Clinical and Statistical Review

Table 1. Application Information

Application Type	NDA
Application Number(s)	216403/S-006
Priority or Standard	Standard
Submit Date(s)	3/13/2025
Received Date(s)	3/13/2025
Initial PDUFA Goal Date	1/13/2026
Extended PDUFA goal Date due to Major Amendment	4/13/2026
Division/Office	Division of Cardiology and Nephrology (DCN)
Review Completion Date	4/13/2026
Established/Proper Name	Sparsentan
(Proposed) Trade Name	FILSPARI
Pharmacologic Class	Endothelin type A and angiotensin II receptor antagonist
Applicant	Travere Therapeutics, Inc.
Dosage form	Tablet, for oral administration
Applicant proposed Dosing Regimen	Weight >50 kg: 400 mg orally once daily for 14 days, then increase to 800 mg orally once daily, as tolerated Weight ≤50 kg: 200 mg orally once daily for 14 days, then increase to 400 mg orally once daily, as tolerated
Applicant Proposed Indication(s)/Population(s)	Treatment of focal segmental glomerulosclerosis in adults and pediatric subjects aged 8 years and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Focal segmental glomerulosclerosis (disorder) – SCTID: 236403004
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	To reduce proteinuria in adult and pediatric patients aged 8 years and older with focal segmental glomerulosclerosis (FSGS) without nephrotic syndrome
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Focal segmental glomerulosclerosis (disorder) – SCTID: 236403004
Recommended Dosing Regimen	Weight >50 kg: 400 mg orally once daily for 14 days, then increase to 800 mg orally once daily, as tolerated Weight ≤50 kg: 200 mg orally once daily for 14 days, then increase to 400 mg orally once daily, as tolerated

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Review Team

Table 2. Review Team Information

Discipline and Role	Reviewer Name, Office/Division	Sections Authored in Full or in Part	Recommendations to Signatory	Comments on Recommendations to Signatory
Clinical Discipline Clinical Reviewer	Christine Garnett, PharmD OND/OCHEN/DCN	Sections: 2, 3, 4, 5, 6, 7.1, 8, 9-13, 14.1, 14.2, 14.4	Based on my assessment of the application: ☒No deficiencies preclude approval. ☐Deficiencies preclude approval. ☐Not applicable.	Substantial evidence of effectiveness (SEE) was not established in the overall population. Agree with approval in patients with FSGS without nephrotic syndrome.
Clinical Discipline Cross Disciplinary Team Leader	Kirtida Mistry, MBBCh, DCH, MRCPCH OND/OCHEN/DCN	Sections: 1-11, 14	Based on my assessment of the application: ☒No deficiencies preclude approval. ☐Deficiencies preclude approval. ☐Not applicable	Agree with approval in patients with FSGS without nephrotic syndrome – see Section 2
Statistical Discipline Statistical Reviewer	William Koh, PhD OTS/OB/DBII	Sections: 7.1, 15.3	Based on my assessment of the application: ☒No deficiencies preclude approval. ☐Deficiencies preclude approval. ☐Not applicable	SEE was not established in the overall population. SEE for proteinuria was established in the patient population without nephrotic syndrome. See Sections 2.1 and 7.1.3.4
Statistical Discipline Statistical Reviewer	Jared Kabara, MS OTS/OB/DAI	Sections: 7.1.2.2.3, 7.1.2.2.5	☒Not applicable	

Discipline and Role	Reviewer Name, Office/Division	Sections Authored in Full or in Part	Recommendations to Signatory	Comments on Recommendations to Signatory
Statistical Discipline Statistical Secondary Reviewer	Jennifer Clark, PhD OTS/OB/DBII	Sections: 7.1, 15.3	Based on my assessment of the application: ☒No deficiencies preclude approval. ☐Deficiencies preclude approval. ☐Not applicable	
Statistical Discipline Tertiary Reviewer	Jialu Zhang, PhD OTS/OB/DBII	Sections: 7.1, 15.3	Based on my assessment of the application: ☒No deficiencies preclude approval. ☐Deficiencies preclude approval. ☐Not applicable	SEE was not established in the overall population. Agree with approval in patients with FSGS without nephrotic syndrome.

Acknowledgements

Silvia Bartlett, Melissa Button, Austin Hu, Deepa Rao, Hebing Liu, Hongshan Li, Vishnu Sharma, Selena DeConti, Michael Monteleone

Signatory:

Aliza Thompson, MD, MS
Director, Division of Cardiology and Nephrology

Glossary

ACE	angiotensin-converting enzyme
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ARB	angiotensin receptor blocker
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CKD	chronic kidney disease
DILI	drug-induced liver injury
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ERA	endothelin receptor antagonist
ETAR	endothelin type A receptor
E-R	exposure-response
FAS	full analysis set
FDA	Food and Drug Administration
FPRE	FSGS partial remission endpoint
FSGS	focal segmental glomerulosclerosis
ICE	intercurrent event
IgAN	immunoglobulin A nephropathy
IND	investigational new drug
IST	immunosuppressive therapies
KDIGO	Kidney Disease Improving Global Outcomes
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation

MMRM	model for repeated measures
NDA	new drug application
OND	Office of New Drugs
OLE	open-label extension
OCMQ	OND Custom Medical Query
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic
PRO	patient-reported outcomes
PT	preferred term
QD	once daily
RAS	renin-angiotensin system
RAAS	renin-angiotensin-aldosterone system
RD	risk difference
REMS	risk evaluation and mitigation strategy
RGD	Rare Glomerular Disease
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SEE	substantial evidence of effectiveness
SGLT2	sodium-glucose cotransporter-2
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio

1. Executive Summary

1.1. Summary of Regulatory Action

On March 13, 2025, Travere Therapeutics submitted an efficacy supplement under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sparsentan for "the treatment of focal segmental glomerulosclerosis (FSGS) in adults and pediatric patients aged 8 years and older." FSGS is an important cause of proteinuria and nephrotic syndrome (a constellation of heavy proteinuria, low serum albumin levels and swelling/edema) and is the most common primary glomerular disorder causing kidney failure in adult and pediatric patients in the United States. Sparsentan is an angiotensin type II and endothelin type A receptor antagonist that is currently approved to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression.

As principal support for safety and effectiveness, the Applicant submitted the results of DUPLEX, a randomized, double-blind phase 3 trial evaluating the superiority of sparsentan to irbesartan, an angiotensin type II receptor antagonist. DUPLEX was initially designed to support accelerated approval based on an interim analysis that assessed effects on proteinuria. The same trial was to be used to verify the clinical benefit in the post-marketing setting by demonstrating an effect on the loss of kidney function (estimated glomerular filtration rate [eGFR]).

Although there was a statistically significant effect on the proteinuria-based endpoint at the interim analysis, given concerns with the findings (including the size of treatment effect on proteinuria and interim eGFR results), the Division recommended that the Applicant complete the ongoing trial and pursue traditional approval based on the results of the primary eGFR-based endpoint. At the final analysis, DUPLEX did not meet its prespecified eGFR-based endpoint. In the overall trial population, the adjusted mean change from baseline to Week 108 in eGFR was -14.3 mL/min/1.73 m^2 in patients randomized to sparsentan, and -13.3 mL/min/1.73 m2 in patients randomized to irbesartan using FDA's preferred methodology. Compared to irbesartan, the difference in the adjusted mean change from baseline to Week 108 in eGFR was -1.0 mL/min/1.73 m^2 (95% CI: -4.9, 2.8), numerically favoring irbesartan.

Although the trial failed to meet its primary eGFR-based endpoint at final analysis, the review team has concluded that the application provides substantial evidence of sparsentan's effectiveness in reducing proteinuria in adult and pediatric patients 8 years and older with FSGS without nephrotic syndrome and that in the context of this rare, serious disease without approved therapies, the available data are sufficient to support traditional approval. I concur. Key considerations include the following:

- The understanding of eGFR as a clinical trial endpoint in FSGS is evolving. While analyses of observational data suggest that the mean rate of change in eGFR over 24 months is associated with kidney failure in patients with FSGS, analyses of these data have also raised concern that it may be challenging to demonstrate efficacy using eGFR-based endpoints in

clinical trials of FSGS because of the high variability in eGFR in patients with FSGS and the limited size of the affected population, particularly for therapies with more modest treatment effects on the rate of loss of kidney function.

