g., regarding baseline GFR and target population including subjects at risk, considering potential differential acute effects in subgroups.

- To further support the subgroup results that we presented in the qualification document, we now share new analyses that extend the trial-level meta-regression models to test for interactions with baseline mean GFR and median ACR in each study

Collier et al in press CJASN



- **Total slope:** Consistent performance across levels of disease severity
- **Chronic slope**: Steeper relationships between treatment effects on chronic slope vs. the clinical endpoint at less severe disease compared to more severe disease
- Result consistent with subgroup analyses in our submission and further support the total slope across all CKD severity levels

Question 5: Selection of the clinical endpoint for our analyses

- Death: We think there was a misunderstanding about inclusion of death in our prior studies, that we have now clarified (death was not included)
- 57% decline in GFR (doubling of creatinine): We present new results removing doubling of serum creatinine from the composite endpoint, and feel these support strengthen our conclusions.

Question 5 (con't):

Trial level results using endpoint of KFRT or GFR < 15 ml/min per 1.73 m^2					
Slope	**Event**	**Meta-Regression Slope (95% BCI)**	**Intercept (95% BCI)**	**R^2 (95% BCI)**	**RMSE (95% BCI)**
total slope 3y	**Primary CE:** KFRT/GFR < 15, doubling of SCr	-0.35 (-0.42, -0.29)	-0.04 (-0.09, 0.01)	0.97 (0.83, 1.00)	0.05 (0.02, 0.12)
	Secondary CE: KFRT/GFR < 15	-0.22 (-0.31, -0.12)	-0.1 (-0.18, -0.04)	0.91 (0.54, 0.99)	0.05 (0.02, 0.11)
chronic slope	**Primary CE**: KFRT/GFR < 15, doubling of SCr	-0.33 (-0.46, -0.20)	0 (-0.10, 0.10)	0.55 (0.24, 0.78)	0.19 (0.12, 0.27)
	Secondary CE: KFRT/GFR < 15	-0.15 (-0.24, -0.05)	-0.1 (-0.19, -0.03)	0.73 (0.13, 0.98)	0.05 (0.02, 0.13)

- **Total slope:**
  - Modest reduction in the median R^2
  - Due to decreased estimated variation in the treatment effects across the 66 trials for the secondary CE than for the primary CE
- **Chronic slope:**
  - Higher R^2 and lower RMSE for the chronic slope vs secondary CE
  - Possibly due to reduced impact of the acute effect on the secondary CE compared to our primary CE

Question 5 (con't)

We still consider the current analyses as the main analyses for the following reasons, with the secondary CE as providing supporting evidence

1. Compared to the main analysis, trial level analyses for secondary CE
   - Reduced precision due to fewer events, expected to be larger in subgroups
   - Weighted to subset of studies with lower baseline GFR
   - Large impact of the competing risk of death

2. The primary CE is the widely accepted clinical endpoint. Using this endpoint in our analyses increases generalizability as very few trials will only include KFRT +GFR < 15 as endpoint.

Questions 7, 10, 11, 12: Computation of GFR slope

There were several questions about the shared-parameter GFR slope model

The model has a number of features to support broad applicability:

1. Applicability to a wide range of designs with differing GFR measurement schedules and follow-up durations
2. Accommodates acute effects
3. Accounts for informative censoring by KFRT and death, with straightforward extensions that can be applied to handle artificial censoring by designated intercurrent events
4. Accounts for variation in GFR trajectories through variation in intercepts, acute and chronic slopes
5. Accounts for heterogeneity in variability of individual GFR measurements across different levels of GFR and for heterogeneity in variability of GFR slopes between treatment groups.

