**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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**Research in Context**

*Evidence before this study*

We searched PubMed for randomized controlled trials published between January 1, 2013, and September 26, 2023, with the terms “immunoglobulin A nephropathy” AND “treatment” AND “randomized controlled trial.” Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide and often causes kidney failure for a significant portion of affected patients. The mainstay of disease management has been supportive care using renin-angiotensin system (RAS) blockers to attenuate proteinuria and control blood pressure, as outlined in the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Because glucocorticoid trials in IgAN have largely been inconclusive, the KDIGO guidelines suggested use of systemic glucocorticoids only for exceptional circumstances. Recently, however, the TESTING trial showed that adding a 6‑month course of systemic glucocorticoids to supportive care attenuated the decline in kidney function over time, but at the expense of markedly more serious adverse events, versus supportive care alone. Other approaches, including tonsillectomy, and other drugs, including hydroxychloroquine and mycophenolate mofetil, have shown some benefit in certain IgAN populations, but these results have not been generalized. In 2023, Nefecon (budesonide), an oral glucocorticoid designed for targeted release in the vicinity of the distal ileal Peyer patches, received accelerated approval from the US Food and Drug Administration and conditional approval from the European Medicines Agency based on the part 1 results of the phase 3 NEFIGARD trial, which demonstrated significant improvement in proteinuria over standard of care after 9 months of treatment. NEFIGARD part 2 results, published in 2023, showed ongoing significantly lower proteinuria and higher estimated glomerular filtration rate (eGFR) in patients treated with Nefecon versus those treated with supportive care alone. Sparsentan, a nonimmunosuppressive dual endothelin angiotensin receptor antagonist (DEARA), received accelerated approval for IgAN in February 2023 based on interim analysis results of the PROTECT trial, which demonstrated a 41% greater decline in proteinuria for sparsentan-treated patients versus those treated with an angiotensin II receptor blocker (ARB) alone (irbesartan) after ≈280 patients completed 36 weeks of treatment. Patients received treatment in PROTECT for up to 110 weeks to determine whether kidney function was positively affected by sparsentan versus irbesartan. The results of the PROTECT final analysis over ≈2 years are given here.

*Added value of this study*

Sparsentan is a novel nonimmunosuppressive therapy for IgAN that targets the endothelin receptor type A and the angiotensin receptor type 1, both known to facilitate damage to the kidneys through direct effects on the glomerular filtration barrier after engaging endothelin-1 and angiotensin II, their respective ligands. The phase 3 PROTECT trial demonstrates that sparsentan treatment results in significantly greater decline in proteinuria than treatment with an ARB alone, and that this decline in proteinuria is associated with a clinically meaningful preservation of kidney function. Given the data demonstrating that patients with IgAN are at risk of progression to kidney failure even with levels of proteinuria well below 1·0 g/d, the results of PROTECT provide a pathway to maximally impact proteinuria and preserve kidney function without subjecting patients to immunosuppression.

*Implications of all the available evidence*

While the value of lowering proteinuria in patients with IgAN has been established for some time, it has become increasingly clear that patients with proteinuria below the commonly used threshold of 1·0 g/d (KDIGO) are still at significant risk of progression to kidney failure. A reasonable interpretation of the collective data is that the management goal for IgAN is to reduce proteinuria in individual patients as much as possible and well below 1·0 g/d if this can be done safely. The recent trials in IgAN have demonstrated that systemic glucocorticoids, gut-targeted glucocorticoids, and sparsentan lower proteinuria more effectively than RAS blockade alone, and that this additional reduction in proteinuria provides a significant benefit to GFR preservation. Importantly, each of these therapeutics acts through different pathways, suggesting that combination therapy is likely to be additive in terms of proteinuria reduction and preservation of kidney function. Because sparsentan is not an immunosuppressive agent, we suggest its placement in the IgAN treatment paradigm as a long-term foundational therapy upon which immunosuppressive agents can be used intermittently as required to achieve maximum proteinuria suppression to prolong kidney survival in patients with IgAN.

# Summary (300/300 words)

**Background:** Sparsentan, a novel, nonimmunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist (DEARA), significantly reduced proteinuria versus irbesartan, an angiotensin II receptor blocker, at 36 weeks (primary endpoint) in patients with immunoglobulin A nephropathy (IgAN) in the phase 3 PROTECT trial’s previously reported interim analysis. Here we report kidney function and outcomes over 110 weeks from the double-blind final analysis.

**Methods:** PROTECT is a randomized, double-blind, active-controlled study (NCT03762850) that assessed the efficacy and safety of sparsentan versus irbesartan in adults (aged ≥18 years) with biopsy-proven IgAN and proteinuria of ≥1·0 g/d despite maximized renin-angiotensin system inhibition for ≥12 weeks. PROTECT’s primary endpoint was proteinuria change between treatment groups at 36 weeks. Secondary endpoints included rate of change (slope) of the estimated glomerular filtration rate (eGFR), changes in proteinuria, a composite of kidney failure (confirmed 40% eGFR reduction, kidney failure, or all-cause mortality), and safety and tolerability through 110 weeks.

**Findings:** Patients were randomized to and received sparsentan (n=202) or irbesartan (n=202). Sparsentan-treated patients had a slower rate of eGFR decline versus irbesartan-treated patients. eGFR chronic 2-year slope (week 6-110) was −2·7 versus −3·8 mL/min/1·73 m2/year (difference=1·1, 95% CI 0·1-2·1; p=0·037); total 2-year slope (day 1-week 110) was −2·9 versus −3·9 mL/min/1·73 m2/year (difference=1·0, 95% CI −0·03 to 1·94; p=0·058). The significant reduction in proteinuria at 36 weeks with sparsentan was maintained throughout the study period; at 110 weeks, proteinuria was 40% lower in sparsentan- versus irbesartan-treated patients. The composite clinical endpoint was reached by 18 (9%) sparsentan- versus 26 (13%) irbesartan-treated patients (risk reduction for sparsentan/irbesartan=0·68, 95% CI 0·37-1·24). Adverse events were well balanced between sparsentan and irbesartan, with no new safety signals.

**Interpretation:** Over 110 weeks**,** treatment with sparsentan versus maximally titrated irbesartan in IgAN resulted in significant reductions in proteinuria and preservation of kidney function.

**Funding:** Travere Therapeutics

# Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide1 and is associated with significant lifetime risk of kidney failure.2 Current treatment options are limited,3 and it is only within the last 24 months, since December 2021, that a small number of approved treatments became available in the US and Europe.4,5 IgAN is usually found in young adults, and, due to the asymptomatic nature of the disease, most patients already have established chronic kidney disease (CKD) at presentation. Data from the largest global IgAN registry, the UK National Registry of Rare Kidney Diseases, showed that most patients progressed to kidney failure within 15-20 years of diagnosis, with a mean age of 48 years at kidney failure or death.2 On the basis of estimated glomerular filtration rate (eGFR) and age at diagnosis, almost all patients were at risk of progression to kidney failure within their expected lifetime. These real-world data reflect the limitations of what has been regarded as standard of care in IgAN for the past 30 years: optimized, goal-directed, supportive care with or without systemic glucocorticoids.6 There is a clear need for new targeted treatments for IgAN to slow the rate of progression, with the ultimate goal of preventing kidney failure in the lifetime of all patients.