- FSGS is a heterogenous condition, and key drivers of disease are likely to depend on the underlying etiology of FSGS. Based on sparsentan's mechanism of action, patients without nephrotic syndrome might be expected to have a greater response to sparsentan than patients with the nephrotic syndrome (which is primarily immune-mediated). In DUPLEX, approximately two thirds of the overall trial population did not have nephrotic syndrome. In these patients, the treatment effect of sparsentan relative to irbesartan on proteinuria was larger (estimated reduction: 29%; 95% CI: 8%, 44%) than in the overall trial population (estimated reduction: 22%; 95% CI: 2%, 37%), and the findings were robust to assumptions about missing data. In contrast, there was no evidence of a treatment effect in patients with nephrotic syndrome.
- Data supporting the use of proteinuria as a surrogate endpoint for a treatment's effect on progression to kidney failure in FSGS include a strong understanding of the pathophysiology of FSGS and the role of proteinuria in the pathophysiology, as well as epidemiologic evidence. Although data from randomized controlled trials indicating that treatment effects on proteinuria above some magnitude reliably predict treatment effects on outcomes in FSGS are currently lacking, analyses of effects on the loss of kidney function (eGFR) and kidney failure outcomes in patients without nephrotic syndrome in DUPLEX provide reassurance that sparsentan's effect on proteinuria will translate into a clinically meaningful benefit on the rate of loss of kidney function and progression to kidney failure in patients with FSGS without nephrotic syndrome.

The major safety concern is the risk of hepatotoxicity. While no Hy's law cases or cases of liver failure have been observed in sparsentan-treated patients in clinical trials, some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To ensure that the benefits of sparsentan for the treatment of FSGS without nephrotic syndrome outweigh this risk, sparsentan will only be available through a restricted program under a risk evaluation and mitigation strategy.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness was established with one adequate and well-controlled clinical investigation and confirmatory evidence. To address the requirement for substantial evidence of effectiveness, the Applicant submitted the results of DUPLEX, a randomized, double-blind, active-controlled phase 3 trial in adults and pediatric patients aged 8 years and older with FSGS. Confirmatory evidence of effectiveness is provided by DUET, an 8-week, double-blind, active-controlled phase 2 trial in adults and pediatric patients aged 8 years and older with FSGS. Post-hoc analyses of treatment effects on proteinuria in patients without nephrotic syndrome in this phase 2 study were generally consistent with those in DUPLEX supporting that there is a true effect of sparsentan on proteinuria in patients with FSGS without nephrotic syndrome.

Although the phase 3 trial failed to meet its primary endpoint, for the reasons discussed above, the application provides substantial evidence of sparsentan's effectiveness in reducing proteinuria in adult and pediatric patients 8 years and older with FSGS without nephrotic syndrome.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Focal Segmental Glomerulosclerosis (FSGS) is a serious, rare, and heterogeneous kidney condition that affects adults and children of all ages. It is an important cause of proteinuria. FSGS disproportionately affects African Americans who also experience worse kidney survival outcomes compared to Whites. • FSGS requires a kidney biopsy for diagnosis. It is not a single disease; rather, it describes characteristic histopathologic findings of partial scarring of some glomeruli in the kidney. • FSGS is classified according to etiology as primary (usually immune-mediated), secondary, genetic, or FSGS of undetermined cause. Regardless of the etiology, the condition is characterized by injury to the podocytes (specialized cells in kidney glomeruli that are essential for normal filtration), which results in glomerular scarring. Podocyte loss, and subsequent injury to the parietal and capillary endothelial cells, lead to further scarring of the glomeruli and progression of disease. • Primary FSGS usually presents with the nephrotic	• FSGS is a heterogeneous, serious, rare, and progressive kidney condition that causes proteinuria, nephrotic syndrome, chronic kidney disease and kidney failure, resulting in the need for long-term dialysis or a kidney transplant to maintain life. • Patients with nephrotic syndrome usually have immune mediated disease, which is thought to be the key driver of disease progression. In contrast, in patients without nephrotic syndrome, other processes, such as maladaptive glomerular hemodynamics, and activation of pro-inflammatory and pro-fibrotic pathways are thought to lead to podocyte injury and loss and may play a more important role.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	syndrome and an immune-mediated process (attributed to a circulating permeability factors) is thought to be a key driver of disease progression. In contrast, in patients without nephrotic syndrome, other processes, such as maladaptive glomerular hemodynamics (chronic glomerular hypertension and hyperfiltration), and activation of pro-inflammatory and pro-fibrotic pathways leading to podocyte injury and loss may play a more important role.	
Current Treatment Options	• Currently, there are no approved pharmacologic treatments specifically for FSGS in the United States. • The standard of care (SOC) for all types of FSGS includes off-label use of renin-angiotensin-aldosterone system (RAAS) inhibitors. • In patients with nephrotic syndrome, SOC also includes management of nephrotic syndrome (diuretics, lipid lowering agents, anticoagulation) and immunosuppressive therapies such as glucocorticoids and calcineurin inhibitors with variable efficacy.	• There is unmet need for treatments for FSGS that can reduce the rate of loss of kidney function and progression to kidney failure.
Benefit	• As principal support for effectiveness, the Applicant submitted the results of DUPLEX, a phase 3, randomized, active-controlled trial in 371 adult and pediatric subjects aged 8 to 75 years with biopsy-proven FSGS or documentation of a genetic mutation in a podocyte protein associated with FSGS, UPCR ≥1.5 g/g, and eGFR ≥30 mL/min/1.73 m^2. The trial	• The submitted data demonstrate that sparsentan reduces proteinuria in the overall trial population; however, the magnitude of reduction varies depending on the analytic method used to handle missing data, the findings are not robust to tipping point analyses exploring different missing data assumptions,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	excluded patients with FSGS secondary to other conditions and recurrent FSGS after kidney transplant. • The trial was designed to support accelerated approval and met the proteinuria-based endpoint (FPRE) at interim analysis. However, the effect on FPRE was smaller than the assumed effect used to power the confirmatory phase of DUPLEX, and the total slope estimates did not favor sparsentan. As such, the Division recommended that the Applicant complete the ongoing trial and pursue traditional approval based on the results of the primary eGFR-based endpoint. *Findings in Overall Population* • At the final analysis, DUPLEX did not meet its prespecified eGFR-based endpoint. When using all available data and FDA's preferred approach to handing missing data (i.e., imputing death and initiation of renal replacement therapy based on the worst 5% of the observed data and multiple imputation for remaining missing data) the adjusted mean change from baseline to Week 108 in eGFR was -14.3 mL/min/1.73 m^2 in the sparsentan arm and -13.3 mL/min/1.73 m^2 in the irbesartan arm. Compared to irbesartan, the difference in the adjusted mean change from baseline to Week 108 in eGFR was -1.1 mL/min/1.73 m^2 (95% CI: -4.9, 2.8).	and the effect on proteinuria appears to reflect a reversible pharmacodynamic effect (as opposed to an effect on the underlying disease). • There is no consistent numerical trend in eGFR favoring sparsentan across various analytical models in the overall population. In some analyses, eGFR may, on average, be worse in the sparsentan arm compared with irbesartan, though analyses are challenging to interpret given the amount of missing eGFR data and the hemodynamic effects of sparsentan and irbesartan on eGFR. As such, there is uncertainty regarding whether sparsentan's effect on proteinuria will translate into a clinically meaningful effect on progression to kidney failure in the overall trial population. • FSGS is a heterogeneous condition, and key drivers of disease progression may be different in patients with and without nephrotic syndrome. Based on sparsentan's mechanism of action, patients without nephrotic syndrome might be expected to have a greater response to sparsentan than patients with nephrotic syndrome (which is primarily immune-mediated). • The subgroup without nephrotic syndrome comprised the majority of the overall trial population (approximately two thirds). Post-hoc