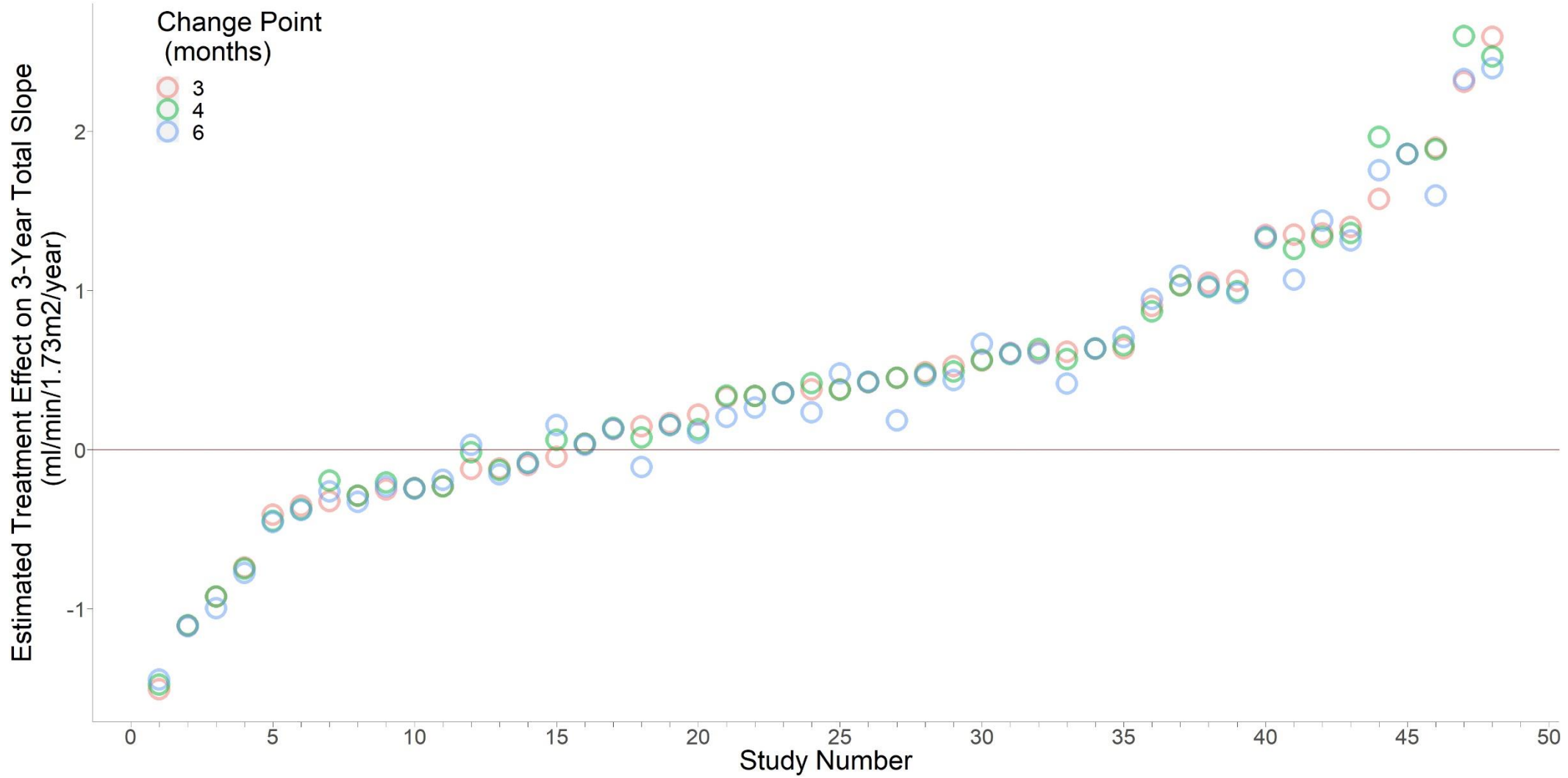
- Easy to pre-specify an algorithm in which analysis of the full shared parameter model reverts to a simpler model when convergence cannot be achieved using the full model
- We recommend that the GFR slope model used should be that which fits the needs of the trial, which may not always be the shared parameter model.
- One approach is to treat the shared parameter as a sensitivity analysis to assess whether informative censoring is a concern

Questions 7, 10, 11, 12: Computation of GFR slope

Questions 7: Are the conclusions from our unified mixed effects model in the trial level analysis applicable if we anticipate that future trials would use a tailored approach to compute slope. It is not obvious that conclusions on Type 1 error and bias or GFR threshold to infer a beneficial effect on a clinical endpoint would be the same.

- Similar to analyses validating other surrogate endpoints, we used a common approach to estimate GFR slope.
- We do not expect that a tailored method for analysis for slope that improves the model for individual trials would worsen performance relative to the clinical endpoint, and thus expect our results provide a conservative assessment of the validity of slope-based endpoints
- In sensitivity analyses, we have found that estimated treatment effects on the total slope are relatively robust to issues such as designation of the change point, and model for informative censoring

Impact of change in knot point to define acute effect on estimated treatment effects



