**Supplementary appendix**

Supplement to: Rovin B, et al. Efficacy and safety of sparsentan vs irbesartan in patients with IgA nephropathy: 2-year results from PROTECT, a phase 3 randomized active controlled clinical trial.

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**Supplemental Methods**

**Protocol deviations**

During the double-blind period, the number of participants with major protocol deviations was similar between treatment groups. The major protocol deviations that occurred in ≥20 participants were regarding informed consent (primarily involving not signing an updated informed consent form, not reconsenting to updated informed consent form, or collection of 24-hour urine sample or vital signs prior to time of informed consent), eligibility and entry criteria (most commonly women of childbearing potential enrolled without using two forms of contraception, participants enrolled with exclusionary blood pressure readings, participants enrolled without being on a stable dose of angiotensin converting-enzyme inhibitor and/or angiotensin II receptor blocker therapy for ≥12 weeks that was both their maximum tolerated dose and ≥50% of the label dose), investigational product compliance (most commonly compliance <80% and compliance >120%), and study procedure criteria.

A total of 34 randomized patients were identified with protocol deviations that excluded them from the per protocol sensitivity analysis set. The assessment was performed prior to the locking of the database for the final double-blind analysis.

**Statistical analysis methods**

For the key secondary endpoint of estimated glomerular filtration rate (eGFR) total slope through week 110, a sample size of approximately 380 randomized patients provides 90% power to detect an underlying treatment effect of 2·9 mL/min/1·73 m2/year, as well as 80% power to detect an effect of 2·55 mL/min/1·73 m2/year. For the key secondary endpoint of eGFR chronic slope through week 110, this sample size provides >90% power to detect an effect of 3·15 mL/min/1·73 m2/year. These sample-size and power calculations follow the method described by Dupont,1 with a one-sided α level of 0·02 and a residual error of 5·8 mL/min/1·73 m2 estimated from a random coefficient analysis of the Leicester University Hospital Registry. The projected treatment effects on the eGFR slope were based on a meta-analysis of clinical studies of immunoglobulin A nephrology that used the methodology presented by Inker.2

For the analysis of the key secondary endpoint of rate of change of eGFR, missing data were imputed using the multiple imputation procedure specified in the statistical analysis plan based on the missing at random (MAR) assumption, consistent with previously published methods.3,4 A Bayesian multivariate normal model for the data was fitted using a Markov chain Monte Carlo (MCMC) approach with a noninformative prior distribution. Quasi-independent samples were drawn from the posterior distributions for the parameters of the multivariate normal distribution for each treatment group. Imputation of intermittent missing data was accomplished using the MCMC option in SAS PROC MI (SAS Institute; San Francisco, CA) by treatment group prior to performing imputations of values following the discontinuation event. Missing data following a discontinuation event (ie, discontinuation of randomized therapy or early permanent dropout) were imputed by treatment group under the assumption of MAR using the regression option from the monotone statement of SAS PROC MI. Baseline and postbaseline scheduled visits were used in the regression option to impute the missing values. A total of 30 multiply imputed datasets were generated. The analytic model (ie, mixed model random coefficients analysis) was applied to each multiply imputed dataset. The estimated treatment effects were combined across imputations using Rubin’s approach implemented through SAS PROC MIANALYZE.

Change from baseline in eGFR, urine protein/creatinine ratio (UP/C), urine albumin/creatinine ratio (UA/C), urine protein excretion, urine albumin excretion up to week 110, and change from baseline in blood pressure were analyzed via a mixed model for repeated measures as described for the analysis of the primary efficacy endpoint;5 missing data were not imputed using the multiple imputation procedure. Briefly, analyses were performed on log-transformed data with fixed effects of treatment group, baseline value in log scale, time (ie, analysis visit in weeks), treatment group by time interaction, and randomization stratification variable (four levels based on screening eGFR and urine protein excretion); patient was included as a random effect. An unstructured covariance matrix was used; if the algorithm failed to converge, then the following structures were executed: heterogeneous Toeplitz, heterogeneous compound symmetry, heterogeneous first-order autoregressive, Toeplitz, compound symmetry, and first-order autoregressive. The treatment effect was the contrast between sparsentan and irbesartan least squares (LS) means. The LS means, treatment effect estimate, 95% CI, and two-sided p values were extracted from the model. Results for UP/C, UA/C, urine protein excretion, and urine albumin excretion that were natural-log transformed prior to analysis were back-transformed to present treatment effects on the ratio scale. Of note, log transformation is typically used to address the positive skewness of proteinuria data; review of log-transformed data at baseline indicated that this was achieved.

Change in eGFR from baseline to week 6, baseline to week 114, and end of treatment (ie, week 110) to week 114 were analyzed via analysis of covariance (ANCOVA). For baseline to week 114, fixed effects were treatment group, baseline eGFR, and randomization stratification variable (four levels based on screening eGFR and urine protein excretion); for baseline to week 6 and week 110 to week 114, treatment group and randomization strata were fixed effects, and baseline value was covariate.