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Across all study visits, the adjusted mean decrease from baseline in eGFR was numerically greater (i.e., worse) in the sparsentan arm compared to the irbesartan arm. • In post hoc exploratory analyses conducted in the overall population, the relative percent change from baseline in UPCR between the sparsentan and irbesartan arms ranged from 20% to 26% depending on the multiple imputation approach used to handle the missing data (overall, 28% of randomized subjects did not have a UPCR assessment at Week 108). In the overall population, when imputing missing data according to the irbesartan arm from the timepoint of the missing value, and imputing ICEs of death and RRT based on the worst 5% of the observed data, UPCR reduction from baseline to Week 108 was 46% and 30% in the sparsentan and irbesartan arms, respectively, resulting in a nominally significant between arm (sparsentan-irbesartan) UPCR reduction from baseline to Week 108 of 22% (95% CI: 2%, 37%; p=0.03). • In an analysis of the Week 112, off study treatment data, when excluding data due to intercurrent events and using similar model assumptions as the Applicant's primary analysis, the geometric LS mean percent change from baseline to Week 112 in UPCR was -10% in the sparsentan arm and -24% in the irbesartan arm. Based on these results, sparsentan's	analyses conducted by the review team indicate that the magnitude of the treatment effect of sparsentan relative to irbesartan on proteinuria was larger in subjects without nephrotic syndrome compared to the overall trial population. • In contrast, there was no evidence of a treatment effect in subjects with nephrotic syndrome. Sensitivity analyses also indicate that the findings for proteinuria in subjects without nephrotic syndrome were robust to different missing data assumptions, despite a significant amount of missing data. • In these post hoc analyses, kidney failure event rates were numerically lower and eGFR was numerically better in the sparsentan as compared to the irbesartan arm in subjects without nephrotic syndrome. These findings provide reassurance that sparsentan's effect on proteinuria in this subgroup will likely translate into a clinically meaningful benefit on the rate of loss of kidney function and progression to kidney failure.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	effect on proteinuria seems to reflect a reversible pharmacodynamic effect (as opposed to an effect on the underlying disease). Post hoc analyses to assess for a sustained response did not indicate a clear responder population across the range of UPCR threshold from 0.3 g/g to 1.5 g/g. *Findings in Subjects Without Nephrotic Syndrome* • Given sparsentan's mechanism of action and because key drivers of disease progression may be different in patients with and without nephrotic syndrome, subgroup analyses were conducted in this subset. • In the subgroup of subjects without nephrotic syndrome (68% of the overall trial population), there was a 48% reduction in UPCR in the sparsentan arm compared to 27% in the irbesartan arm, translating to a 29% (95% CI: 8%, 44%) greater reduction in the ratio of the adjusted mean log-transformed UPCR at Week 108 from baseline in the sparsentan as compared to the irbesartan arm. In contrast, there was no difference between treatment arms in UPCR reduction from baseline to Week 108 in the subgroup of subjects with nephrotic syndrome (39% in sparsentan, 37% in irbesartan). • The adjusted mean change from baseline in eGFR at Week 108 in subjects without nephrotic syndrome was -11.2 and -12.2 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively,	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	resulting in a between group difference (sparsentan-irbesartan) of 1.0 mL/min/1.73 m^2 (95% CI: -2.6, 4.8). • Kidney failure event rates were numerically lower in the sparsentan as compared to the irbesartan arm in subjects without nephrotic syndrome. Three and eight subjects in the sparsentan and irbesartan arms, respectively, progressed to kidney failure (defined as a confirmed eGFR <15 mL/min/1.73 m^2 based on two consecutive measurements made at least 14 days apart, or initiated RRT) based on data up to Week 108. In the subgroup of subjects with nephrotic syndrome, 11 subjects from each arm met these criteria.	
Risk and Risk Management	• Sparsentan is approved for the treatment of primary IgAN at risk of disease progression. The current Prescribing Information (PI) includes a boxed warning for hepatotoxicity and embryofetal toxicity. Because of the risk of hepatotoxicity, sparsentan is available only through a restricted program under a REMS. The PI also includes a contraindication for sparsentan use in pregnancy, and concomitant use with ARBs, ERAs, or aliskerin. Warnings and Precautions include hypotension, acute kidney injury, hyperkalemia, and fluid retention. • In DUPLEX, 184 subjects (168 adults and 16 pediatric subjects 9 years of age and older) were exposed to sparsentan and 187 (168 adults and 19 pediatric subjects) to irbesartan for a median of 108 weeks.	• The submitted safety data together with the known safety experience with sparsentan in patients with IgAN are considered adequate to assess the safety of sparsentan in patients with FSGS. The safety profile observed in the DUPLEX trial is largely consistent with sparsentan's known safety profile. • Sparsentan is currently only available through a REMS for the treatment of IgAN because of the risk for hepatotoxicity. The REMS will also be extended to the FSGS population without nephrotic syndrome. To mitigate the risk of serious hepatotoxicity, serum aminotransferase levels and total bilirubin should be measured prior to initiation of sparsentan then every 3

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• SAEs occurred in 37% of subjects receiving sparsentan and 44% of subjects receiving irbesartan. Approximately 14% of subjects in the sparsentan arm and 12% of subjects in the irbesartan arm discontinued treatment because of an adverse event. • Risks of sparsentan observed in the DUPLEX trial were consistent with the risks described in the sparsentan PI. The most common adverse events that were ≥5% higher in frequency in the sparsentan arm compared to the irbesartan arm were hypotension including orthostatic hypotension, anemia and hyperkalemia. • There were no Hy's Law cases. Three subjects in the sparsentan group had aminotransferases >8 × upper limit of normal (1 subject with elevated aspartate aminotransferase (AST); 1 subject with elevated alanine aminotransferase (ALT); and 1 subject with both elevated AST and ALT). None of the subjects had elevations in AST or ALT accompanied by concurrently elevated total bilirubin.	months during treatment, and sparsentan should not be initiated in patients with serum aminotransferase levels greater than 3-times the upper limit of normal.

2.2. Conclusions Regarding Benefit-Risk

FSGS is a heterogeneous, rare, and serious kidney condition that commonly leads to progressive loss of kidney function and kidney failure requiring dialysis or kidney transplant to maintain life. While there are two approved products for the treatment idiopathic nephrotic syndrome, there are no approved medications for the treatment of adults or pediatric patients with FSGS. As such, there is significant unmet need.

Given the size of the treatment effect on proteinuria relative to irbesartan and with some analyses showing a numerically greater rate of kidney function decline in the sparsentan as compared to the irbesartan arm, there is uncertainty about whether the magnitude of proteinuria reduction will translate to a clinically meaningful effect on progression to kidney failure in the overall DUPLEX trial population.

The ability to sub-divide the heterogeneous FSGS population according to key drivers of disease progression is currently limited. The available DUPLEX trial data suggest a larger treatment effect on proteinuria in patients without nephrotic syndrome, a subgroup that might be expected to have a greater response to sparsentan given its mechanism of action than that seen in the overall trial population, which included patients with nephrotic syndrome. The DUPLEX trial was not adequately powered to demonstrate a treatment effect on proteinuria or rate of kidney function decline in the subgroup of patients without the nephrotic syndrome; however, the size of this subgroup (approximately two thirds of the overall trial population), the larger and statistically more robust reduction in proteinuria compared to irbesartan in this subgroup, as well as numerically favorable trends in the rate of loss of kidney function and kidney failure outcomes compared to irbesartan, provide support for effectiveness in this subgroup.

The major safety concern is the risk for hepatotoxicity. To ensure that the benefits of sparsentan for the treatment of FSGS without nephrotic syndrome outweigh this risk, sparsentan will only be available through a restricted program under a risk evaluation and mitigation strategy. Known risks of sparsentan including hypotension, anemia and hyperkalemia, occurred in patients with FSGS. No new safety findings will be added to the Prescribing Information based on the findings in patients with FSGS. Given the measures that will be put in place, sparsentan's benefits outweigh its risks in adult and pediatric patients 8 years and older with FSGS without the nephrotic syndrome.