Questions 7, 10, 11, 12: Computation of GFR slope

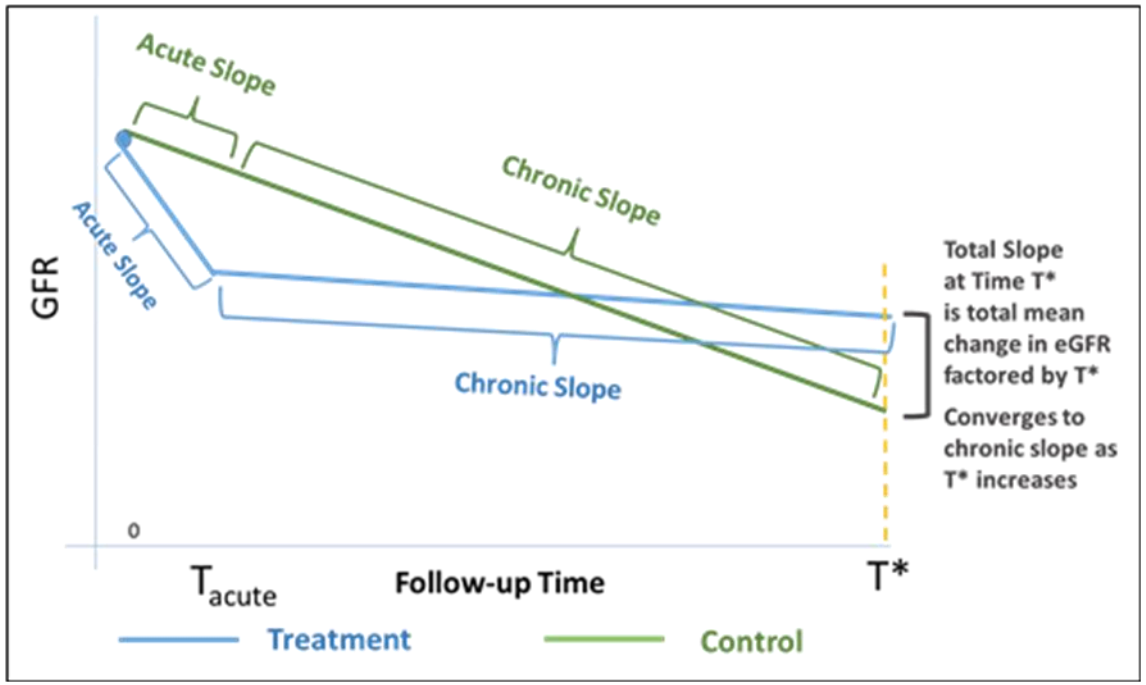
Question 10b: Need for threshold analysis in a chronic slope

- Our most recent analyses suggest that the most appropriate threshold for inferring benefit based on the chronic slope should be informed by the size and direction of the acute effect.

Question 10b: EMA asked our views on use of a change from baseline analysis

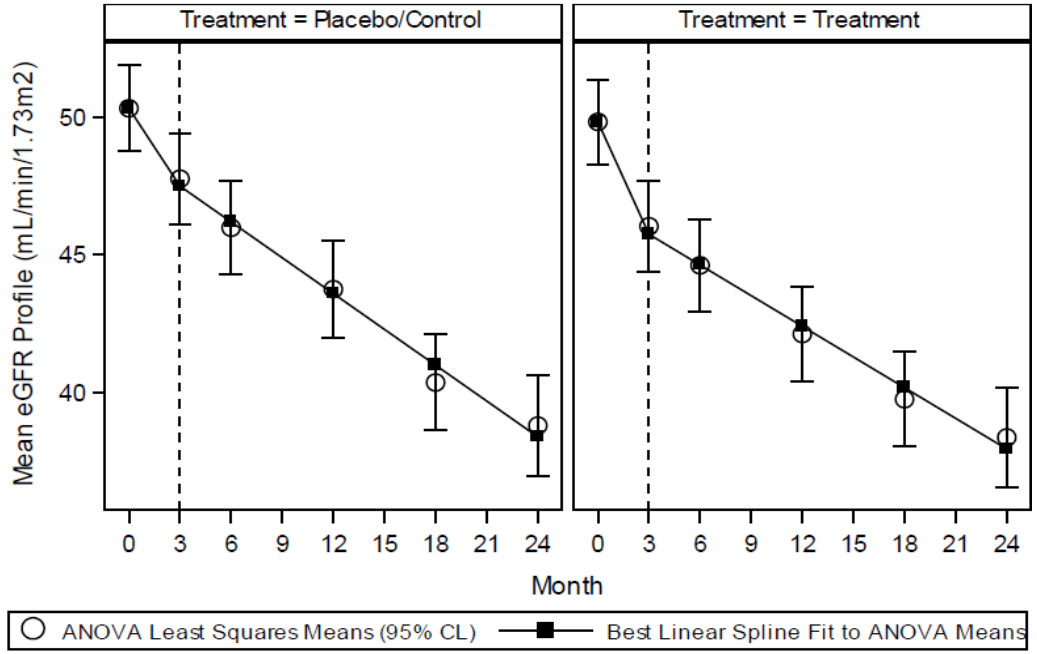
- Not accounting for GFR values in the intermediate period can introduce bias from those who drop out or die before the last measurement, leading to reduction in power
- Nevertheless, there may be a role for this analysis due to its simplicity, for example where a fixed and relatively short follow-up period for each patient is plausible

Questions 12: Elaborate on clinical interpretability of the model



IDNT study: RASB vs CCB

Vonesh et al SIM 2019



- **Acute slope:** rate of change in GFR during the first several months after randomization,
- **Chronic slope:** rate of change in GFR starting after the first several months after randomization,
- **Total slope:** the change in GFR from baseline to a designated time towards the end of the follow-up period normalized for time.
- Treatment effect evaluated based on the difference between mean slopes
- Other terms in the shared parameter model are of explanatory interest but not central to clinical evaluation of the treatment effect on slope.