To address this unmet need, this trial focused on the potential therapeutic application of dual endothelin-1 and angiotensin II antagonism to treat IgAN using sparsentan, a nonimmunosuppressive, single-molecule, dual endothelin and angiotensin receptor antagonist (DEARA) with high selectivity for the endothelin receptor type A (ETAR) and angiotensin II receptor type 1 (AT1R).7,8 Endothelin-1, via activation of ETAR on multiple kidney cell types, plays a key role in driving many processes associated with nephron loss in kidney disease, including [vasoconstriction](https://www.sciencedirect.com/topics/medicine-and-dentistry/vasoconstriction), [cell proliferation](https://www.sciencedirect.com/topics/medicine-and-dentistry/cell-proliferation), inflammation, [apoptosis](https://www.sciencedirect.com/topics/medicine-and-dentistry/programmed-cell-death), and fibrosis.9 Endothelin-1 expression is increased in the kidneys in IgAN,10 and blockade of ETAR is renoprotective in experimental models of IgAN11,12 and reduces [proteinuria](https://www.sciencedirect.com/topics/medicine-and-dentistry/proteinuria) in patients with IgAN.5,13 This dual approach with sparsentan delivers the core component of supportive IgAN care—maximized inhibition of the renin-angiotensin system (RAS)6—alongside simultaneous ETAR blockade.

The efficacy and safety of sparsentan in IgAN have been assessed in the international, randomized, double-blind, active-controlled PROTECT study that included patients with IgAN at high risk of progression despite optimized supportive care.14 In a prespecified interim analysis, treatment with sparsentan resulted in a statistically significant and clinically meaningful greater reduction from baseline in proteinuria (−49·8%) versus irbesartan (−15·1%) at 36 weeks (primary endpoint), resulting in a between-group relative reduction of 41% (least-squares [LS] mean ratio=0·59, 95% CI 0·51-0·69; p<0·0001).5 Treatment-emergent adverse events (TEAEs) with sparsentan were comparable to irbesartan. Based on this, sparsentan was granted accelerated approval by the US Food and Drug Administration in 2023 for the treatment of patients with IgAN at high risk of progression.15 Here we report the final analysis of the PROTECT double-blind period over 110 weeks of treatment, particularly the impact of sparsentan on kidney function, and longer-term proteinuria and safety results.

**Methods**

*Study design and participants*

PROTECT was a phase 3, randomized, active-controlled, double-blind, parallel-group, international, multicenter clinical trial designed to evaluate the efficacy and safety of sparsentan versus irbesartan in adults with IgAN who continued to have proteinuria despite maximized treatment with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs). The trial was conducted at 134 clinical practice sites in 18 countries throughout the Americas, Europe, and Asia. Study design and enrollment criteria have been previously reported and are briefly summarized here.5,14,16

The study included a 114-week double-blind period (up to 110 weeks of randomized study drug followed by 4 weeks without study drug) followed by a 156-week open-label extension period (270 weeks total). The final analysis of the double-blind period was conducted when all participants had either completed that period or discontinued the study early. Participant inclusion criteria were age ≥18 years with biopsy-proven primary IgAN (biopsies may have been performed at any time), a 24-hour proteinuria of ≥1·0 g/d, an eGFR of ≥30 mL/min/1·73m2, a systolic and diastolic blood pressure of ≤150 and ≤100 mm Hg, and stable ACEi or ARB therapy for ≥12 weeks before screening at the patient’s maximum tolerated dose, which was at least half of the maximum labeled dose. Exclusion criteria included IgA vasculitis or secondary IgAN, cellular glomerular crescents in >25% of glomeruli on kidney biopsy ≤6 months before screening, another CKD besides IgAN, receipt of systemic immunosuppressive medications (including glucocorticoids) for ≥2 weeks within 3 months before screening, or major hepatic, cerebrovascular, or cardiovascular comorbidities.

Participants were enrolled following institutional review board or ethics committee approvals at each investigational site in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent before study enrollment.

*Randomization and masking*

Participants were randomized 1:1 to sparsentan (400 mg once daily; oral administration) or irbesartan (300 mg once daily; oral administration) based on a permuted-block randomization method. A predefined computer-generated randomization schedule was used that stratified the allocation by screening eGFR (30 to <60 mL/min/1·73m2 and ≥60 mL/min/1·73m2) and screening urine protein excretion (UPE) (≤1·75 g/d and >1·75 g/d). During the double-blind period, all parties involved with study conduct remained masked to participant treatment allocation except the data monitoring committee, serious AE monitoring contact, and a limited unmasked team responsible for the prespecified interim analysis; members of this interim-analysis team were precluded from further participation in study-related activities. Sparsentan and irbesartan were packaged identically with uniform capsule appearance, labeling, and administration schedule.

*Procedures*

Before the randomization visit, participants discontinued prohibited concomitant medications, including RAS inhibitors. The initial study drug dose for the first 2 weeks was half of the target dose (ie, 200 mg once daily sparsentan; 150 mg once daily irbesartan). At the week-2 visit, doses were titrated to the target dose (ie, 400 mg once daily sparsentan; 300 mg once daily irbesartan) following evaluation of dose tolerability. Dose tolerance was defined as systolic and diastolic blood pressure higher than 100 and 60 mm Hg, respectively, and lack of TEAEs. Participants with asymptomatic blood pressure of ≤100/60 mm Hg or clinical symptoms of orthostatic hypotension continued the initial dose. Dose titrations (down or back up) were permitted at any time at the investigator’s discretion. Medications to lower blood pressure could be initiated or adjusted at the investigator’s discretion to reach the guideline-recommended target of 125/75 mm Hg.6 Patients who discontinued study drug at any point could continue on study monitoring in the double-blind period. After week 110, during the 4-week period without study drug, standard-of-care treatments including RAS inhibitors could be resumed. Study visits occurred at weeks 2, 4, 6, 12, 24, 36, 48, 58, 70, 82, 94, 106, 110, and 114. Proteinuria and albuminuria were assessed by 24-hour urine collection and analyzed at a central laboratory (Q2 Solutions, Valencia, CA, USA). eGFR for each visit was determined using the 2009 CKD-Epidemiology Collaboration equation.17

*Outcomes*

The prespecified primary efficacy endpoint has been reported.5 Prespecified key secondary efficacy endpoints were chronic eGFR slope (ie, rate of eGFR change over weeks 6-110) and total eGFR slope over the full double-blind treatment period (ie, day 1-week 110). Prespecified other secondary efficacy endpoints were change from baseline over time in eGFR, urine protein/creatinine ratio (UP/C), urine albumin/creatinine ratio (UA/C), 24-hour UPE, and 24-hour urine albumin excretion (UAE), and proportion of patients reaching the composite endpoint (confirmed 40% eGFR reduction, kidney failure, or all-cause mortality). Prespecified exploratory endpoints included change in eGFR from baseline to week 6, week 110 to week 114, and baseline to week 114; proportion of patients achieving partial (<1·0 g/d) or complete (<0·3 g/d) proteinuria remission at any time up to week 110; and proportion of patients requiring systemic immunosuppressive medication during the study. Proportion of patients achieving proteinuria <0.5 g/d was assessed as a post hoc analysis.