3. Clinical and Statistical Assessment

3.1. Introduction

Sparsentan (Filspari) is a dual antagonist of the endothelin type A receptor (ETAR) and the angiotensin II type 1 receptor (AT1R), with high affinity for these receptors. Sparsentan is currently approved in the US to slow kidney function decline in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk of progression. On March 13, 2025, the Applicant submitted an efficacy supplement to support approval for the treatment of FSGS in adult and pediatric patients aged 8 years and older. As principal support for safety and effectiveness for the treatment of FSGS, the Applicant submitted the results of a randomized, double-blind, active-controlled study (DUPLEX).

FSGS is a serious, rare condition with unmet medical need. FSGS is an important cause of proteinuria and nephrotic syndrome (a constellation of heavy proteinuria, low serum albumin levels and swelling/edema). It is the most common primary glomerular disorder causing kidney failure in adult and pediatric patients in the United States (USRDS, 2023).

FSGS is not a single disease; rather, it encompasses a wide spectrum of diseases with their own pathophysiology that cause podocyte injury and death, all manifesting as a common histologic phenotype on kidney biopsy. The characteristic histopathologic lesion on microscopic examination of kidney biopsy tissue includes partial (segmental) scarring in some (focal) glomeruli (the filtering units of the kidney). Injury to podocytes, specialized cells in glomeruli that are critical for normal filtration, and which prevent most proteins (e.g., albumin) from being filtered and excreted in the urine, is believed to trigger the cascade of events that lead to FSGS. Podocyte injury and loss, and subsequent injury to other cells in the glomeruli including the parietal and capillary endothelial cells, lead to further scarring of the glomeruli and progression of disease.

More recently, studies in animal models of FSGS have suggested that the glomerular endothelium may play an early role in the pathogenesis of FSGS, and that there may be “cross-talk” between the glomerular endothelium and podocytes via paracrine and autocrine signaling (Ebefors K, 2019; Sun YBY, 2013). ETAR expression has been shown to be increased in the endothelial cells of glomeruli from patients with primary FSGS and may contribute to the pathogenesis of FSGS and disease progression (van de Lest NA, 2021).

FSGS is typically classified according to etiology as primary, secondary, genetic, or FSGS of undetermined cause (KDIGO 2021). Although the applicant has proposed a broad claim for the treatment of FSGS, based on the DUPLEX eligibility criteria, subjects with secondary forms of FSGS were to be excluded. As such, the discussion below focuses on primary and genetic FSGS.

Primary FSGS does not have a “secondary” identifiable (e.g., hyperfiltration, viral infections, drugs) or genetic cause, and is thought to be immune mediated, possibly due to circulating permeability factor(s), although these have not been identified. Genetic FSGS is caused by mutations in genes encoding proteins in the podocyte (e.g., nephrin, podocin) or glomerular basement membrane (e.g., laminin alpha-5). FSGS of undetermined cause typically includes

FSGS lesions with features suggestive of secondary FSGS on pathology, but without an identifiable cause.

All patients with FSGS have proteinuria (a manifestation of podocyte injury). Hypertension is common. Kidney function may be normal or decreased at presentation and generally decreases over time. Primary FSGS typically presents with rapid onset of nephrotic syndrome, characterized by heavy proteinuria, low serum albumin levels, and swelling/edema. Secondary FSGS is usually associated with variable and slower onset of proteinuria, and nephrotic syndrome is rare even if proteinuria is heavy. Histopathology could help to differentiate primary from secondary FSGS, in that podocyte foot process effacement on electron microcopy of kidney biopsy tissue is typically diffuse in primary FSGS and segmental in secondary FSGS, although these findings are not pathognomonic. In patients with primary FSGS, the reported rate of recurrent FSGS in the transplanted kidney is variable, but appears to be approximately 30%, and can lead to loss of the transplant kidney (Uffing A, 2020; Fine RN, 2007).

The presentation of genetic FSGS varies based on the genetic mutation. Patients with autosomal recessive mutations usually present during infancy or childhood, have severe nephrotic syndrome, and can progress rapidly to kidney failure. Patients with autosomal dominant mutations tend to present in adulthood, are less likely to have nephrotic syndrome, and progress to kidney failure more slowly. Genetic FSGS does not recur after kidney transplant.

Regardless of etiology, FSGS carries a poor prognosis. According to recent data from the UK National Registry of Rare Kidney Diseases, 10-year kidney survival rates for patients with FSGS are approximately 58% (95% CI, 55%, 61%), with mean (SD) annual rates of kidney function (as assessed by estimated glomerular filtration rate [eGFR]) loss of 6.2 (14.3) mL/min per 1.73 m^2 per year (Wong K, 2024). The disease exhibits significant racial disparities, with African Americans experiencing higher incidence rates and worse renal survival outcomes compared to whites, largely attributed to high-risk APOL1 gene variants (G1 and G2) that confer a 35-fold increased association with FSGS and predispose individuals to rapid progression to kidney failure (D'Agati VD, 2011; De Vriese AS, 2018).

Currently, there are no approved pharmacologic treatments specifically for FSGS in the United States. Two products are approved for the treatment of idiopathic nephrotic syndrome, i.e., corticosteroids (prednisone/prednisolone) and Acthar Gel (adrenocorticotropic hormone).

The etiology/classification of FSGS is critical for decisions about how patients with FSGS are managed. The current standard of care for all types of FSGS includes off-label use of renin-angiotensin-aldosterone system (RAAS) inhibitors, salt restriction, and in patients with nephrotic syndrome, treatment with diuretics, lipid lowering agents (e.g., statins), and anticoagulation. Adults with FSGS may also be treated with sodium glucose transporter 2 inhibitors (SGLT2i) and dietary protein restriction.

Patients with primary FSGS are usually also treated with immunosuppressive therapies (IST), including glucocorticoids (as first line) and calcineurin inhibitors (cyclosporine or tacrolimus). These treatments are associated with significant side effects and variable efficacy (KDIGO 2021). Approximately 28%-74% of adults with primary FSGS achieve complete remission of

proteinuria, and approximately 0%-50% achieve partial remission after 4 to 24 months of glucocorticoid therapy (KDIGO 2021). The risk of kidney failure is high in patients who do not respond to steroid therapy. Calcineurin inhibitors are effective in patients with steroid resistant FSGS; however, the rate of relapse after discontinuation is high. Other immunosuppressive agents that have been used include mycophenolate mofetil (MMF), rituximab, and adrenocorticotropic hormone.

Genetic FSGS is typically steroid-resistant and rarely responds to conventional immunosuppression (De Vriese AS, 2018).

3.2. Review Issue List

The review team identified the following efficacy review issues. These issues are discussed in Section 7.1.3.

1. Clinical significance of the treatment effect on proteinuria.
2. Sparsentan's effect on the rate of loss of kidney function (eGFR) and kidney failure events.
3. Impact of missing data on interpretation of the efficacy findings.
4. Efficacy in subjects without nephrotic syndrome.

No safety finding rose to the level of a key safety review issue.

3.3. Approach to the Review

Table 4 provides an overview of the clinical trials conducted in subjects with FSGS to support safety and effectiveness. The review focuses on the results of the phase 3 study, DUPLEX. Efficacy and safety data were reviewed by Christine Garnett, and the statistical review was completed by William Koh and Jared Kabara.