The composite endpoint and proteinuria remission endpoints were analyzed via a logistic regression model with treatment as a fixed effect and baseline eGFR as a covariate and stratified by the randomization strata. Relative risk and its 95% CI were estimated from a Poisson regression model with log link and the same fixed effects as the logistic regression model. Reductions in eGFR required confirmation ≥4 weeks later unless the reduction observed was the last value on randomized treatment. For the time-to-event analysis of the composite endpoint, the time to the first event was calculated as (date of first event - date of first dose of study medication + 1)/7. In the case when multiple conditions were met, the earliest occurrence was used. Patients without any documentation of events were censored at the time of analysis (if still on randomized treatment) or the time of discontinuation of randomized treatment, whichever was earlier. Analogous approaches were used for the analysis of time to achieving proteinuria remission.

Multiple hypothesis testing correction was performed using a combination of a gatekeeping and fixed sequence procedure. If the primary endpoint analysis yielded a two-sided p value <0·05, then formal testing of key secondary endpoints would occur (differently for US and non-US countries); as previously reported, the primary endpoint was statistically significant.

* Analyses of key secondary endpoints in non-US countries proceeded as follows:
  + Step 1: At the time of the primary analysis of proteinuria, the key secondary endpoint of rate of eGFR change from 6 to 58 weeks will be tested at a significance level of α=0·01
  + Step 2: If this key secondary endpoint is significant at step 1, then α=0·01 will be recycled, and the next key secondary efficacy endpoint, eGFR rate of change from 6 to 110 weeks, will be tested at a significance level of α=0·05 at the final analysis
  + Step 3: If the key secondary endpoint is not significant at step 1, the eGFR rate of change from 6 to 110 weeks will be tested at a significance level of α=0·04 at the final analysis
  + Step 4: The next key secondary efficacy endpoint, eGFR rate of change from initiation of randomized therapy to 110 weeks, will be tested at a significance level of α=0·05 (if significant at step 1 and 2) or α=0·04 (if significant at step 3)
  + If, at step 2 or 3, the statistical comparison of treatment group is not statistically significant at the specified significance level, then the remaining comparisons will be considered descriptive and exploratory
* Analyses of key secondary endpoints in the US proceeded as follows:
  + At the time of the primary analysis, no formal testing will be conducted on the key secondary endpoint of eGFR rate of change from 6 to 58 weeks
  + Step 1: The key secondary endpoint of eGFR rate of change from initiation of randomized therapy to 110 weeks will be tested at a significance level of α=0·05
  + Step 2: If this key secondary endpoint is significant at step 1, eGFR rate of change from 6 to 110 weeks will be tested at a significance level of α=0·05
  + If, at step 1, the statistical comparison of treatment group is not statistically significant at the specified significance level, then the remaining comparisons will be considered descriptive and exploratory
* At the time of the final (confirmatory) analysis, if all the key secondary endpoints achieve statistical significance in the US or non-US countries, then the other secondary endpoints will be statistically tested at the available α in the order specified below:
  + Mean change from baseline in UP/C at week 110
  + Mean change from baseline in urine protein excretion at week 110
  + Mean change from baseline in UA/C at week 110
  + Mean change from baseline in urine albumin excretion at week 110
  + Proportion of patients experiencing a confirmed 40% reduction in eGFR, kidney failure, or death from any cause
  + Mean change from baseline in eGFR at week 110

Sensitivity analyses of the eGFR chronic (week 6-110) and total (day 1-week 110) slopes were performed (1) with all randomized patients irrespective of whether they discontinued treatment early (modified intention-to-treat analysis), (2) excluding assessments after initiation of rescue immunosuppression for renal disease, (3) including local laboratory data, and (4) using the per protocol at final analysis set, which included all patients who met study eligibility criteria and had no protocol deviations that might have impacted the assessment of efficacy measurements.

**Database management and data handling**

The study uses electronic case report forms (eCRFs) for data collection. The data are entered by trained site personnel only. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that the data can be verified against source data. Adverse events (AEs) and medical history are coded using the Medical Dictionary for Regulatory Activities. Similarly, prior and concomitant medications and concomitant therapies are coded using the World Health Organization Drug Dictionary. To ensure compliance with good clinical practice and all applicable regulatory requirements, the sponsor or its designee may conduct a quality assurance audit. Data management is performed by a qualified vendor under their standard operation procedures, and the sponsor provides oversight.

**Impact of COVID-19**

Overall, no participants discontinued from treatment or from the study due to COVID-19. The impact of COVID-19 on missed visits or use of alternative (ie, off-site) visits was low: a maximum of 1% of participants missed any scheduled visit due to COVID-19, and a maximum of 5% attended an off-site visit for any scheduled visit due to COVID-19.