Safety outcomes included TEAEs, serious TEAEs, and TEAEs that led to treatment discontinuation. TEAEs were coded with the Medical Dictionary for Regulatory Activities version 23·0. Abnormal liver function test results and COVID-19 AEs were assessed as TEAEs of interest. Drug-induced liver injury was defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) with total bilirubin >2x ULN. Change from baseline in vital signs, including body weight and blood pressure, physical examination results, clinical laboratory parameters, and use of diuretics were also evaluated.

*Statistical analysis*

Efficacy analyses (including sensitivity analyses) and safety analyses were based on the full analysis set and safety analysis set, respectively, each of which were defined as all patients who were randomized and received ≥1 dose of randomized study drug. All prespecified statistical analyses were performed according to the statistical analysis plan using SAS (version 9·4 or later).

eGFR slope was analyzed using a random coefficients analysis with fixed effects of treatment group (sparsentan and irbesartan), baseline eGFR, time (ie, analysis visit in weeks), treatment group by time interaction, and randomization stratification variable (four levels based on screening eGFR and UPE); a random intercept and random slope for each patient were included. The analysis used on-treatment eGFR assessments and missing data were imputed using the multiple imputation procedure under the assumption of missing at random.18,19 An unstructured covariance matrix was assumed; if convergence issues arose, a first-order autoregressive structure was used. Treatment effect was the contrast between sparsentan and irbesartan marginal slope estimates. The slope estimates, differences in slopes, 95% CI, and two-sided p values were extracted from the model; slopes and differences in slopes over approximately 2 years were annualized for ease of presentation and interpretation and estimated using data through week 110. Prespecified sensitivity analyses were performed to evaluate the robustness of the analyses, including a modified intention-to-treat (mITT) approach (mITT excluded 2 patients who were randomized but did not receive study drug and used eGFR measurements during the double-blind period regardless of randomized treatment status) (appendix, p 7).

Change from baseline in eGFR, UP/C, UA/C, UPE, and UAE up to week 110 and change from baseline in blood pressure were analyzed via mixed model for repeated measures as described for the analysis of the primary efficacy endpoint;5 missing data were not imputed. The treatment effect was the contrast between sparsentan and irbesartan LS means. LS means, treatment effect estimate, 95% CI, and two-sided p values were extracted from the model. Results for UP/C, UA/C, UPE, and UAE that were natural-log transformed before analysis were back-transformed to present treatment effects on the ratio scale. 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).

The composite and proteinuria remission endpoints were analyzed via a logistic regression model. Relative risk and 95% CI were estimated from a Poisson regression model with log link and the same fixed effects as the logistic regression model. Safety was analyzed descriptively.

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 occurred; as previously reported, the primary endpoint was statistically significant.5 If all key secondary endpoint analyses achieved statistical significance, then other secondary endpoints were tested. Additional statistical methods are in the appendix and include sample size calculations (p 5), analysis methods (pp 5–6), and hypothesis testing correction (p 6). This trial is registered with ClinicalTrials.gov, NCT03762850 (EudraCT, 2017-004605-41).

*Role of the funding source*

Travere Therapeutics contributed to study design, data collection, data analysis, and data interpretation. **SB**, **UAD**, **JKI**, **RK**, **PP**, and **WER** are employees of the sponsor and participated in writing, review, and approval of the manuscript. **BHR**, **JB**, **SB**, **UAD**, **JKI**, **RK**, **AM**, **PP**, and **WER** had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

**Results**

Between December 20, 2018, and May 26, 2021, of 669 individuals screened, 406 were enrolled and randomized, and 404 received sparsentan (n=202) or irbesartan (n=202) (appendix p 10) (last assessment of double-blind period: August 7, 2023); all 404 patients were included in efficacy and safety analyses. At screening, 130 (64%) sparsentan-treated and 125 (62%) irbesartan-treated patients were receiving ACEi or ARB treatment at the maximum labeled dose. Baseline demographic, clinical, and biochemical characteristics and concomitant medications are in Table 1. In the sparsentan and irbesartan groups, 174 (86%) and 154 (76%) patients completed 110 weeks of treatment and 199 (98%) and 191 (94%) completed the double-blind study period. More patients discontinued treatment prematurely with irbesartan (n=48 [24%]) than sparsentan (n=28 [14%]); patient or physician decision led to most of these discontinuations with irbesartan (n=28 [14%]) versus sparsentan (n=5 [2%]); preliminary review suggests that these cases were associated with lack of efficacy or disease progression. In the sparsentan and irbesartan groups, 192 (95%) and 196 (97%) patients reached target doses (sparsentan 400 mg and irbesartan 300 mg), and 34 (17%) and 23 (11%) required dose reductions after reaching the target dose.

eGFR chronic slope (week 6-110) was −2·7 mL/min/1·73m2/year (95% CI −3·4 to −2·1) with sparsentan and −3·8 mL/min/1·73m2/year (95% CI −4·6 to −3·1) with irbesartan (difference=1·1, 95% CI 0·1-2·1; p=0·037) (Table 2; Figure 1). eGFR total slope (day 1-week 110) was −2·9 mL/min/1·73m2/year (95% CI −3·6 to −2·2) with sparsentan and −3·9 mL/min/1·73m2/year (95% CI −4·6 to −3·1) with irbesartan (difference=1·0, 95% CI −0·03 to 1·94; p=0·058). Statistical hypotheses for other prespecified secondary efficacy endpoints were not formally tested under the hierarchical testing procedure after missing the eGFR total slope p value; for these and other efficacy endpoints, nominal 95% CIs are presented.

From baseline to week 6, LS mean absolute change in eGFR was similar between sparsentan and irbesartan (−1.2 [95% CI −2·2 to −0·3] mL/min/1·73m2 and −1·6 [95% CI −2·6 to −0·7] mL/min/1·73m2, respectively; difference=0·4, 95% CI −1·0 to 1·7) (appendix p 8). LS mean absolute change in eGFR from baseline to week 110 was lower with sparsentan versus irbesartan (−5·8 [95% CI −7·4 to −4·2] mL/min/1·73m2 and −9·5 [95% CI −11·2 to −7·9] mL/min/1·73m2, respectively; difference=3.7, 95% CI 1·5-6·0, mL/min/1·73m2) (Table 2). Importantly, this effect was durable 4 weeks after stopping study treatment and resuming standard of care; change from baseline to week 114 was −6·1 (95% CI −7·7 to −4·5) mL/min/1·73m2 with sparsentan and −9·0 (95% CI −10·7 to −7·2) mL/min/1·73m2 with irbesartan (difference=2·9, 95% CI 0·5-5·3) (appendix p 8).