3.4. Approach to Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

   FILSPARI is indicated to reduce proteinuria in adult and pediatric patients aged 8 years and older with focal segmental glomerulosclerosis (FSGS) without nephrotic syndrome

2. SEE was established with:
   a. Adequate and well-controlled clinical investigation(s):
      ☐ Two or more adequate and well-controlled clinical investigations, OR
      ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations OR

b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence
OR
c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)

3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established

Table 4. Clinical Trials Submitted to Support Efficacy and/or Safety Determination

Trial Identity (NCT #)	Study Population	Trial Design	Regimen (Number Treated), Duration	Primary and Secondary Study Endpoints	Number of Subjects Planned; Actual Randomized	No. of Centers and Countries
Phase 3/ 021FSGS16010 /DUPLEX (NCT03493685)	Adults and pediatrics (8-18 years) with primary and genetic focal segmental glomerulosclerosis	Control type: active control Randomization: 1:1 ratio to sparsentan or irbesartan. Stratification by screening eGFR and UPCR Blinding: double-blind Subjects had the option to participate in an open label extension (OLE) period for up to 156 weeks, for a total of 268 weeks (double-blind and open label).	Drug: sparsentan Dosage: 800 mg QD (body weight >50 kg); 400 mg QD (body weight 20 to 50 kg) Number treated: 184 Irbesartan: 300 mg QD (body weight >50 kg); 150 mg QD (body weight 20 to 50 kg). Number treated: 187 Duration (quantity and units): up to 112 wk Sparsentan dose for the OLE Period was 800 mg QD (body weight >50 kg); 400 mg QD (body weight 20 to 50 kg).	Accelerated approval: Primary: The proportion of patients achieving FPRE, defined as UPCR ≤1.5 g/g (170 mg/mmol) and a >40% reduction from baseline of the Double-Blind Period in UPCR at Week 36 at the interim analysis Traditional approval: Primary: slope of eGFR over approximately 2 years Secondary: FSGS partial emission endpoint; change in eGFR from baseline to Week 112; acute and chronic slopes.	300 planned, 371 randomized A total of 226 (61%) subjects continued into the OLE Period.	179 centers in 22 countries
Phase 2/ RET-D-001/DUET (NCT01613118)	Adults and pediatrics (8-75 in US and 18 to 75 in Europe) with primary and genetic focal segmental glomerulosclerosis	Control type: active control Randomization: 1:1 ratio to sparsentan or irbesartan within each dose cohort	Drug: sparsentan (200 mg, 400 mg, and 800 mg QD) Irbesartan (150 mg QD titrated to 300 mg)	Primary: Change from Baseline to Week 8 in UPCR	109 randomized (73 sparsentan, 36 irbesartan)	45 centers in 3 countries

Source: Reviewer.
1 Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
2 If no randomization, then replace with “Actual Enrolled.”

Abbreviations: BID, twice daily; DB, double-blind; OLE, open label extension; MC, multicenter; N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; QD, once daily; R, randomized; h, hour; d, day; wk, week(s); mo, month(s); y, year(s)

Appears this way on original

4. Patient Experience Data

The review team considered the experience and perspectives shared by patients and caregivers during an Externally-Led Patient-Focused Drug Development Meeting on primary FSGS hosted by the National Kidney Foundation and NephCure Kidney International on August 28, 2020, in its benefit-risk assessment. The report highlighted the importance to patients of kidney failure as an outcome, as well as the unmet need for treatments that are effective in slowing the loss of kidney function in FSGS (National Kidney Foundation, NephCure Kidney International, 2021). The review team also considered letters and comments received from patients, caregivers, physicians, and patient advocacy groups during the review cycle (Table 5).

The Applicant included exploratory results of patient-reported outcomes (PRO) data collected in DUPLEX. PROs were assessed using health-related quality of life (HRQoL) questionnaires and included the Kidney Disease QoL Survey and the EQ-5D-5L for 315 adult subjects and the Pediatric QoL Inventory and the EQ-5D-Y for 29 pediatric subjects. The Applicant's analyses suggested that subjects' HRQoL assessments were similar between the sparsentan and irbesartan arms for both adult and pediatric populations. The DUPLEX study was not powered to evaluate differences in HRQOL between the two treatment arms and none of these HRQOL assessments were specifically targeted for the FSGS population.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	4
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting summary report	
☒	Other stakeholder meeting summary report	7.3.1 Efficacy Issues
☐	Observational survey studies	
☒	Other: (please specify) • Letter of support from Drs. (b) (6) and (b) (6)) • Letter of support from NephCure (December 9, 2025) and FSGS community petition (March 2, 2026) • Letter of support from American Kidney Fund (November 19, 2025, and February 25, 2026)	

5. Regulatory Background

There were numerous interactions with the Applicant over the course of the development program. DUPLEX was designed to support accelerated approval using an endpoint that compared the proportion of patients in each treatment arm who achieved an FSGS partial remission endpoint (FPRE), defined as a UPCR ≤1.5 g/g and proteinuria reduction >40% from baseline, at an interim analysis after the first 190 patients reached 9 months of treatment. According to the SAP (version 3.0), submitted to the Agency in January 2019, the endpoint that would verify the benefit in the confirmatory phase of the trial was eGFR slope from Week 6 to Week 108 (i.e., "chronic slope").

Key discussions pertaining to the design of the phase 3 program and study results

- In an Advice letter dated June 29, 2020, the Division

  - indicated that it did not agree with the chronic slope endpoint and recommended that the Applicant request a meeting to discuss the issue
  - raised concern about the proposed 2-sided alpha allocation of 0.05 for the FPRE endpoint, noting that to support accelerated approval, the effect on UPCR would need to be highly significant and clinically persuasive
  - asked the Applicant to address how they would account for uncertainty in the quantitative relationship between the effect on proteinuria at Week 36 and 2-year eGFR slope
  - expressed concerns about the Applicant's proposal to conduct a blinded "assessment of population comparability" after 190 subjects had been randomized to compare six baseline and demographic characteristics (i.e., age, log UPCR, eGFR, sex, race, and eGFR ≤ or >120 mL/min/1.73 m^2) with the characteristics of subjects included in the datasets used for the quantitative model
  - recommended that, in addition to the Applicant's proposal to handle missing data as missing at random (MAR) for the primary analysis and sensitivity analyses of eGFR slope, the Applicant should propose sensitivity analyses based on a "missing not at random" assumption that considers the reason data were missing.

- During a meeting with the Applicant on October 1, 2020, to discuss the issues raised in the June 29, 2020, Advice letter, the Division indicated that
  - it had not accepted chronic slope as an endpoint because of concern for potential bias with chronic slope, and that it generally recommended assessing effects on CKD progression using pre- and post-treatment values when drugs are expected to have a large acute hemodynamic effect on eGFR. The Division, however, also acknowledged issues related to the interpretability of such an endpoint for this program given how the trial was designed
  - the Applicant's proposal to change the primary analysis for the FPRE from a Cochran-Mantel-Haenszel (CMH) approach to a longitudinal mixed model with binary responses after substantial trial data had accrued would be a review issue

- A pre-NDA meeting was held on April 15, 2021, to discuss the results of the interim analysis to support accelerated approval. The Division indicated that the interim analysis results were unlikely to be adequate to support accelerated approval because the treatment effect on FPRE was much smaller than the assumed effect on FPRE used for power calculations for the confirmatory phase of DUPLEX, and the total slope estimates did not favor sparsentan. The Division indicated that it might be possible to submit an application for accelerated approval in the future, after additional data had accrued (i.e., data from the previously conducted interim analysis, enhanced by additional eGFR data).
- A Type A meeting on August 2, 2021, focused on the Applicant's proposal to use interim analysis data from January 2021 (discussed during the April 15, 2021, meeting) supplemented with additional "more mature" eGFR data with a data cutoff in April 2022, to support an application for accelerated approval. The Division expressed significant concerns regarding this approach, primarily related to the extent of unblinding and the proposed

timeline. The Division considered the trial to be fully unblinded, raising concerns about potential changes to the analytic plan influenced by trial data knowledge. Additionally, the Division questioned the timeline that could result in accelerated approval occurring almost simultaneously with full trial results.

  - The Applicant addressed these concerns by clarifying that subjects, investigators, site personnel, and those directly involved in conducting the study remained blinded. They emphasized that no changes had been made to the SAP since the interim analysis and that the April 2022 data cut was intended to allow Division review of more mature eGFR trends before accelerated approval.
  - While the Division agreed that no alpha adjustment was necessary for the planned exploratory eGFR analyses, they emphasized the need for further discussion on the issues raised. The Division acknowledged that the proposed data package could potentially support an accelerated approval application.