Questions 7, 10, 11, 12: Computation of GFR slope

- **Questions 11 and 12:** EMA asked whether the 2 linear slope mixed effects model can adequately describe the GFR trajectories in all target populations and across all disease stages, and asked about model choice with high censoring events

  - As noted above, the shared parameter model includes a number of features to support broad applicability.
  - Trial level analyses show accurate and consistent performance of the 3-year total slope estimated under this model across disease subgroups, CKD stage and CKD severity.
  - Tailoring required for specific settings:
    - Low event rates: may not require shared-parameter component
    - High event rates: slope may be better suited as a secondary outcome in trials

Question 13: Definition of an appropriate estimand

- We agree that intercurrent events and missing data are critical to GFR slope analyses.
- The shared parameter model accounts for informative censoring by KFRT and death.
- Both intent-to-treat and on-treatment estimands may be considered
  - Intent-to-treat
    - Incorporate GFR measurements following medication-related intercurrent events
    - Used in the analyses of our submission
  - On-treatment
    - Artificial censoring after medication-related intercurrent events
    - Can be estimated by an extension of the shared parameter model
- Either approach might be considered primary and the other secondary in different settings
- Conceptual difficulties with truncation-by-death addressed by algebraic interpretation of total-slope estimands.

Question 9: Please discuss if the currently proposed CoU could provide guidance for the design of phase 3 studies using GFR slope as a primary endpoint, including:

We provide some general concepts and recognize that the specific design and analysis will be dependent upon the specific settings.

A successful trial design for a slope endpoint requires the following inputs:

i) An estimate of the mean and SD of the progression rate (chronic slope in the control arm)

- independent of the treatment being investigated
- Most often obtained from prior studies with slope-based outcomes.

ii) A projection for the direction and magnitude of the acute effect.

- Investigators should have some understanding of the direction and magnitude of the acute effect from previous studies and from knowledge of the physiology of the intervention.

iii) Exact timing of the acute effect is not critical but general understanding is helpful.

- Likely known from prior studies or understanding of the physiologically of the drug.
- Assessment of the timing of the acute effect may be obtained in a phase 2 trial
- If the exact timing is unknown, investigators can use similar model to our model that makes no assumptions of the pattern of GFR changes prior to this time point

Under or overestimating the acute effect in the design stage should not substantially affect the risk of a false positive conclusion as long as a 2-slope model is used, but would impact power.

Question 9f: Choice of study population to entities in which longer-term outcome trials and use of clinical endpoints are difficult / not feasible to perform.

- Slope-based analyses can be more efficient from sample size or duration, relative to the clinical endpoints, in trials where the expected proportion of patients with clinical events within that time period is expected to be low
  - Populations with relatively high baseline GFR (e.g., early stage CKD) in which the follow-up time to reach clinical events is prohibitively long.
  - Populations with intermediate or low levels of GFR which do not have a high event rates expected over the trial's follow-up period.
- There may be appropriate indications for use of GFR slope in other settings depending upon other factors including stage of regulatory approval

Summary

- GFR slope is a valid surrogate primary endpoint due to
  - Its strong biological rationale
  - Evidence from our previously conducted epidemiological analyses
  - The strong, robust, and consistent scientific evidence demonstrating that treatment effects on GFR slope accurately predict treatment effects on the clinical endpoint across a broad and heterogeneous range of study populations and treatment interventions.

- Sponsors proposing to use GFR slope in a particular trial would be responsible for demonstrating to the regulatory agency the soundness of use of GFR slope in the study design and analysis plan for the specific setting in which the trial is conducted

Back up slides

Revised context of use

- Our revised context of use is as follows

  - **General setting**: The proposed novel method, GFR slope, is intended to be used as a validated surrogate endpoint for CKD progression in clinical trials for standard marketing authorization and indication extension approvals.
  - **Target population**: Broad population of patients with CKD or at risk for progressive CKD, including early and late disease across cause of CKD

Question 1: Subgroup definition

Table A-5	Categories of underlying causal diseases	Study inclusion (all GFR > 15 and Follow up more than 12 months after first follow up measurement of urine protein or GFR	Definition
Disease category	**Basic disease category (N studies, N participants)**		
Diabetes	Diabetes, not specified as DKD (11, 75464)	follow-up 1000 or more person-years and 30 or more clinical kidney failure events	Patients with diabetes where an inclusion criteria for the study did not require ACR > 30 or GFR > 90
	Diabetes with CKD (10, 26552)	follow-up 500 or more person-years and 30 or more clinical kidney failure events	Patients with diabetes where an inclusion criteria for the study did require ACR > 30 or GFR > 90
CKD	CKD-Hypertension (3, 2621)	follow-up 500 or more person-years and 30 or more clinical kidney failure events	Patients with CKD (GFR > 90 or ACR > 30 with a diagnosis of hypertension
	Polycystic kidney disease (3, 1546)		Patients with PKD
	Other CKD (could not specify) (22, 15982)		Patients with CKD (GFR > 90 or ACR > 30 and the diagnosis was other or not specified
Glomerular	IgA nephropathy (7, 1037)	Clinical endpoint > 10 events	Patients with IgA nephropathy
	Lupus nephritis (1, 79)		Patients with Lupus nephritis
	Membranous nephropathy (1, 273)		Patients with Membranous nephropathy
	Focal segmental glomerulosclerosis (1, 138)		Patients with FSGS
Cardio-vascular	High cardiovascular risk (3, 12788)	follow-up 1000 or more person-years and 30 or more clinical kidney failure events	Patients at high risk for CKD (diabetes, hypertension, cardiovascular disease)- not selected for having kidney disease
	Heart failure (4, 50843)		Patients with chronic heart failure enrolled in studies to evaluate treatments on chronic HR, not selected for having kidney disease