**History of study protocol amendments**

To date, six global amendments to the original study protocol (April 2018) have occurred. The first global amendment (March 2019) achieved global harmonization of the protocol and addressed comments from the US Food and Drug Administration. The second global amendment (May 2019) removed the mandate for contraception in male participants. The third global amendment (March 2020) added orthostatic hypotension blood pressure measurements based on the recommendation of the Data Monitoring Committee. In the fourth global amendment (July 2020), the open-label extension period was added to the study, the overall sample size was updated, the sample size assessment was removed, and guidance for working with restrictions related to COVID-19 was added. The fifth global amendment (April 2021) included a new protocol section to clarify the timing of the interim analysis (prespecified in the earliest protocol) to avoid confusion following the updated sample size in amendment four, revised efficacy endpoints, revised schedules of study events, updated information for physical examination, specified measurement of heart rate for orthostatic hypotension detection, specified conditions under which study medication cannot be resumed, included updates for the open-label extension (ie, specified single-tablet consumption based on availability, revised clinical laboratory assessments, removed serum pregnancy test), and revised the list of concomitant medications for both double-blind and open-label extension periods. The sixth global amendment (November 2022) was specifically directed at the open-label extension and added a sparsentan plus sodium-glucose cotransporter 2 inhibitor substudy to the protocol, implemented global consolidation of the protocol, and provided updated information for COVID-19 AE and serious AE reporting.

**Supplemental Tables**

**Supplemental Table 1.** Other eGFR endpoints

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Sparsentan (n=202)** | **Irbesartan (n=202)** | **Between-group difference** |
| **Observed eGFR value, mL/min/1·73 m2** | **Mean (SD)** | **Mean (SD)** |  |
| Baseline | 56·8 (24·3) | 57·1 (23·6) | NA |
| Week 6\* | 55·8 (23·6) | 55·5 (23·0) | NA |
| Week 58† | 53·8 (24·6) | 52·7 (23·7) | NA |
| Week 110‡ | 52·4 (25·1) | 48·3 (24·7) | NA |
| Four weeks after cessation of randomized treatment (week 114)§ | 51·2 (25·3) | 49·7 (25·6) | NA |
|  |  |  |  |
| **Change in eGFR from baseline, mL/min/1·73 m2** | **LS mean**  **(95% CI)** | **LS mean**  **(95% CI)** | **Difference**  **(95% CI)** |
| Week 6\* | −1·2  (−2·2 to −0·3) | −1·6  (−2·6 to −0·7) | 0·4  (−1·0 to 1·7) |
| Week 58† | −4·0  (−5·2 to −2·7) | −5·6  (−6·9 to −4·4) | 1·7  (−0·1 to 3·5) |
| Week 110‡ | −5·8  (−7·4 to −4·2) | −9·5  (−11·2 to −7·9) | 3·7  (1·5-6·0) |
| Four weeks after cessation of randomized treatment (week 114)§ | −6·1  (−7·7 to −4·5) | −9·0  (−10·7 to −7·2) | 2·9  (0·5-5·3) |
| **Change in eGFR from end of treatment (week 110) to 4 weeks after cessation of randomized treatment (week 114), mL/min/1·73 m2**§ | −1·1  (−1·9 to −0·2) | 0·1  (−0·8 to 1·0) | −1·2  (−2·4 to 0·1) |

eGFR, estimated glomerular filtration rate; LS, least squares; NA, not applicable; SD, standard deviation.

\* Sparsentan, n=193; irbesartan, n=193.

† Sparsentan, n=180; irbesartan, n=162.

‡ Sparsentan, n=159; irbesartan, n=138.

§ Sparsentan, n=170; irbesartan, n=148.