Sensitivity analyses (Figure 2; appendix p 11) were consistent with and supported the conclusions from the primary analyses for chronic and total slopes through week 110, as were results from all other prespecified sensitivity analyses. An imbalance in intercurrent events was observed, particularly rates and reasons for premature treatment discontinuation (appendix p 10) and initiation of immunosuppressive rescue therapy (appendix p 12). A prespecified sensitivity analysis that used a mITT approach (including all patient data during the double-blind period irrespective of premature treatment discontinuations) was supportive of benefit, with total slope of –3·0 mL/min/1·73m2/year with sparsentan and –4·2 mL/min/1·73m2/year with irbesartan (difference=1·2, 95% CI 0·23‑2·16) (Figure 2; appendix p 11). Rescue immunosuppressive medications were initiated sooner and more frequently with irbesartan (n=15 [7%]) than sparsentan (n=6 [3%]) and were mostly corticosteroids (appendix p 12). In a prespecified sensitivity analysis excluding assessments after immunosuppressive therapy use, the difference in chronic and total slopes again favored sparsentan with CIs excluding the null (total slope of –3·0 mL/min/1·73m2/year with sparsentan and –3·9 mL/min/1·73m2/year with irbesartan; difference=1·0, 95% CI 0·03-1·99) (Figure 2; appendix p 11).

The composite endpoint of confirmed 40% eGFR reduction, kidney failure, or all-cause mortality was reached by 18 (9%) patients in the sparsentan group vs 26 (13%) in the irbesartan group (relative risk=0·68, 95% CI 0·4-1·2) (Figure 3). Within this endpoint, 18 (9%) and 22 (11%) patients in the sparsentan- and irbesartan-treated groups had confirmed 40% eGFR reduction, 9 (4%) and 11 (5%) reached kidney failure, and zero and one (0·5%) died, respectively.

At week 110, the geometric LS mean percent change from baseline in UP/C was −42·8% (95% CI −49·8% to −35·0%) with sparsentan versus −4·4% (95% CI −15·8% to 8·7%) with irbesartan (geometric LS mean ratio=0·6, 95% CI 0·5-0·7) (Table 2; Figure 4). At week 110, decreases from baseline were observed in 24-hour UPE, UA/C, and UAE with sparsentan versus irbesartan. Geometric LS mean percent change from baseline in UA/C at each visit is shown in appendix p 13.

Patients on sparsentan achieved complete proteinuria remission (UPE <0·3 g/d) earlier and more frequently versus irbesartan (n=62 [31%] versus n=23 [11%], respectively; relative risk=2·5, 95% CI 1·6-4·1) (appendix p14-15); UPE <0·5 g/d was achieved by 103 (51%) and 48 (24%) patients (relative risk=2·1, 95% CI 1·5-2·9) and partial proteinuria remission (<1·0 g/d) was achieved by 157 (78%) and 106 (53%) (relative risk=1·5, 95% CI 1·1-1·9), respectively.

Blood pressure values over 110 weeks are reported in appendix p 16. LS mean change from baseline at week 110 in systolic and diastolic blood pressure was −3·8 (95% CI −5·5 to −2·1) and −3·4 (95% CI −4·6 to −2·2) mm Hg, respectively, with sparsentan and −2·5 (95% CI −4·3 to −0·8) and −1·2 (95% CI −2·5 to 0·0) mm Hg, respectively, with irbesartan.

TEAEs were reported in 187 (93%) patients in the sparsentan group and 177 (88%) in the irbesartan group (Table 3). TEAEs that occurred more frequently with sparsentan than irbesartan (≥5 percentage points) included dizziness (n=30 [15%] vs n=13 [6%]) and hypotension (n=26 [13%] vs n=8 [4%]). In the sparsentan and irbesartan groups, serious TEAEs were reported in 75 (37%) and 71 (35%) patients, and TEAEs led to treatment discontinuation in 21 (10%) and 18 (9%) patients. TEAEs of acute kidney injury occurred in 12 (6%) sparsentan- and five (2%) irbesartan-treated patients (serious: n=4 [2%] and n=1 [<1%]; led to treatment discontinuation: n=3 [1%] and n=0).

In the sparsentan and irbesartan groups, TEAEs of COVID-19 were reported in 53 (26%) and 46 (23%) patients. Liver TEAEs of interest of ALT or AST increasing to >3x ULN occurred in five (2%) and seven (3%) patients in the sparsentan and irbesartan groups. In the sparsentan and irbesartan groups, serious hepatic TEAEs were reported in zero and two (1%) patients. No cases of drug-induced liver injury occurred in either group.

Hypotension-associated TEAEs (hypotension, orthostatic hypotension, and blood pressure systolic decreased) were reported in 33 (16%) and 13 (6%) patients with sparsentan and irbesartan, and led to treatment discontinuation in three (1%; hypotension, n=2 [1%]; orthostatic hypotension, n=1 [<1%]) and zero patients. No patients discontinued treatment due to heart failure or edema. There were no serious TEAEs of study drug–related edema. In the sparsentan and irbesartan groups, change in semiquantitative edema from no edema at baseline to severe edema occurred in zero and two patients, respectively, and to moderate edema occurred in two and zero patients; diuretic use (started on or after initial study dose) was reported in 49 (24%) and 54 (27%) patients – most frequently used class was thiazides (sparsentan, n=35 [17%]; irbesartan, n=42 [21%]). There was one death in the irbesartan group (cardiorespiratory arrest) and none in the sparsentan group (Table 3).

Mean (SD) body weight was 84·2 (20·1) kg at baseline and 83·8 (20·9) kg at week 110 with sparsentan and 84·7 (19·7) kg at baseline and 85·0 (19·0) kg at week 110 with irbesartan (appendix p 17). Mean potassium concentration remained stable over 110 weeks (appendix p 9).

**Discussion**

Sparsentan received accelerated regulatory approval for IgAN based on the results of PROTECT, which demonstrated that sparsentan-treated patients had significantly greater reductions in proteinuria versus irbesartan (relative reduction, 41%) during 36 weeks of treatment.5,15 PROTECT continued until week 114 to determine whether the proteinuria advantage for sparsentan-treated patients was durable and to verify that this large decrease in proteinuria translated into superior preservation of kidney function versus those titrated to the maximal approved irbesartan dose. Importantly, patients and investigators remained blinded to treatment during this period. Over the course of the double-blind period, the superior reduction of proteinuria in sparsentan- versus irbesartan-treated patients was maintained with a relative reduction of 40% at 110 weeks, similar to the relative reduction observed at 36 weeks.5 As expected for patients with IgAN,20 the relationship between the magnitude of proteinuria reduction and rate of loss of kidney function was successfully demonstrated in PROTECT. Kidney function decline, assessed as chronic or total eGFR slope through week 110, was lower with sparsentan versus irbesartan, indicating better preservation of kidney function (chronic, −2·7 vs −3·8 mL/min/1·73m2/year, respectively; total, −2·9 vs −3·9 mL/min/1·73m2/year). The difference in chronic slope (1·1 mL/min/1·73m2/year) between treatment arms reached statistical significance (p=0·037). For total slope, although the difference between arms was of similar magnitude, favoring sparsentan, statistical significance was narrowly missed (p=0·058). Sensitivity analyses for chronic and total slopes that used an mITT approach (all participants who received study drug) and therefore had somewhat greater statistical power, or that excluded data subsequent to initiation of rescue therapy, strongly suggest that the favorable impact of sparsentan was robust. Notably, a meta-analysis assessing eGFR slope as a surrogate endpoint showed greater variability in this measurement’s treatment effect with glomerular disease than CKD.21 Given that sparsentan and irbesartan affect glomerular hemodynamics and cause an acute decrease in GFR,22 we believe that chronic slope20,23 most accurately measures the nephroprotective impact of long-term treatment with both sparsentan and irbesartan.