Question 1: Proportion with GFR > 90 or GFR > 90 and ACR < 30

Study name	Disease	Intervention	N	Baseline GFR	Baseline ACR	% GFR > 90	%GFR > 90 and ACR < 30	Hazard Ratio	Event % in control	chr slope in control arm
ABCD(CCB)	DM	RASB v CCB	392	72.1	127	17.35	0.77	1.1(0.5,2.5)	5.6	-1.57
ABCD(BP)	DM	Low v Usual BP	392	72.1	127	17.35	0.77	1.4(0.6,3.3)	4.5	-1.67
ALTITUDE	DM	RASB vs Con	8150	58.4	284	11.72	0.04	1.1(0.9,1.3)	6.3	-3.71
ADVANCE(ACE)	DM	RASB vs Con	10876	78.3	15	28.84	20	1.3(0.9,1.8)	1.1	-1.42
ADVANCE(GLUC)	DM	Int Glu	10876	78.3	15	28.84	20	1(0.8,1.5)	1.3	-1.23
CANVAS	DM	SGLT2-I	10031	78.7	12	Data NA	Data NA	0.6(0.4,0.9)	0.9	-1.38
EMPA-REG	DM	SGLT2-I	6936	76.2	18	28.72	19.46	0.5(0.4,0.7)	3.4	-2.15
CAROLINA	DM	DPP-4 I	5985	78.7	10	30.03	23.16	1.4(0.9,2.1)	1.2	-1.33
EXAMINE	DM	DPP-4 I	5377	75.2	72	Data NA	Data NA	1(0.7,1.3)	3.1	0.13
Harmony	DM	GLP-1 A	8913	78.8	24	35.55	ACR NA	1.1(0.8,1.5)	2.0	-2.22
LEADER	DM	GLP-1 A	7533	65.1	20	39.56	0.00	0.8(0.7,1.1)	3.4	-2.81
TOPCAT	HF	MRA	3435	70.2	11	11.15	ACR NA	1.6(1.2,2.1)	4.4	-0.74
PARADIGM-HF	HF	RASB vs Con	8440	73.3	NA	17.37	ACR NA	0.8(0.6,1)	3.9	-2.18
CHARM-Added	HF	RASB vs Con	913	72.5	10	26.94	ACR NA	1.3(0.7,2.1)	5.5	-1.81
SPRINT	CV	Low v Usual BP	8885	75.0	13	20.45	17.83	1.7(1.2,2.4)	1.1	-0.76
ACCOMPLISH	CV	RASB+CCB	11482	74.6	NA	30.49	ACR NA	0.5(0.4,0.7)	3.7	-1.23
PEGASUS	CV	Antiplatelet	17782	82.6	NA	22.49	ACR NA	0.9(0.7,1.3)	0.8	-0.84
PLATO	CV	Antiplatelet	12679	78.8	24	43.32	ACR NA	1.4(0.9,2.1)	0.6	-1.03

Questions 3 and 4:

3. Please elucidate the moderate association of chronic slope and clinical events in the FIDELIO DKD and CREDENCE studies.
4. Please discuss the weaker association as regards chronic slope in the trial level surrogacy analysis when adding the FIDELIO-DKD and CREDENCE studies. A sensitivity analysis conducted excluding these studies (p. 54 briefing document) showed an increase in R^2 from 0.56 to 0.73. This finding may be considered at odds with the simulation results (p. 61 briefing document), which found that the relative efficiency of chronic slope is larger than for the time-to-event endpoints when the acute effect is negative. In both studies negative acute effects were observed.

Question	Analysis	Use
Does the chronic slope indicates benefit for a specific trial?	Mean difference within studies	Efficacy of a specific intervention in a specific trial
What is the consistency of the association between treatment effect on the chronic slope and the treatment effect on the clinical endpoint across trials	Trial level analyses across studies	Validity of a surrogate
What is the relative efficacy of chronic slope vs other endpoints?	Simulations across hypothetical trial settings varying parameters	Study design decisions for a future trial

Questions 3 and 4 (con't):