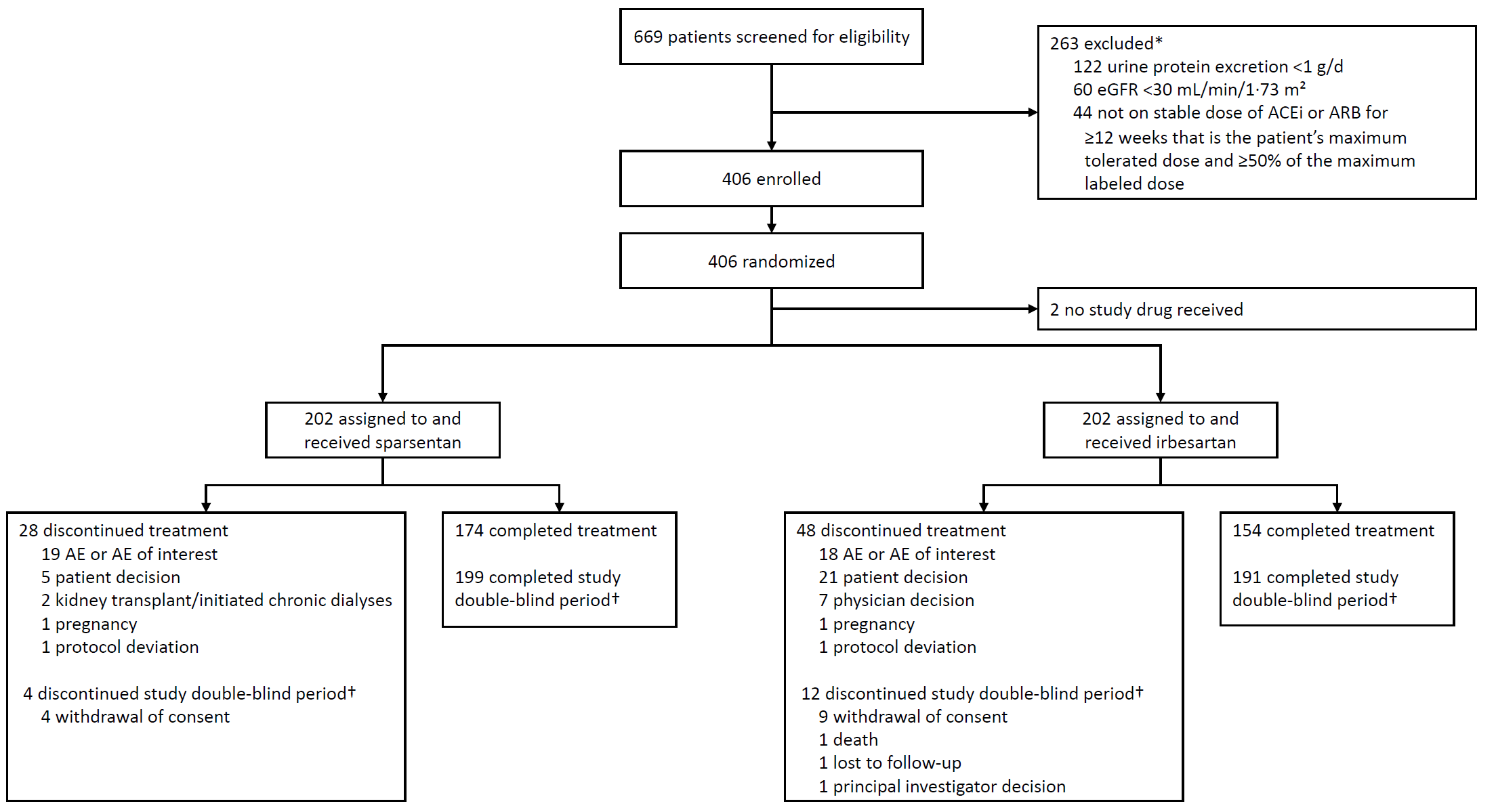
**Supplemental Table 2. Potassium levels by visit**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Sparsentan (n=202)** | | **Irbesartan (n=202)** | |
|  | **Potassium, mean (SD), mmol/L** | **n** | **Potassium, mean (SD), mmol/L** | **n** |
| **Baseline** | 4·7 (0·4) | 202 | 4·6 (0·4) | 202 |
| **Week 4** | 4·7 (0·4) | 199 | 4·6 (0·4) | 192 |
| **Week 6** | 4·7 (0·5) | 195 | 4·6 (0·4) | 197 |
| **Week 12** | 4·6 (0·4) | 197 | 4·6 (0·4) | 191 |
| **Week 24** | 4·7 (0·4) | 194 | 4·6 (0·4) | 182 |
| **Week 36** | 4·7 (0·4) | 191 | 4·6 (0·5) | 186 |
| **Week 48** | 4·7 (0·4) | 188 | 4·6 (0·4) | 185 |
| **Week 58** | 4·7 (0·4) | 189 | 4·6 (0·4) | 175 |
| **Week 70** | 4·7 (0·4) | 191 | 4·7 (0·5) | 173 |
| **Week 82** | 4·7 (0·4) | 186 | 4·7 (0·5) | 171 |
| **Week 94** | 4·7 (0·4) | 184 | 4·7 (0·5) | 167 |
| **Week 106** | 4·8 (0·5) | 181 | 4·7 (0·5) | 162 |
| **Week 110** | 4·7 (0·4) | 171 | 4·7 (0·5) | 154 |

SD, standard deviation.