Beyond the key secondary endpoint of eGFR slope, sensitivity, secondary, and exploratory analyses consistently support the efficacy of sparsentan. The change in eGFR from baseline to week 110 and particularly to week 114 (4 weeks off study drug) suggest clear benefits for sparsentan. The number of patients reaching the composite endpoint of confirmed 40% eGFR reduction, kidney failure, or death, and the time to reach this endpoint also trended in favor of sparsentan, despite more patients having an eGFR <30 mL/min/1.73m2 at baseline in the sparsentan (n=15 [7%]) than irbesartan (n=5 [3%]) arm. Furthermore, a greater proportion of sparsentan- versus irbesartan-treated patients (n=157 [78%] vs n=106 [53%]) achieved UPE <1·0 g/d, the therapeutic target suggested by management guidelines.6 Since a significant number of patients with IgAN who have proteinuria of <1·0 g/d still have progressive kidney failure,2 suggesting that this proteinuria target may be too high, the 2·5-fold greater proportion of sparsentan- versus maximally tolerated irbesartan-treated patients that achieved UPE <0·3 g/d is especially noteworthy (n=62 [31%] vs n=23 [11%]). Finally, the blood pressure–lowering effects of sparsentan are not thought to be the reason for its efficacy given the lack of difference in systolic blood pressure and the small difference in diastolic blood pressure over the study.

As with any proposed new therapeutic, safety is a primary consideration for clinical implementation. AEs, including TEAEs and severe AEs, were well balanced between treatment arms, except for dizziness and hypotension, although these did not result in many discontinuations (2 patients discontinued sparsentan due to hypotension). While increases in serum creatinine levels and decreases in eGFR-related TEAEs were similar between groups, peripheral edema (n=31 [15%] and n=24 [12%]) and hyperkalemia (n=32 [16%] and n=26 [13%]) were only slightly higher in the sparsentan vs irbesartan group. Abnormal liver function test results were of particular interest given a regulatory focus around a potential class risk, but there were few events overall and the number of events was similar in both arms. There were far more study treatment discontinuations due to patient or physician decision with irbesartan (n=28) than sparsentan (n=5), and 75% (21/28 with irbesartan) of these were initiated by the patient, not the physician. Given the few study treatment withdrawals for AEs, it is interesting to speculate that withdrawals from the irbesartan group were due to a perception of not improving, considering that more irbesartan- (n=15 [7%]) versus sparsentan-treated patients (n=6 [3%]) started rescue therapy.

Several IgAN therapeutic trials completed in recent years examined eGFR slope. Data from trials reporting a benefit of study drug over placebo based on total eGFR slope are available for reduced-dose plus high-dose systemic glucocorticoid (methylprednisolone), reduced-dose glucocorticoid (methylprednisolone), a gut-mucosa–targeted glucocorticoid (Nefecon), and a sodium-glucose cotransporter-2 inhibitor (SGLT2i; dapagliflozin), which had treatment effects of 2·47, 2·76, 1·8, and 1·2 mL/min/1·73m2/year, respectively.24-26 The annual rate of loss of kidney function during the trial for patients receiving high-dose and reduced-dose methylprednisolone, reduced-dose methylprednisolone, Nefecon, and dapagliflozin were −2·5, −2·18, −3·6, and −3·5 mL/min/1·73m2/year. Given that all these potential IgAN therapeutics have different mechanisms of action, it is intriguing to speculate that the effects on kidney function preservation may be additive and support the idea that IgAN, like other immune-mediated glomerular diseases, may benefit from a multitargeted therapeutic approach,27 especially if the goal for long-term preservation of kidney function is to achieve the lowest proteinuria level possible.2 Given that sparsentan is not an immunosuppressive agent, we suggest it could be used long term as a foundational therapy for IgAN, upon which immunosuppressive drugs may be added, as appropriate, to control immunologic manifestations of IgAN (eg, galactose-deficient IgA production, anti–galactose-deficient IgA autoantibodies, and complement activation).28 SGLT2is are also nonimmunosuppressive and have shown efficacy in slowing progression of kidney failure in IgAN.29 SGLT2i and sparsentan combination therapy is currently being evaluated for safety and efficacy in the PROTECT (NCT03762850)30 open-label extension and SPARTACUS (NCT05856760) trials.31

To illustrate the potential long-term impact of the eGFR advantage with sparsentan versus irbesartan, consider a patient with IgAN beginning treatment with an eGFR of 57 mL/min/1·73m2 (mean baseline eGFR of patients enrolled into PROTECT) who receives sparsentan or irbesartan. If the patient’s eGFR fell by 3·8 mL/min/1·73m2/year with irbesartan, but only 2·7 mL/min/1·73m2/year with sparsentan as in PROTECT, the patient theoretically would reach kidney failure (eGFR <15 mL/min/1·73m2) in 11·1 years on irbesartan and 15·6 years on sparsentan (appendix p 18).

This study has several strengths and limitations. PROTECT is one of the largest interventional, randomized, active-controlled trials for IgAN comparing a novel therapeutic to an active control. The study was successfully completed despite coinciding with the COVID‑19 pandemic. Almost all patients in the irbesartan arm were titrated to the maximum recommended dose (n=196 [97%]), attesting to the rigor of the study. This level of treatment with RAS inhibition may have accounted for the slower eGFR decline in the irbesartan group (−3·8 to −3·9 mL/min/1·73m2/year) versus that reported in other studies that have relied on clinician attestation of maximal tolerated RAS inhibition (an average of −5·3 mL/min/1·73m2/year).24,25,32-34 This finding attests to the generalizability of our results and provides external validation of our kidney function estimates. Limitations of PROTECT include the inability to generalize the results to at-risk patients with proteinuria <1·0 g/d, not taking into consideration kidney histology, and that due to the total slope narrowly missing statistical significance, formal hypothesis testing was not available for other endpoints per the hierarchical testing procedure.

In conclusion, the totality of data from PROTECT suggests that sparsentan is an effective and safe treatment for IgAN that delivers meaningful clinical benefit beyond RAS inhibition alone.