Ratio of Treatment effect on chronic slope compared to treatment effect on clinical endpoint for Fidelio and CREDENCE compared to similar r studies								
Intervention	Disease	Study	N	eGFR	ACR	Tx effect on CS	Tx effect on CE (Log HR)	Ratio CS: log HR
SGLT-2	DM	CANVAS	10031	78.7 (18.8)	12(7, 42)	1.18 (0.08)	-0.56 (0.23)	-2.11
SGLT-2	DM	CREDENCE	4399	55.9 (16.8)	927 (463,1833)	2.45 (0.2)	-0.41 (0.1)	**-5.98**
SGLT-2	CKD-CNS	DAPA-CKD	4041	43.3 (12.4)	900 (500,1900)	1.47 (0.16)	-0.36 (0.1)	-4.08
SGLT-2	DM	EMPA-REG	6936	76.2 (19.9)	18 (7, 72)	1.7 (0.12)	-0.68 (0.16)	-2.50
MRA	DM	FIDELIO-DKD	5671	44.3 (12.6)	852 (446,1634)	1.32 (0.13)	-0.18 (0.07)	**-7.33**
MRA	HF	TOPCAT	3435	65.1 (18.6)	20 (7, 88)	0.15 (0.15)	0.45 (0.15)	0.33
ERA	DM	SONAR	3659	42.5 (14.2)	483 (239, 979)	0.68 (0.19)	-0.27 (0.11)	-2.52

Interpretation

- Compared to other studies, the size of the treatment effects on the chronic slope in FIDELIO and CREDENCE were larger compared to the treatment effects on the clinical endpoint (#1)
- This explains why they were considered outliers in our analyses (#2).
- This is distinct from the question as to whether the chronic slope will achieve relative efficacy with respect to sample size or power compared to the clinical endpoint

Question 6: Validity and Impact of assumptions for acute effects in the simulation study on results for the chronic slope analysis.

- The simulations manuscript examined relative efficiency of slope vs. time-to-event outcomes and a kind of Type 1 error, defined as the probability that a slope-based analysis would indicate a statistically significant benefit when there is no true effect on KFRT, under a range of models for GFR trajectories defined by the input parameters in Table 1 of that paper.

Parameter	Magnitude in Simulation	Validity and impact
Variability	SD 0 or 1	Our simulations indicated little impact of the assumed variability of the acute effect
Mean acute effect	(-2.5, -1.25, 0, +1.25, or +2.5	Neuen et al (JASN 2022) showed true acute effects have a mean of roughly -0.33 (SD 1.56) ml/min/1.73m^{2,} consistent with our results
Attenuation	Fully to 0 at GFR of 15 No attenuation	Neuen et al showed some but not complete attenuation. We expect this to have subtle impact on the results

Questions 8: Clinical importance of GFR difference

- We review our prior data on individual level association of change in GFR with subsequent development of clinical events
- We review data demonstrating that what might appear to be small differences in mean change in GFR between treatment arms translates to a large effect on the clinical endpoint from our models
- We describe results from the Stakeholder meeting chaired by Drs Heerspink and Inker supported by the NKF and FDA where there was consensus by all, including patients, about the need for treatment in CKD early in the disease process that slows progression

Question 9

c) Approach to study design, including (but not limited to) (primary) endpoint definition, study population; length of study; GFR assessment schedule;. assessment of GFR after study completion etc., to minimize the risk of false conclusions.

- Study design features will need to be considered on a case-by-case basis. Several considerations are as follows:
    1. Selection of endpoints: Slope should generally not be used in settings in which the use of slope would not substantially reduce the required follow-up time and/or the sample size relative to the clinical endpoint.
    2. If GFR slope is selected, the expected positive vs negative acute effect may guide for or against total vs chronic slope.
    3. Measurement schedule: for phase 3 trials we generally recommend two eGFR assessments at baseline, and then at 6-month intervals for min. 2 years. A post-washout GFR measurement could be considered.

d) Relative efficiency and risk of Type 1 error of a GFR slope endpoint compared to clinical event-based endpoints to determine optimal choice of primary endpoints,

- See responses to a, b and c above.

e) Guidance on handling post randomisation observations and intercurrent events, as e.g., treatment withdrawal and adverse events

- We address this item in our response to Question 13

Question 13: Defining the Estimand for 3-Year Total Slope

Definition of mean 3-year total slope:

$(3/36)\times\ \theta_{acute}\ +(33/36)\times\theta_{chronic}$

where θ_{acute} = mean acute slope; $\theta_{chronic}$ = mean chronic slope

Intent-to-treat:

$\theta_{chronic}=\left(\frac{1}{\mathrm{N}}\right)\Sigma_i\theta_i$ and θ_i is the chronic slope for the i^{th} patient starting at month 3 and continuing until the end of follow-up, KFRT, or death, whichever comes first

As-treated:

$\theta_{chronic}=\left(\frac{1}{\mathrm{N}}\right)\Sigma_i\theta_i$ and θ_i is the chronic slope for the i^{th} patient starting at month 3 and continuing until the end of follow-up, KFRT, death or medication-related intercurrent event, whichever comes first

Question 14: Confirmatory Phase 3 trials

a) Please discuss using non-linear mixed effects model software for analysis for a confirmatory Phase 3 trial. The discussion should cover the need for pre-specification and potential convergence problems.