**Supplemental Figures**

**Supplemental Figure 1. CONSORT diagram**

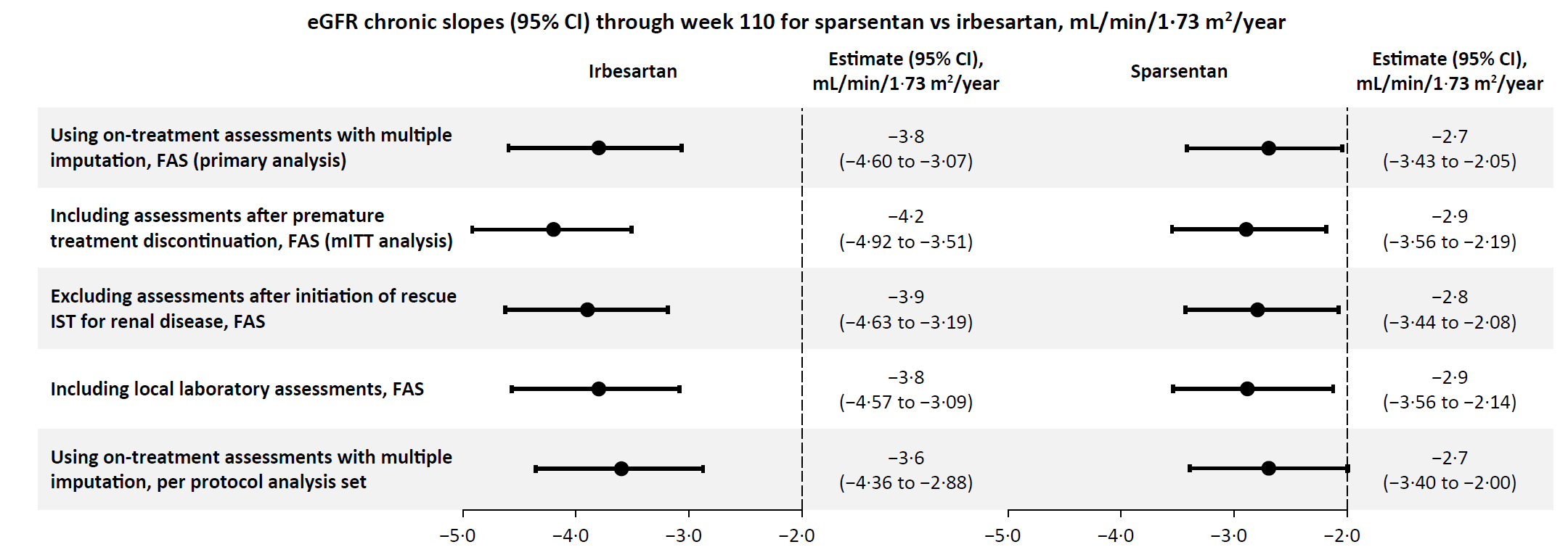


ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

\* Counts across reasons for exclusion were not unique, and only the most common reasons are shown.

† Values for study double-blind period completion and discontinuation are based on all randomized patients (N=406); 203 patients were randomized to each treatment group and 202 in each then received study drug.

**Supplemental Figure 2. Prespecified sensitivity analyses of rate of change in eGFR through week 110. Chronic slope within each group (a) and total slope within each group (b)\***