**Contributors**

**BHR**, **JB**, **HJLH**, **UAD**, **JKI**, **RK**, **AM**, **WER**, **MGW**, and **VP** contributed to the conception and design of the PROTECT study. **BHR**, **JB**, **JKI**, **RK**, **AM**, **PP**, and **WER** wrote the first draft of the paper. **UAD**, **JKI**, **RK**, and **PP** provided the data analyses. **BHR**, **JB**, **UAD**, **JKI**, **RK**, **AM**, and **PP** directly accessed and verified the underlying data reported in the manuscript. All authors contributed to the interpretation of the data and critically revised the paper. **BHR**, **JB**, **SB**, **UAD**, **JKI**, **RK**, **AM**, **PP**, and **WER** had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

**Declaration of interests**

**BHR** reports consulting fees from Alexion Pharmaceuticals, Alpine Pharma, BioCryst Pharmaceuticals, Calliditas Therapeutics, Novartis, Q32 Bio, Omeros, Otsuka Pharmaceuticals, Travere Therapeutics, and Vera Therapeutics; and has a leadership role at NephroNet, Lupus ABC/LRA, and Lupus Foundation of America. **JB** reports a research grant from Travere Therapeutics; and consulting fees from Travere Therapeutics. **HJLH** reports honoraria from Travere Therapeutics for membership of the DUPLEX clinical trial steering committee; grants for clinical trials and clinical research from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk paid to his institution; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, CLS Behring, Chinook Therapeutics, Dimerix, Lilly, Gilead Sciences, Janssen, Mitsubishi Tanabe Pharma, Novartis, Novo Nordisk, and Travere Therapeutics paid to his institution; honoraria from AstraZeneca, Bayer, and Novo Nordisk; and travel support from AstraZeneca and Lilly. **CEA** reports consulting fees from Travere Therapeutics; 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**Data sharing**

Qualifying researchers who wish to access the data described in this manuscript should submit a proposal with a valuable research question to Travere Therapeutics (medinfo@travere.com), the company sponsoring the clinical development of sparsentan for the treatment of IgA nephropathy and focal segmental glomerulosclerosis. Proposals will be considered following conclusion of the PROTECT study.

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**Tables**

**Table 1.** Demographics and baseline characteristics

|  |  |  |
| --- | --- | --- |
|  | **Sparsentan (n=202)** | **Irbesartan (n=202)** |
| **Age at informed consent, mean (SD), years** | 46·6 (12·8) | 45·4 (12·1) |
| **Sex, n (%)** |  |  |
| Male | 139 (69) | 143 (71) |
| Female | 63 (31) | 59 (29) |
| **Race, n (%)** |  |  |
| Asian | 67 (33) | 48 (24) |
| Black or African American | 1 (<1) | 3 (1) |
| Native Hawaiian or Other Pacific Islander | 0 (0) | 1 (<1) |
| White | 130 (64) | 142 (70) |
| Other | 4 (2) | 9 (4) |
| **Ethnicity, n (%)** |  |  |
| Hispanic or Latino | 17 (8) | 16 (8) |
| Not Hispanic or Latino | 185 (92) | 183 (91) |
| Not reported | 0 (0) | 3 (1) |
| **Age at IgAN diagnosis, mean (SD), years\*** | 40·2 (13·4) | 39·0 (12·4) |
| **Time from initial kidney biopsy to informed consent, median (IQR), years†** | 4·0 (1·0-10·0) | 4·0 (1·0-10·0) |
| **History of hypertension, n (%)** | 146 (72) | 144 (71) |
| **Blood pressure, mean (SD), mm Hg** |  |  |
| Systolic | 128·0 (14·4) | 129·9 (12·4) |
| Diastolic | 81·6 (10·6) | 83·2 (10·6) |
| **Urine protein excretion, median (IQR), g/d** | 1·8 (1·2-2·9) | 1·8 (1·3-2·6) |
| **Urine protein/creatinine ratio, median (IQR), g/g** | 1·3 (0·8-1·8) | 1·2 (0·9-1·7) |
| **Hematuria, n (%)** | 111 (55) | 114 (56) |
| **eGFR, mean (SD), mL/min/1·73 m2‡** | 56·8 (24·3) | 57·1 (23·6) |
| **eGFR category, n (%)** |  |  |
| ≥90 mL/min/1·73 m2 | 26 (13) | 25 (12) |
| ≥60 to <90 mL/min/1·73 m2 | 49 (24) | 48 (24) |
| ≥45 to <60 mL/min/1·73 m2 | 45 (22) | 49 (24) |
| ≥30 to <45 mL/min/1·73 m2 | 67 (33) | 75 (37) |
| <30 mL/min/1·73 m2§ | 15 (7) | 5 (3) |
| **Serum albumin, mean (SD), g/L** | 41·2 (3·9) | 41·7 (3·8) |
| **ACEi or ARB at maximum labeled dose at screening, n (%)¶** | 130 (64) | 125 (62) |
| **Baseline concomitant medication use, n (%)‖** |  |  |
| Antihypertensive medications\*\* | 90 (45) | 88 (44) |
| Lipid-lowering medications | 114 (56) | 116 (57) |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy.

\* Age at IgAN diagnosis is derived based on the year of diagnosis and year of birth.

† Time from initial biopsy is derived based on the year of the initial kidney biopsy and year of signed informed consent.

‡ eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration equation.17

§ Patients progressed from chronic kidney disease stage 3 to 4 between randomization and first dose of study drug.

¶ ACEi and ARB treatment at screening; renin-angiotensin system inhibitors were prohibited during the study.

‖ Baseline concomitant medications were started before and continued after the initial dose of study medication.

\*\* Antihypertensive medications exclude ACEis, ARBs, aldosterone blockers, and aliskiren.

**Table 2.** Key secondary and other secondary endpoints

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Sparsentan (n=202)** | **Irbesartan (n=202)** | **Between group difference** |
| **Rate of change in eGFR through week 110** | LS mean (95% CI),  mL/min/1·73 m2/year | | |
| Week 6 to week 110 (chronic slope) | –2·7  (–3·4 to –2·1) | –3·8  (–4·6 to –3·1) | 1·1  (0·1-2·1)  p=0·037 |
| Day 1 to week 110 (total slope) | –2·9  (–3·6 to –2·2) | –3·9  (–4·6 to –3·1) | 1·0  (−0·03 to 1·9)  p=0·058 |
|  | LS mean  (95% CI) | | Difference  (95% CI) |
| **Absolute change in eGFR from baseline to week 110, mL/min/1·73 m2** | −5·8  (−7·4 to −4·2) | −9·5  (−11·2 to −7·9) | 3·7  (1·5-6·0) |
| **Change from baseline in proteinuria at week 110** | Geometric LS mean  (95% CI), % | | Geometric LS mean ratio (95% CI) |
| UP/C, g/g | −42·83  (−49·75 to −34·97) | −4·36  (−15·84 to 8·70) | 0·60  (0·50-0·72)  (40% reduction) |
| Urine protein excretion, g/d | −46·88  (−53·38 to −39·47) | −5·86  (−17·88 to 7·92) | 0·56  (0·47-0·68)  (44% reduction) |
| UA/C, g/g | −56·03  (−62·05 to −49·06) | −17·27  (−29·06 to −3·52) | 0·53  (0·43-0·66)  (47% reduction) |
| Urine albumin excretion, g/d | −58·80  (−64·65 to −51·98) | −17·89  (−30·06 to −3·61) | 0·50  (0·40-0·63)  (50% reduction) |
|  | n (%) | | Relative risk  (95% CI) |
| **Patients reaching confirmed 40% eGFR reduction, kidney failure, or death** | 18 (9) | 26 (13) | 0·68  (0·37-1·24) |

eGFR, estimated glomerular filtration rate; LS, least squares; UA/C, urine albumin/creatinine ratio; UP/C, urine protein/creatinine ratio.