- Our main GFR slope model is a non linear model with a spline at set knot point
- Rate of KFRT and death events will effect whether the primary analysis should be based on time to the clinical endpoint, analysis of GFR slope under a shared parameter model that accounts for these informative censoring events of death or KFRT, or simpler mixed effects model without explicitly accounting for KFRT and death
- Pre-specify and implement an algorithm in which the analysis reverts to a simpler model when convergence cannot be achieved using the more complex model

b) The Applicant should also comment on the use of kappa values in the analysis models to account for heterogeneity in the treatment arms and parameters to account for heterogeneity of (baseline) GFR values in the trial level analysis in context of a pre-specified analysis.

- Inclusion of kappa in the shared parameter model improves statistical inference by accounting for a possible difference in slope variance in the intervention group compared to the control group.
- Similar to the parameters that define the relationship between slope and KFRT and death events, we do not view kappa as the primary target of inference, although it may be of secondary interests for explanatory purposes.

Parameters of the Joint Shared Parameter Model

Parameter Name	Core Parameter for Clinical Interpretation
Mean Acute Slope, Control Group	YES
Mean Acute Slope, Treatment Group	YES
Mean Chronic Slope, Control Group	YES
Mean Chronic Slope, Treatment Group	YES

Parameter Name	Core Parameter for Clinical Interpretation
Mean Intercept, Control Group	NO
Mean Intercept, Treatment Group	NO
Variances of Acute, Chronic Slope Random Effects	NO
Covariances among random effects	NO
Residual Variance Intercept	NO
Residual Variance Power of the Mean	NO
Chronic Slope Treatment vs. Control Variance Ratio	NO
Coefficients Relating Censoring Event Hazard to treatment group, and random effects	NO

The Statistical Model of the Trial Level Analysis

The model contains two stages. Stage 1 relates the estimated treatment effects to the true treatment effects within each individual trial, while accounting for random sampling error and its correlation between the two endpoints.

Trial i model: $$\begin{bmatrix}\hat{\theta}_i \\ \hat{\gamma}_i\end{bmatrix} \sim N\left(\begin{bmatrix}\theta_i \\ \gamma_i\end{bmatrix}, \begin{bmatrix}\sigma_i^2 & r_i\sigma_i\delta_i \\ r_i\sigma_i\delta_i & \delta_i^2\end{bmatrix}\right)$$ (Stage 1 Model)

σ_i= Standard error of treatment effect on clinical endpoint in trial i
δ_i= Standard error of treatment effect on surrogate endpoint in trial i
r_i= Correlation between sampling errors of treatment effects on the clinical and surrogate endpoints

Stage 2 models the variation in the true treatment effects across the population of RCTs

Joint Model Across RCTs: $$\begin{bmatrix}\theta_i \\ \gamma_i\end{bmatrix} \sim N\left(\begin{bmatrix}\mu_\theta \\ \mu_\gamma\end{bmatrix}, \begin{bmatrix}\sigma_\theta^2 & R\sigma_\theta\sigma_\gamma \\ R\sigma_\theta\sigma_\gamma & \sigma_\gamma^2\end{bmatrix}\right)$$ (Stage 2 Model)

$\mu_\theta, \sigma_\theta$ = Mean and standard deviation of true treatment effects on clinical endpoint
$\mu_\gamma, \sigma_\gamma$ = Mean and standard deviation of true treatment effects on surrogate endpoint
R = Correlation between true treatment effects on the clinical and surrogate endpoints

The Statistical Model of the Trial Level Analysis: Interpretation of Stage 2

Joint Model Across RCTs: $\begin{bmatrix}\theta_i \\ \gamma_i\end{bmatrix} \sim N\left(\begin{bmatrix}\mu_\theta \\ \mu_\gamma\end{bmatrix}, \begin{bmatrix}\sigma_\theta^2 & R\sigma_\theta\sigma_\gamma \\ R\sigma_\theta\sigma_\gamma & \sigma_\gamma^2\end{bmatrix}\right)$ (Stage 2 Model)

We can write:

$E(\theta_i|\gamma_i) = \alpha + \beta\gamma_i$, $Var(\theta_i|\gamma_i) = \lambda^2$ where

$\beta = R\sigma_\theta/\sigma_\gamma$ and $\alpha = \mu_\theta - \beta\mu_\gamma$

Treatment effect on clinical endpoint if no treatment effect on surrogate endpoint