**a**

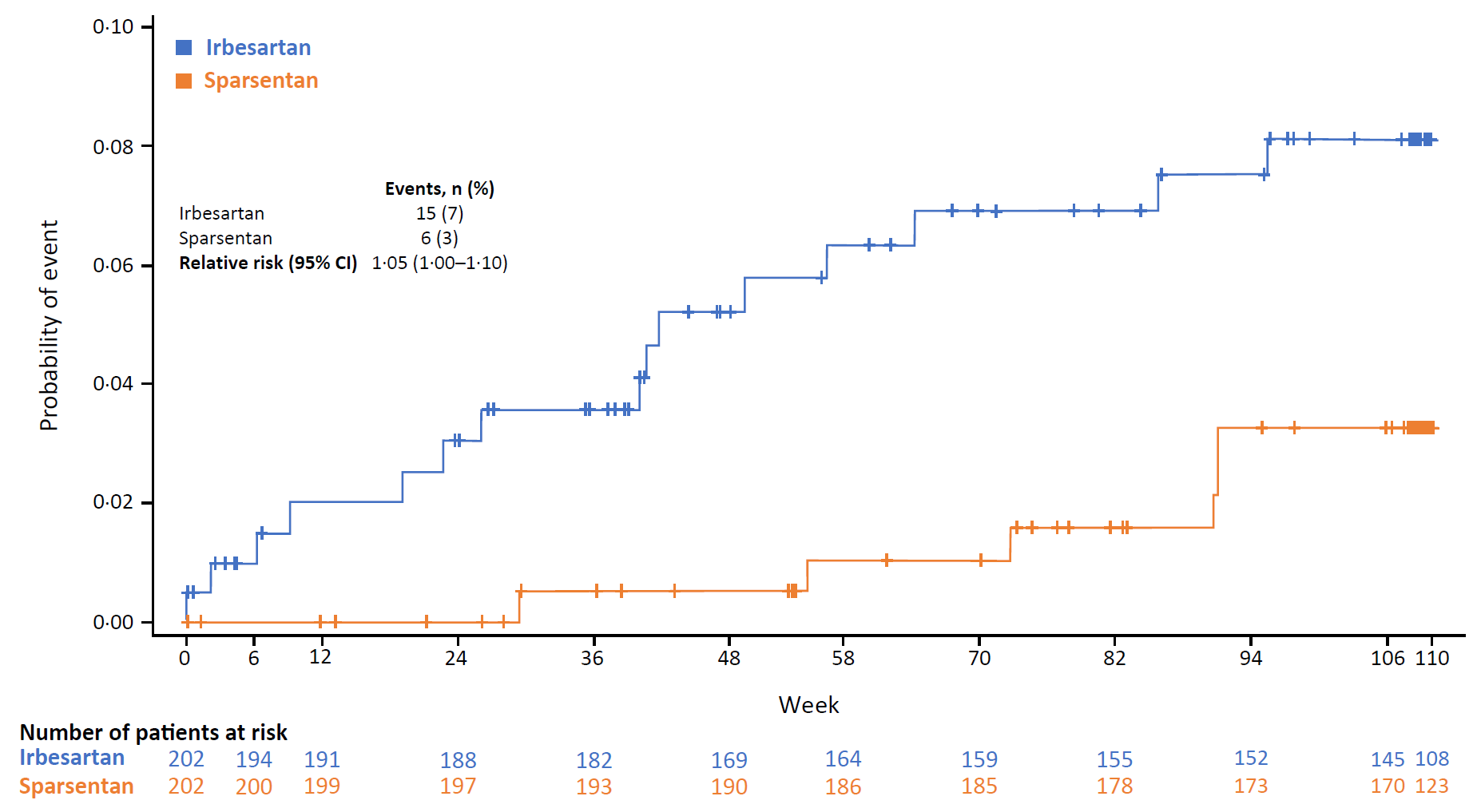
**b**A screenshot of a computer

Description automatically generated

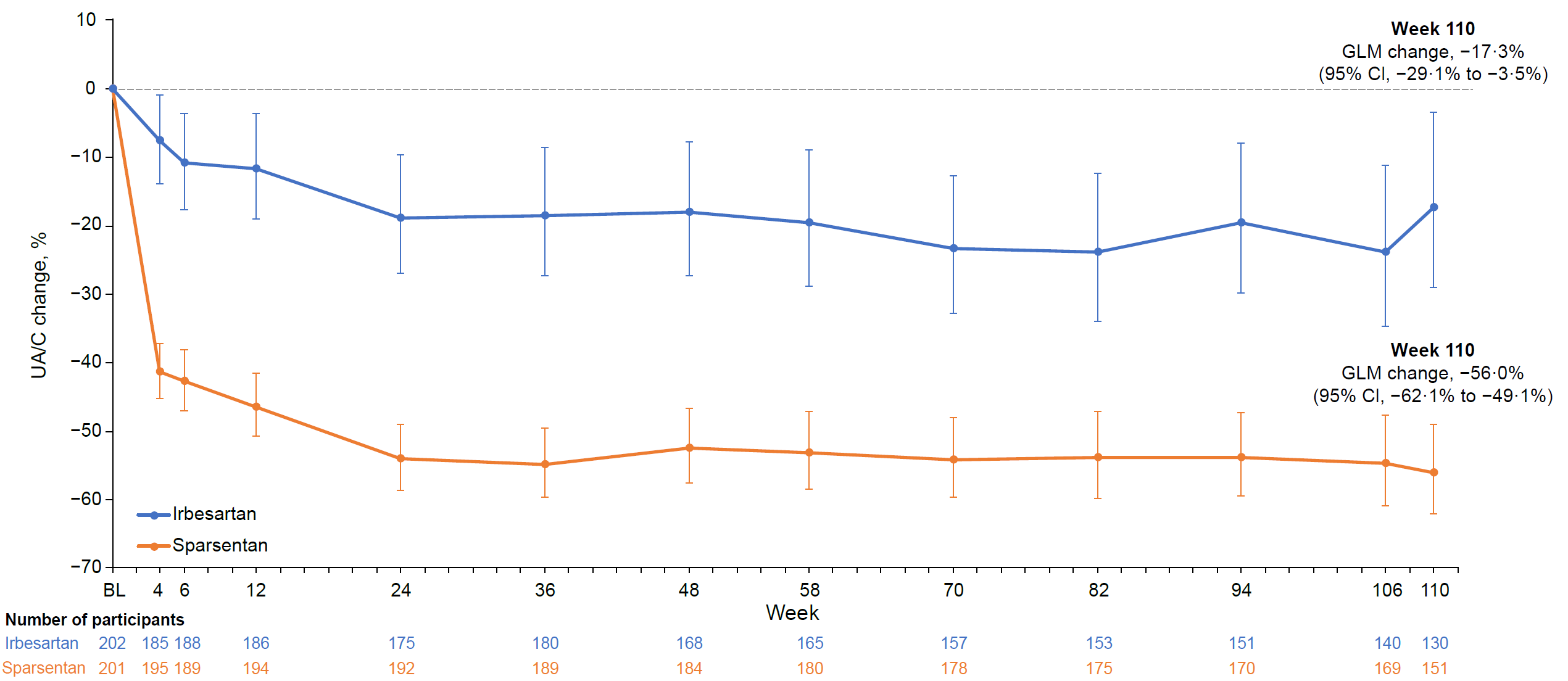
eGFR, estimated glomerular filtration rate; FAS, full analysis set; IST, immunosuppressive therapy; mITT, modified intention-to-treat.