**Table 3.** Treatment-emergent adverse events

|  |  |  |
| --- | --- | --- |
|  | **Sparsentan (n=202)** | **Irbesartan (n=202)** |
| **Any TEAE, n (%)** | 187 (93) | 177 (88) |
| **TEAEs in ≥5% of patients in ≥1 group** |  |  |
| COVID-19 | 53 (26) | 46 (23) |
| Hyperkalemia | 32 (16) | 26 (13) |
| Peripheral edema | 31 (15) | 24 (12) |
| Dizziness | 30 (15) | 13 (6) |
| Headache | 27 (13) | 26 (13) |
| Hypotension | 26 (13) | 8 (4) |
| Hypertension | 22 (11) | 28 (14) |
| Upper respiratory tract infection | 18 (9) | 18 (9) |
| Fatigue | 17 (8) | 11 (5) |
| Anemia | 16 (8) | 9 (4) |
| Nasopharyngitis | 15 (7) | 16 (8) |
| Blood creatinine phosphokinase increased | 15 (7) | 10 (5) |
| Cough | 15 (7) | 7 (3) |
| Muscle spasms | 14 (7) | 17 (8) |
| Arthralgia | 14 (7) | 13 (6) |
| Proteinuria | 13 (6) | 15 (7) |
| Backpain | 12 (6) | 16 (8) |
| Lipase increased | 12 (6) | 9 (4) |
| Acute kidney injury | 12 (6) | 5 (2) |
| Gout | 11 (5) | 10 (5) |
| Pruritus | 11 (5) | 8 (4) |
| Diarrhea | 10 (5) | 19 (9) |
| Blood creatinine increased | 10 (5) | 14 (7) |
| ALT increased | 10 (5) | 8 (4) |
| Gastroesophageal reflux disease | 10 (5) | 8 (4) |
| Nausea | 10 (5) | 5 (2) |
| Myalgia | 10 (5) | 4 (2) |
| Renal impairment | 7 (3) | 12 (6) |
| Urinary tract infection | 7 (3) | 12 (6) |
| Hyperuricemia | 7 (3) | 11 (5) |
| Pain in extremity | 6 (3) | 12 (6) |
| **Transaminase elevations,\* n (%)** | 5 (2) | 7 (3) |
| **Serious TEAEs, n (%)** | 75 (37) | 71 (35) |
| **Serious TEAEs in ≥2 patients in ≥1 group, n (%)** |  |  |
| COVID-19 | 42 (21) | 38 (19) |
| Chronic kidney disease | 6 (3) | 6 (3) |
| Acute kidney injury | 4 (2) | 1 (<1) |
| Dizziness | 2 (1) | 1 (<1) |
| Proteinuria | 2 (1) | 1 (<1) |
| Malaise | 2 (1) | 0 (0) |
| Appendicitis | 1 (<1) | 2 (1) |
| Cellulitis | 1 (<1) | 2 (1) |
| COVID-19 pneumonia | 1 (<1) | 2 (1) |
| IgAN | 1 (<1) | 2 (1) |
| Meniscus injury | 1 (<1) | 2 (1) |
| **TEAEs leading to treatment discontinuation** **in ≥2 patients in ≥1 group, n (%)** | 21 (10) | 18 (9) |
| Chronic kidney disease | 3 (1) | 3 (1) |
| Acute kidney injury | 3 (1) | 0 (0) |
| ALT increased | 3 (1) | 0 (0) |
| Hypotension | 2 (1) | 0 (0) |
| Lipase increased | 2 (1) | 0 (0) |
| Renal impairment | 1 (<1) | 4 (2) |
| **TEAEs leading to death, n (%)** | 0 (0) | 1 (<1)† |

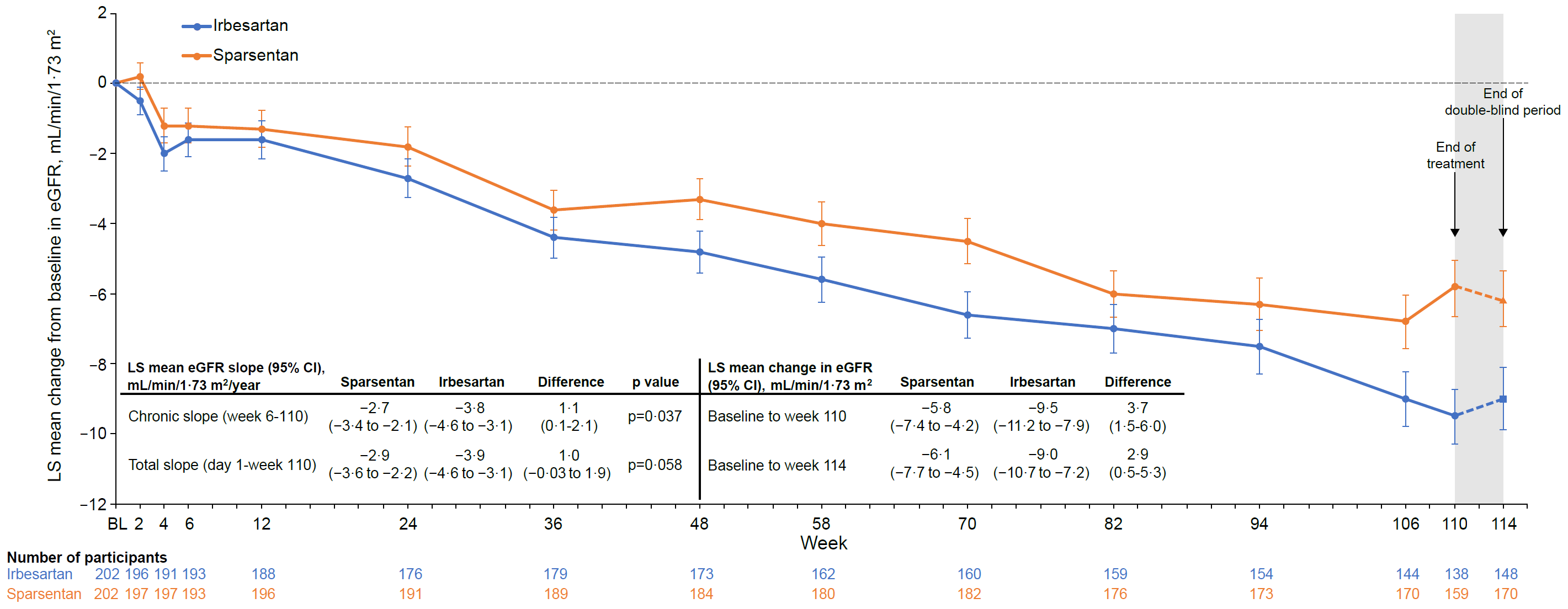
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgAN, immunoglobulin A nephropathy; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

\* Abnormal liver function test results that met the following criteria: (1) new elevation in ALT or AST of >3 x ULN with or without elevation of total serum bilirubin of >2 x ULN and (2) twofold increase in ALT or AST above the baseline value in patients who had elevated values before taking study medication.

† One patient in the irbesartan group died due to a severe adverse event of cardiorespiratory arrest that was considered not related to study drug.