- On June 17, 2022, the Applicant met with the Division to discuss the additional eGFR data. The Division indicated that the information provided did not provide confidence that the confirmatory phase of DUPLEX was adequately powered to verify the clinical benefit. As such, the Division recommended that the Applicant pursue traditional approval based on the pre-specified endpoint that was intended to verify the clinical benefit (i.e., 2-year eGFR slope).

- On August 30, 2023, the Applicant met with the Division to discuss the topline results of DUPLEX and informed the Division that the study did not meet its prespecified 2-year eGFR-based endpoint. During that meeting, the Division stated that it did not believe the data were sufficient to support a marketing application and expressed concerns about the Applicant's proposed post-hoc analyses to support a marketing application i (b) (4)

  - The Division indicated that it was open to considering an argument that the DUPLEX trial was an active-controlled trial, but that to make such an argument, there would need to be a sufficient understanding of the treatment effect of the active control in the study population or an adequate understanding of the progression rate of appropriately matched historical controls.

- On January 8, 2025, the Applicant met with the Division to discuss their proposal to submit an efficacy supplement to support an indication for sparsentan for the treatment of FSGS using FPRE as an endpoint based on the preliminary findings of the Proteinuria and GFR as Clinical Trial Endpoints in FSGS (PARASOL) workgroup presented during a workshop in October 2024. The Applicant indicated that the analyses presented at the workshop suggested that eGFR was likely too variable in this population to be a feasible trial endpoint, and that UPCR reduction below certain thresholds could be a surrogate endpoint for progression to kidney failure in FSGS.
  - The Division indicated that while it was not likely to refuse to file the application, it had significant concerns regarding the data proposed to support a marketing application for

traditional approval of sparsentan for the treatment of FSGS. Key issues included the post-hoc nature of the analyses, the size of the treatment effect on proteinuria, and the adequacy of the data supporting proteinuria as a "validated" surrogate endpoint for kidney failure in FSGS. The Division also encouraged the Applicant to provide additional data or analyses in patients with FSGS with baseline characteristics similar to those in DUPLEX in their marketing application to support the clinical significance of the reduction in proteinuria observed in DUPLEX.

- The Division indicated that it was likely that the application would be discussed with an Advisory Committee and requested a list of experts the Applicant had consulted to assist in identifying unconflicted experts for the review process.

Other regulatory history

- On January 5, 2015, Orphan Drug Designation was granted for the treatment of FSGS.
- On January 22, 2021, the Division denied the Applicant's request for Fast Track Designation.

6. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

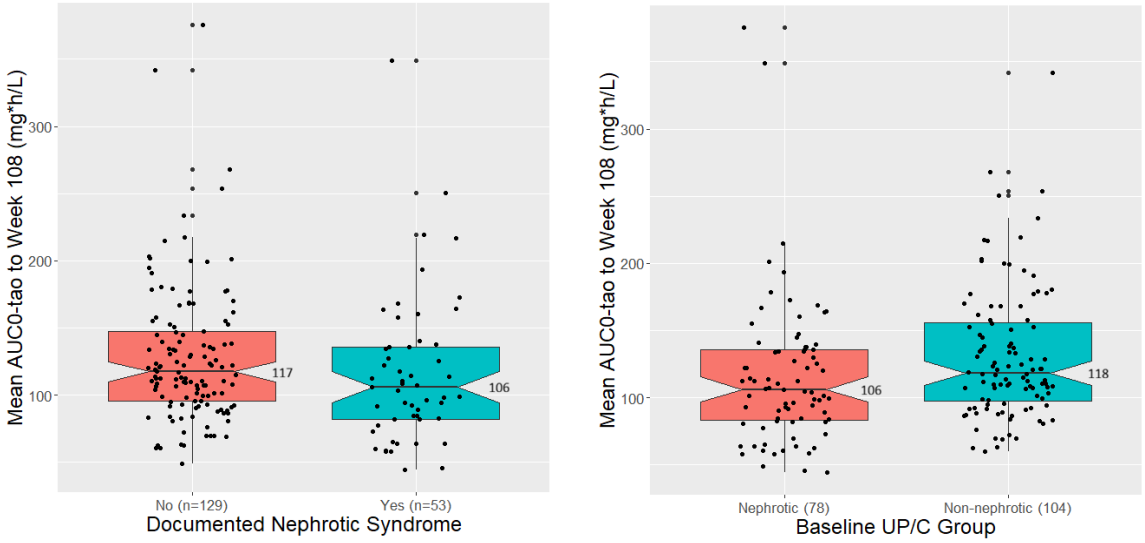
6.1. Office of Clinical Pharmacology

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in the application and concluded that the submitted pharmacokinetic and pharmacodynamic data, along with the dose selection rationale, were adequate to support approval.

Sparsentan is highly protein-bound and urinary excretion could be higher in FSGS patients with heavy proteinuria or nephrotic syndrome compared to patients without these features, which could impact sparsentan's PK. As such, additional analyses were conducted to assess whether the PK exposures of sparsentan were different in subjects with/without nephrotic syndrome (by medical history or meeting clinical criteria for nephrotic syndrome at baseline), and in subjects with nephrotic/non-nephrotic range proteinuria at baseline (nephrotic UPCR was defined as >3.5 g/g for subjects ≥18 years of age and >2 g/g for subjects <18 years of age; non nephrotic UPCR values were below these cutoffs for age. See also Section 7.1.2.1.2. and Table 11).

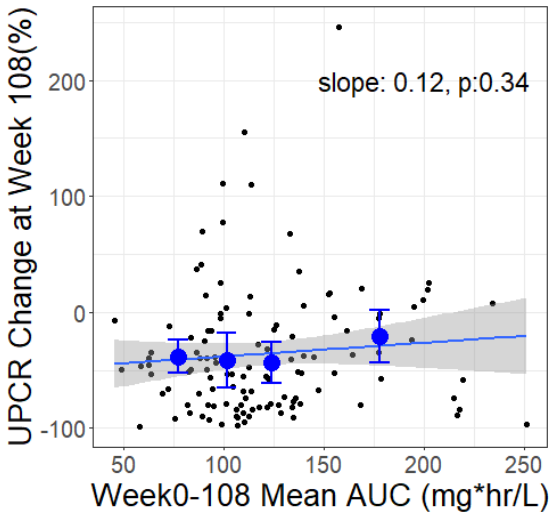
These analyses indicate that subjects with a history of nephrotic syndrome at baseline and those with nephrotic UPCR at baseline had 10-11% lower exposures than those subjects without these characteristics at baseline (Figure 1). As shown in the exposure-response relationship in Figure 2, these exposure differences had minimal impact on the magnitude of change from baseline to Week 108 in UPCR. As such, PK exposures alone may not be able to explain the treatment effect differences observed in efficacy subgroup analyses by baseline nephrotic syndrome status (yes vs. no) and/or baseline UPCR status (nephrotic vs. non-nephrotic).

Figure 1. Sparsentan PK Exposure Comparison by Documented Nephrotic Syndrome at Baseline (left plot) and Baseline UPCR Status (Right plot) for Sparsentan Treated Subjects



Source: FDA Reviewer's Analysis.

Figure 2. Exposure-Response Relationship for UPCR Change from Baseline at Week 108



Source: FDA Reviewer's Analysis.

7. Efficacy Evaluation

7.1. Duplex Trial

7.1.1. Trial Design

DUPLEX was a phase 3, randomized, multicenter, double-blind, parallel, active-control study to determine the safety, tolerability, and long-term nephroprotective potential of treatment with sparsentan as compared to irbesartan. The study enrolled subjects 8 to 75 years of age with biopsy-proven FSGS or a documented genetic mutation in a podocyte protein associated with FSGS, a UPCR ≥1.5 g/g, and eGFR ≥30 mL/min/1.73 m^2. The study excluded subjects with FSGS secondary to another condition, those with positive serological tests that were diagnostic of another primary or secondary glomerular disease, type 1 or uncontrolled type 2 diabetes mellitus, obesity-associated FSGS, or transplant recipients.