\* The FAS consisted of all patients who were randomized and treated (N=404).

**Supplemental Figure 3. Time to initiation of systemic immunosuppressive medication with renal indication\***

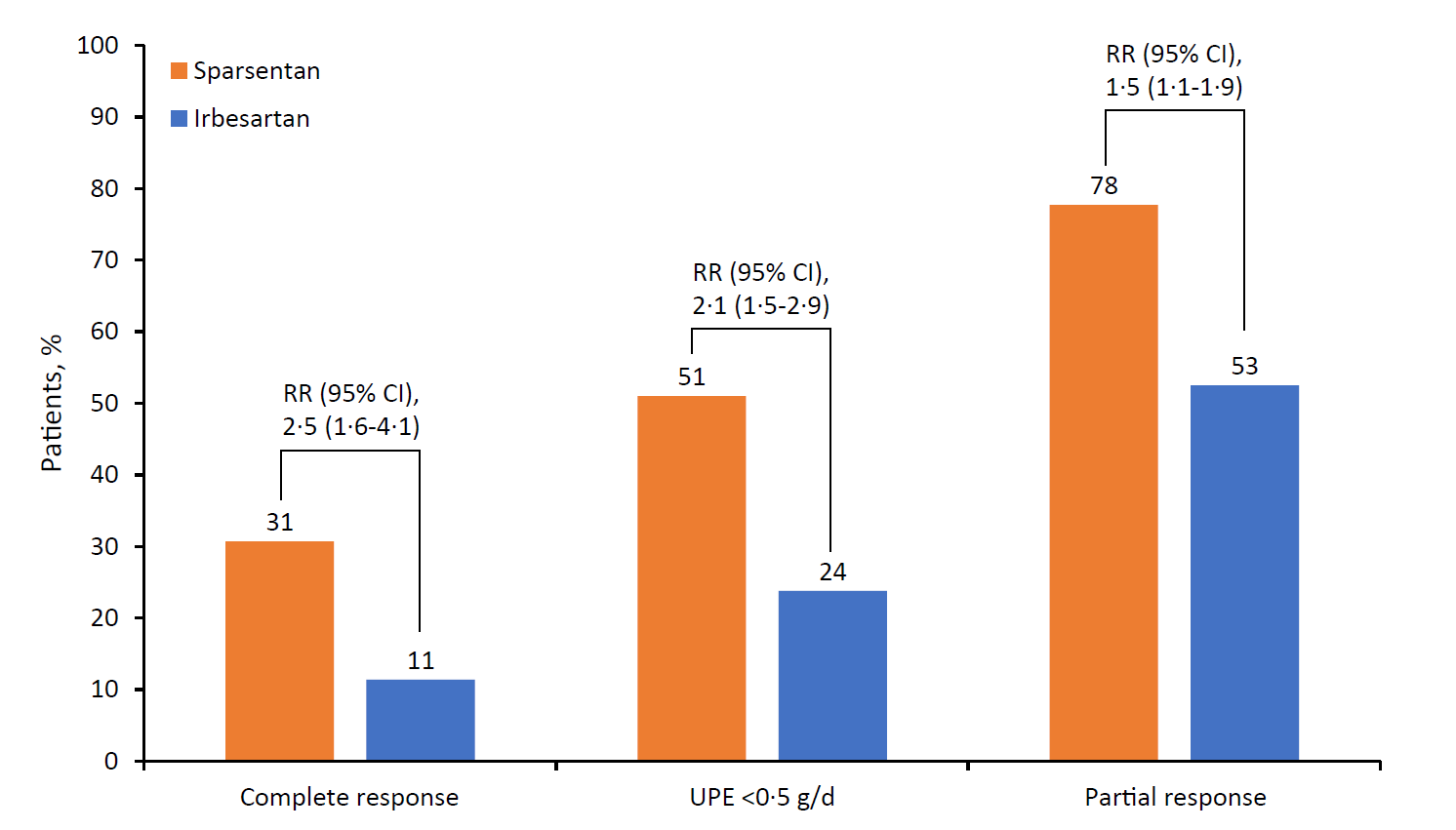
\*Vertical lines indicate censored patients. Median time to initiation of systemic immunosuppressive medication with renal indication was not estimable for either group.

**Supplemental Figure 4. Geometric LS mean percent change from baseline at each visit in UA/C up to week 110**

  
BL, baseline; GLM, geometric least squares mean; LS, least squares; UA/C, urine albumin/creatinine ratio.

Error bars indicate 95% CIs.

**Supplemental Figure 5. Proportion of patients achieving complete or partial proteinuria remission\***

RR, relative risk; UPE, urine protein excretion.

\* Complete response was defined as UPE <0·3 g/d and partial response as UPE <1·0 g/d. The proportion of patients achieving UPE <0·5 g/d was a post hoc assessment.