**Figures**

**Figure 1.** eGFR by visit up to week 114\*

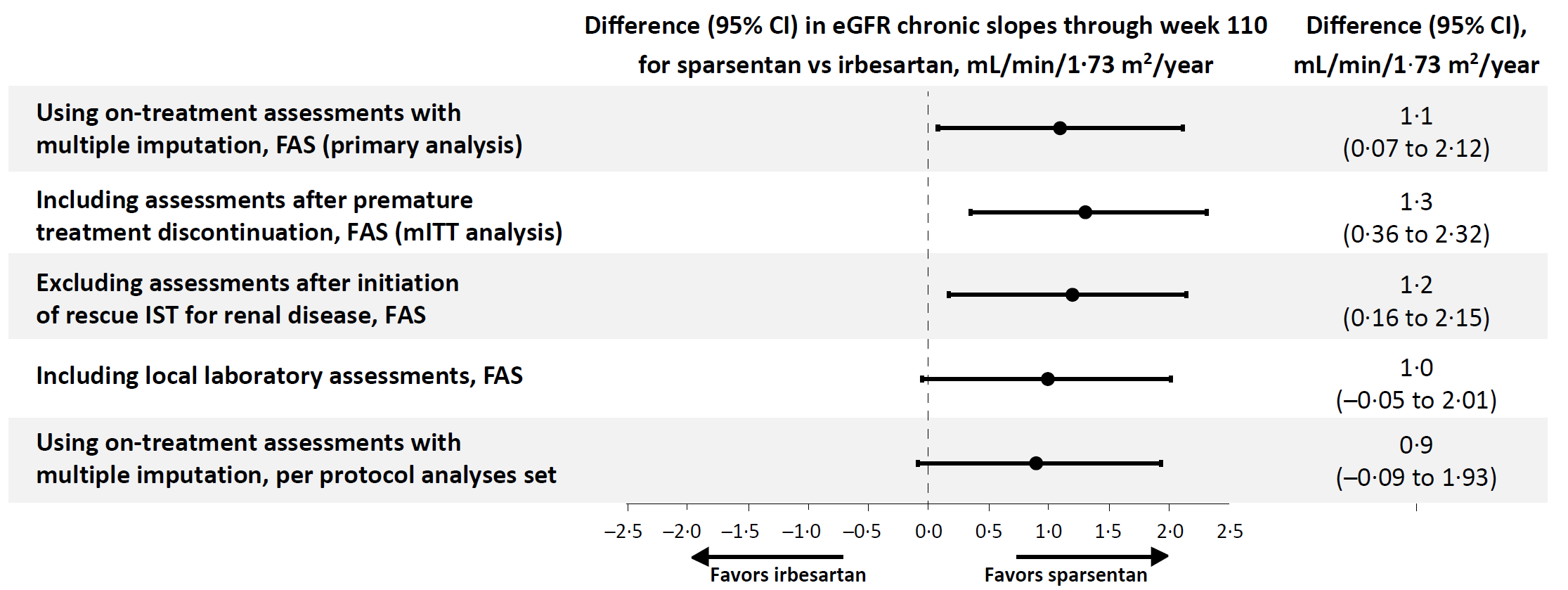


BL, baseline; eGFR, estimated glomerular filtration rate; LS, least squares.

\* Change from baseline in eGFR at week 6 or 114 was analyzed via analysis of covariance, and change from baseline in eGFR to other time points up to week 110 were analyzed via a mixed model for repeated measures. Grey shaded area indicates 4-week period between end of randomized study treatment (ie, week 110) and end of double-blind study period (ie, week 114).

Error bars indicate standard error.

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

**a** **b**  A graph with black and white text

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).

**Figure 3:** Time to reach the composite endpoint of confirmed 40% eGFR reduction, kidney failure, or all-cause mortality\*

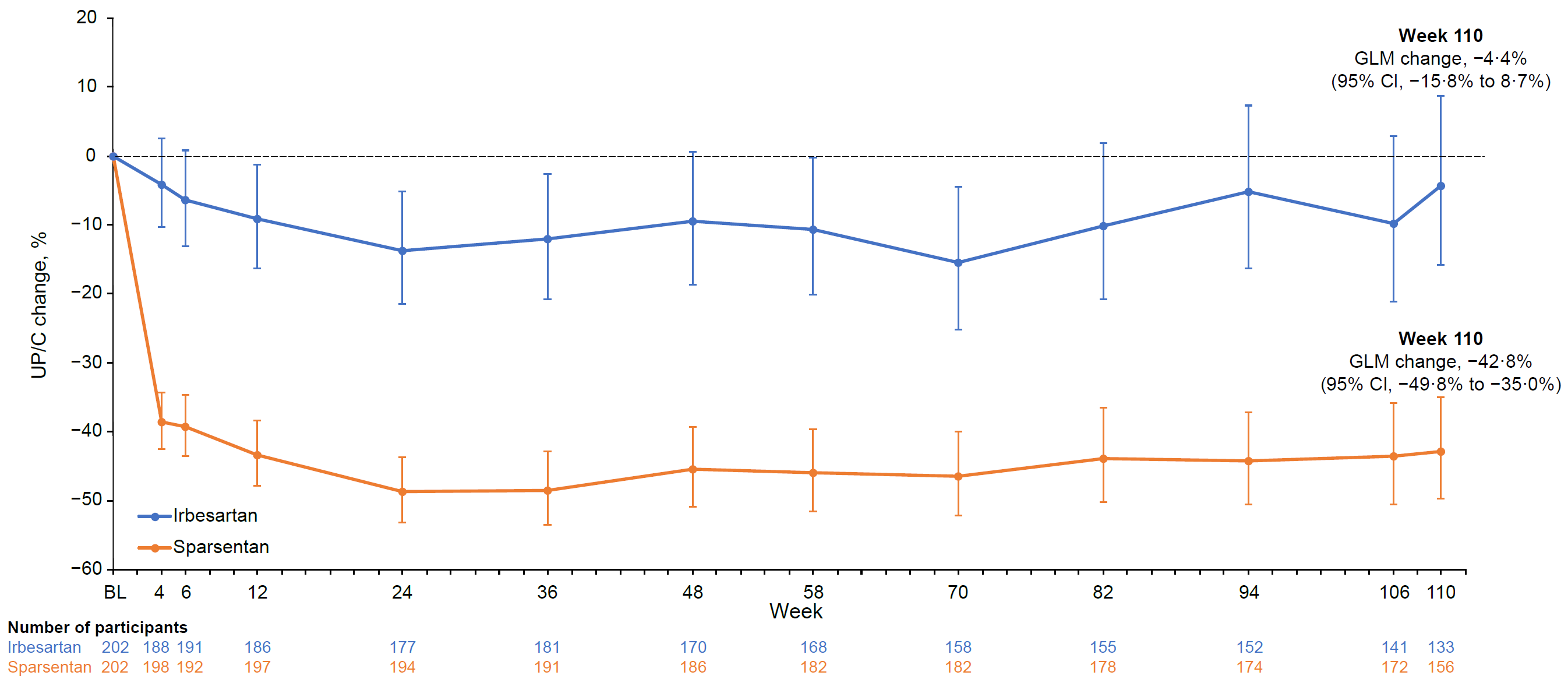
A graph with numbers and a line

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eGFR, estimated glomerular filtration rate.

\* Vertical bars indicate censored patients.

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



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

Error bars indicate 95% CIs.