Subjects who had received rituximab, cyclophosphamide, or abatacept within 3 months before screening were excluded and other chronic immunosuppression (steroids, calcineurin inhibitors, mycophenolate mofetil, and azathioprine) had to be stable for ≥1 month before screening and during the screening period. The protocol "recommended" that systemic corticosteroid and/or immunosuppressive therapy for the treatment of FSGS be avoided for the duration of participation in the study; however, in the investigator's opinion, systemic corticosteroid and/or immunosuppressive therapy was warranted, such intervention could be provided in addition to study medication at the discretion of the investigator.

Subjects taking RAAS inhibitors at screening were required to complete a 2-week washout before Day 1/randomization. Subjects with hypertension were switched to non-RAAS antihypertensive agents during the washout period.

DUPLEX was initially designed to support accelerated approval for the treatment of FSGS based on effects on proteinuria at an interim analysis (effects on the FPRE defined as a UPCR ≤1.5 g/g and a proteinuria reduction >40% from baseline) and to verify the clinical benefit via an estimated glomerular filtration rate (eGFR) slope-based endpoint. However, based on the results of the interim analysis, the Division discouraged the Applicant from submitting the data to support accelerated approval (see Section 5).

An overview of the DUPLEX design is shown in Figure 3. The trial included a screening phase, a 2-week washout period in which subjects who were receiving RAAS inhibitors had their RAAS inhibitor therapy discontinued, a 108- week double-blind treatment period in which subjects were randomized 1:1 to sparsentan or irbesartan and a 4-week "no study medication" period in which treatment with study medication was discontinued and standard of care treatment including with ACEi/ARBs (other than irbesartan) was resumed.

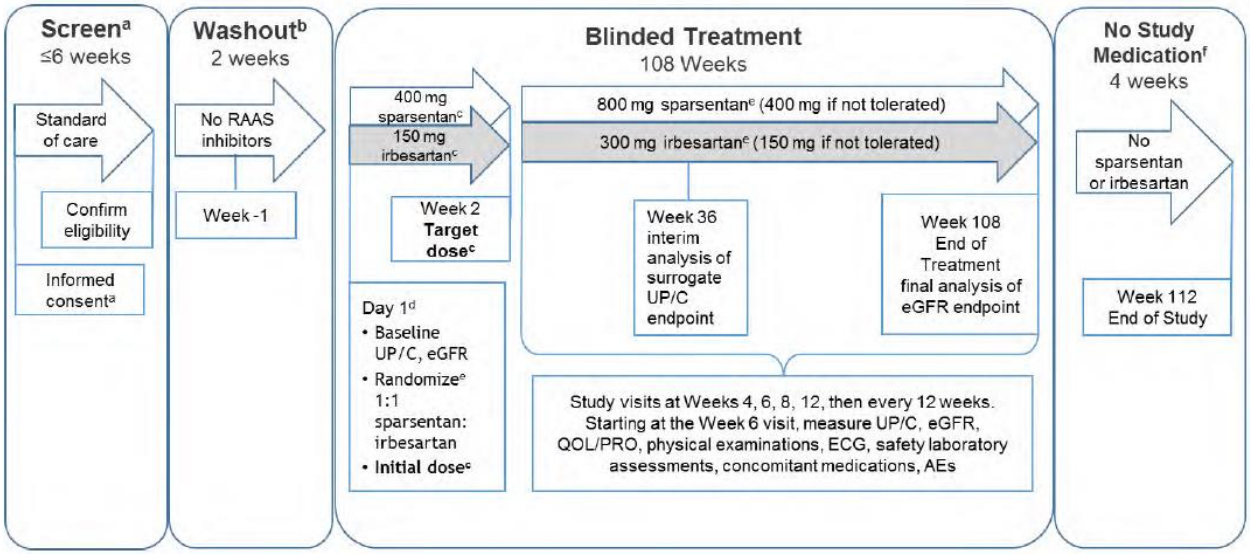
The dose of sparsentan and irbesartan was weight-based. Subjects weighing >50 kg received sparsentan 400 mg or irbesartan 150 mg once daily for 14 days; thereafter, the doses were titrated up to 800 mg and 300 mg once daily, respectively. For subjects weighing ≤50 kg,

sparsentan or irbesartan was initiated at 200 mg or 75 mg once daily, respectively, for 14 days then titrated up to 400 mg or 150 mg once daily, respectively.

Randomization was stratified by eGFR (30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and UPCR (≤3.5 g/g and >3.5 g/g [396 mg/mmol; subjects ≥18 years of age] or ≤2 g/g and >2 g/g [226 mg/mmol; subjects <18 years of age]) at screening. Subjects who permanently discontinued study medication during the double-blind period were encouraged to continue study visits through Week 112 for continued collection of safety and efficacy data despite stopping study medication.

Following the "no study medication" period, eligible subjects could be enrolled in an OLE of up to 156 weeks, for a total study duration of up to 268 weeks. Subjects who permanently discontinued study medication during the OLE were encouraged to complete the final visit assessments and no other study visits were necessary.

Figure 3. DUPLEX Trial Design



Source: Applicant's Figure 1 in DUPLEX clinical study report.
a. Screening was to begin after informed consent had been signed. The screening window was to begin on the day of the subject's first in-clinic study procedure. Subjects were to be screened within the 6-week screening period; however, under extenuating circumstances the screening period may have been extended by a maximum of 2 weeks.
b. For subjects who were undergoing washout from RAAS inhibitors.
c. Subjects whose body weight was ≤50 kg at screening received one-half the otherwise specified doses of either sparsentan or irbesartan (active control).
d. Day 1 events shown were to occur in the order in which they are listed.
e. Randomization was stratified by eGFR value (≥30 to <60 mL/min/1.73 m2 and ≥60 mL/min/1.73 m2 for all subjects) and UPCR (≤3.5 g/g and >3.5 g/g [396 mg/mmol; subjects ≥18 years of age] or ≤2 g/g and >2 g/g [226 mg/mmol; subjects <18 years of age]) at screening.
f. Following the 108-week blinded treatment period, treatment with study medication was discontinued and subjects could be evaluated for eligibility in the OLE.
Abbreviations: AE, adverse event; ARB, angiotensin receptor blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; OLE, open label extension; RAAS; renin-angiotensin-aldosterone system; PRO, patient reported outcome; UPCR, urine protein/creatinine ratio; QoL, quality of life

7.1.1.1. Eligibility Criteria

Key Inclusion Criteria

- Biopsy-proven FSGS lesion(s) or documentation of a genetic mutation in a podocyte protein associated with FSGS
- Sites within the US and UK: Male or female, aged 8 to 75 years, inclusive, weighing ≥20 kg, at screening (sites outside the US and UK: male or female, aged 18 to 75 years, inclusive, weighing ≥20 kg at screening)
- UPCR ≥1.5 g/g (170 mg/mmol) at screening
- eGFR ≥30 mL/min/1.73 m^2 at screening
- Mean seated blood pressure ≥100/60 mmHg and ≤160/100 mmHg (subjects ≥18 years of age) or between the 5^{th} and 95^{th} percentile for age, sex, and height (subjects <18 years of age)
- Women of childbearing potential, beginning at menarche, must agree to the use of 1 highly reliable (i.e., can achieve a failure rate of <1% per year) method of contraception from 7 days prior to the first dose of study medication until 90 days after the last dose of study medication. One additional barrier method must also be used during sexual activity, such as a diaphragm or diaphragm with spermicide (preferred), or male partner's use of male condom or male condom with spermicide (preferred), from Day 1/Randomization until 90 days after the last dose of study medication. Prior to menarche, pregnancy testing and contraceptive use are not required. However, the subject and their parent/guardian must be advised that, immediately upon menarche, the subject will be required to begin pregnancy testing and initiate contraceptive use.