**Supplemental Figure 6. Time to achieve complete proteinuria remission (urine protein excretion <0·3 g/d)\***

A graph of a graph

Description automatically generated with medium confidence\*Vertical lines indicate censored patients. Median time to achieve complete proteinuria remission was not estimable for either group.

**Supplemental Figure 7. Mean systolic and diastolic blood pressure at each visit**

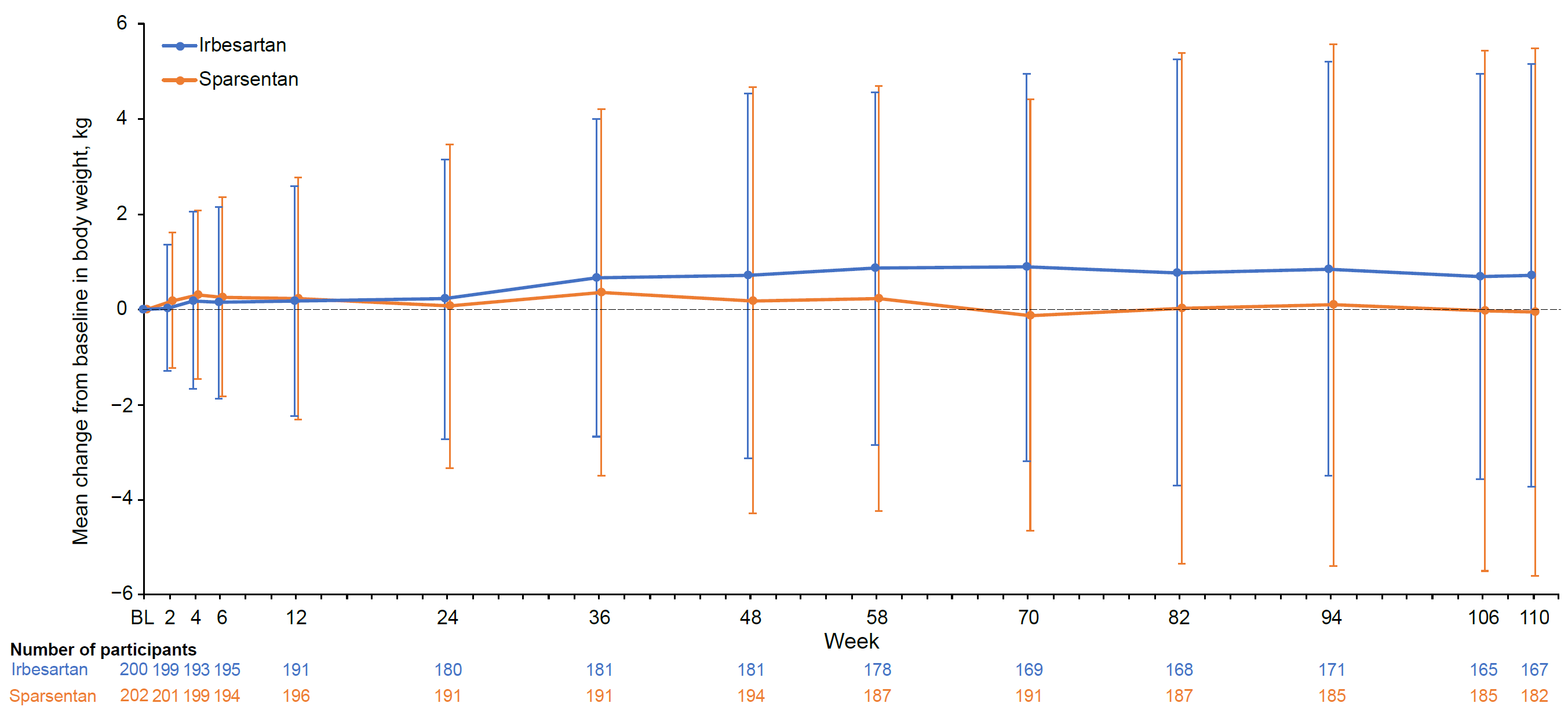
A graph with lines and numbers

Description automatically generated with medium confidenceBL, baseline; DBP, diastolic blood pressure; SPB, systolic blood pressure.

Error bars indicate standard deviation.

\* Irbesartan value for DBP, n=197.

**Supplemental Figure 8. Change from baseline at each visit in body weight**

BL, baseline.

Error bars indicate standard deviation.

**Supplemental Figure 9. Potential long-term impact of improved eGFR slope**

A diagram of a graph

Description automatically generated

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitor; SOC,: standard of care.  
Baseline eGFR was set to=57 mL/min/1·73 m2 (0 years), reflecting the mean eGFR of all patients (N=404) reported in this study.

\* ACEi and/or ARB.

† Mean of observed chronic or total slopes for SOC ACEi/ARB as reported in 5 randomized controlled trials in IgAN6-10

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