$$E(\theta_i|\gamma_i) = \alpha + \beta\gamma_i$$

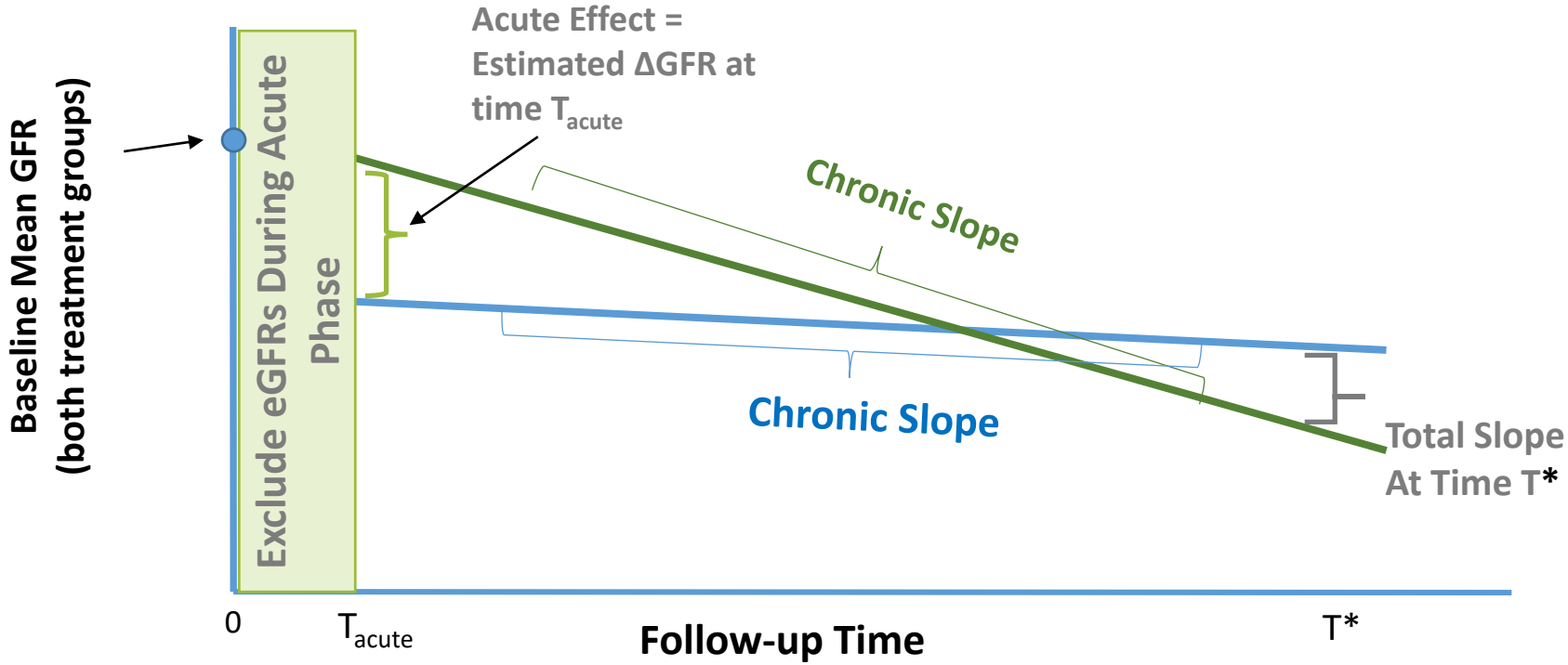
$$Var(\theta_i|\gamma_i) = \lambda^2$$

Indicates slope of relationship between treatment effects on clinical endpoint and surrogate endpoint

Indicates variability in treatment effects on clinical endpoint for a given treatment effect on the surrogate endpoint. λ is the root mean square error (RMSE)

Simplified 1-Slope Shared Parameter Model

- To reduce modeling assumptions and achieve convergence across many RCTs, we simplified the full shared parameter model by excluding follow-up GFRs prior to 3 months, and fit 1 fixed and 1 random slope after 3 months
- Power of the mean for GFR residuals
- Weibull or piecewise exponential model relating time to KFRT or death to GFR slope random effects
- Allows arbitrary GFR trajectories prior to 1st follow-up GFR after 3 months
- Covariate adjustment for baseline GFR



Simplified 1-Slope Shared Parameter Models

T_{ij} = time of the i^{th} subject's j^{th} GFR measurement
Y_{ij} = i^{th} subjects GFR measurement at time t_{ij}
T_i = time of ESRD or Death for the i^{th} subject
Z_i = randomized treatment group for the i^{th} subject (0 or 1)
$SBGFR_i$ = centered baseline GFR for the i^{th} subject

Fixed effects for mean eGFR, allowing different acute effects and chronic slopes for each treatment

$$Y_{ij} = (\beta_{0c} + SBGFR_i\,\beta_{0,bgfr}) + (t_{ij}\beta_{1c} + SBGFR_i\,t_{ij}\beta_{1,bgfr}) + Z_i\beta_{0t} + Z_i t_{ij}\beta_{1t}$$
$$+ b_{0i} + t_{ij}b_{1i} + \varepsilon_{ij},$$

Residual deviations of individual eGFR measurements about underlying trajectories

Random effects for variation in eGFR trajectories of individual patients

$T_i \sim$ Weibull or Piecewise exponential regression models, with regression coefficients for centered baseline GFR, treatment group, b_{0i}, and b_{1i}

$\varepsilon_{ij} \sim Normal(0, \sigma^2 \times (\mu_{ij}^2)^{\theta})$ where μ_{ij} is the subject's expected mean GFR at time j.

Treatment Effects:

β_{0t} = treatment effect on acute GFR change

β_{1t} = treatment effect on chronic slope