Key Exclusion Criteria

- FSGS secondary to another condition
- Positive findings on serological tests that, in the investigator's opinion, are diagnostic of another primary or secondary glomerular disease
- History of type 1 diabetes mellitus, uncontrolled type 2 diabetes mellitus (hemoglobin A1c >8%), or non-fasting blood glucose >180 mg/dL (10.0 mmol/L) at screening
- Undergone organ transplantation, except for corneal transplants
- Documented history of heart failure (New York Heart Association Class II-IV) and/or previous hospitalization for heart failure
- Clinically significant cerebrovascular disease and/or coronary artery disease within 6 months prior to screening
- Has jaundice, hepatitis, or known hepatobiliary disease (excluding asymptomatic cholelithiasis), or ALT and/or AST >2 times the upper limit of the normal range at screening
- Screening hematocrit <27% (0.27 L/L) or hemoglobin <9 g/dL (90 g/L)

- Screening potassium >5.5 mEq/L (5.5 mmol/L)

7.1.1.2. Study Endpoints

Primary and Key Secondary Endpoints

As previously noted, DUPLEX was initially designed to support accelerated approval based on effects on proteinuria at an interim analysis and to verify the clinical benefit via an eGFR slope-based endpoint.

The endpoint intended to support accelerated approval in the US was FPRE, defined as UPCR ≤1.5 g/g and a >40% reduction from baseline in UPCR based on first morning void urine samples at Week 36 and the interim analysis to support accelerated approval was to be conducted in the first 190 subjects who had completed 36 weeks of treatment.

The endpoint intended to support traditional approval in the US was eGFR slope following randomization until the end of the double-blind period (i.e., from Day 1 to Week 108; total slope over 2 years).

In the US, the key secondary endpoints were:

1. eGFR slope from Week 6 to Week 108
2. Change in eGFR from baseline to 4 weeks after discontinuation of randomized treatment at Week 112

In non-US countries, the primary efficacy endpoint was the eGFR slope from Week 6 to Week 108. The key secondary endpoints in non-US countries outside US were:

1. Percent change in eGFR from Week 6 to Week 108
2. Percent change in eGFR from baseline to 4 weeks post-cessation of randomized treatment at Week 112
3. eGFR slope from baseline to Week 108

Planned Exploratory Endpoints (Based on SAP and Protocol Amendment 6 finalized on December 01, 2020)[1]

eGFR Endpoints

- eGFR chronic slope over 1 year
- eGFR total slope over 1 year
- eGFR absolute change from baseline at each visit
- eGFR percent change from baseline at each visit
- eGFR percent change from Week 6 (at each visit beginning at Week 8 and using Week 6 as baseline instead)

[1] There were subsequent amendments to the protocol following the interim unblinding efficacy looks. The planned exploratory endpoints did not differ between protocol amendment 6 and protocol amendment 8.

UPCR Endpoints

- Proportion of subjects achieving FPRE at each visit
- UPCR percent change from baseline at each visit
- Time to achieve FPRE

Other Endpoints

- The proportion of subjects reaching a confirmed 40% reduction[2] in eGFR, ESRD, or death. ESRD was defined as initiation of RRT[3] during the study or sustained eGFR <15 mL/min/1.73[2] while on treatment (confirmed after repeat assessment of at least 14 days after initial assessment).
- The proportion of subjects reaching a confirmed 30% reduction in eGFR, ESRD, or death
- Changes from baseline of the double-blind period in blood pressure at each visit
- Changes from baseline of the double-blind period in QOL scores (including KDQOL, PedsQL, EQ-5D-5L index value and VAS, EQ-5D-Y VAS), measured via PRO at each visit beginning at Week 12
- Proportion of subjects requiring initiation of or intensification in immunosuppressive medication during the study
- Proportion of subjects undergoing reduction in immunosuppressive medication during the study
- Time to initiation or intensification in immunosuppressive medication during the study
- Frequency and number of hospitalization days
- Trough plasma pharmacokinetic (PK) concentrations during the double-blind period

Post-hoc Exploratory Endpoints (After Study was Unblinded for the eGFR)

As discussed in Sections 5 and 7.1.2.2, DUPLEX did not meet its primary endpoint. In support of the proposed indication, the Applicant submitted post-hoc analyses of the following endpoints:

- Time to complete remission (defined as UPCR <0.3)[4] of proteinuria
- Time to near complete remission of proteinuria defined using various thresholds of UPCR <0.5 g/g, <0.7 g/g, <1.0 g/g, <1.5 g/g
- Proportion of subjects achieving complete remission of proteinuria at any time during the double-blind period
- Proportion of subjects who were in sustained complete remission of proteinuria during the study (based on only one confirmed assessment of proteinuria)

[2] Reduction of eGFR required confirmation by a value at least 4 weeks after the initial value. If the last value on randomized treatment was the initial value for reduction or eGFR <15 mL/min/1.73[2], then the last value on randomized treatment was considered confirmed or sustained.
[3] Initiation of RRT is based on the Concomitant Procedures section of the electronic case report form (eCRF) with fields in listed as “chronic dialysis” or “kidney transplant”, or on the Adverse Events section of eCRF listed as “progression of CKD leading to chronic dialysis” or “progression of CKD requiring kidney transplant.”
[4] Reported in Rheault MN, 2023

- Proportion of subjects achieving near-complete remission of proteinuria at any time during the double-blind period defined using various thresholds of UPCR <0.5 g/g, <0.7 g/g, <1.0 g/g, <1.5 g/g
- Durability of complete remission of proteinuria
- FPRE at any time during the study
- The proportion of subjects reaching a confirmed 50% reduction in eGFR, ESRD, or death.
- The proportion of subjects reaching a confirmed 50% reduction in eGFR, ESRD, or renal death.
- Proportion of subjects who have ESRD
- Time to confirmed 40% reduction in eGFR, ESRD, or death
- Time to confirmed 40% reduction in eGFR

Definition of near-complete remission was not well-defined in the clinical study report (CSR). In the CSR, various UPCR threshold values such as 0.5 g/g, 1.0 g/g, 1.5 g/g were used, and 0.7 g/g was included in the summary of clinical efficacy.

7.1.1.3. Statistical Analysis Plan

The statistical analysis plan (SAP), which was drafted on September 26, 2017, was amended four times and finalized on January 4, 2021 (version 4.0). Up to version 3.1 of the SAP, all primary statistical analyses of the endpoints were specified to include all data collected regardless of adherence to randomized treatment. In version 4.0, the SAP was modified to use an on-treatment analysis for all primary statistical analyses of the endpoints, and the multiplicity procedure was separated into US and non-US countries. This final SAP revision did not align with what was pre-specified in the statistical analysis section of the study protocol, which was written to address a treatment policy estimand.

Table 6 shows the relevant unblinding dates, dates of finalization of each SAP version, and the corresponding number of subjects screened and randomized. The Agency reviewed version 3.0 of the SAP, dated January 8, 2019, and key comments were conveyed to the Applicant related to (1) disagreement with the proposed primary endpoint based on the rate of decline in eGFR assessed from Week 6 to Week 108, (2) concerns regarding the Applicant's proposal for potential accelerated approval, (3) multiplicity assessments, (4) sample size re-estimation methodology using promising zone, and (5) assumptions regarding the handling of missing data for the primary analysis. Version 3.1 of the SAP was finalized on August 25, 2020. An unblinded sample size re-assessment based on conditional power was conducted on September 2, 2020. On January 4, 2021, SAP version 4.0 was finalized. An interim efficacy assessment was conducted based on the FPRE endpoint. The Agency did not review SAP version 4.0, submitted just prior to the interim efficacy look. The final database lock was on April 16, 2023.

Table 6. Relevant Unblinding Dates and SAP Version Timestamp with Number of Subjects Screened, and Randomized, DUPLEX

Date	SAP Versions/Relevant Unblinding Activities	Subjects Screened (N=724)	Subjects Randomized (N=371)
September 26, 2017	SAP version 1.0	0 (0%)	0 (0%)
January 19, 2018	SAP version 2.0	0 (0%)	0 (0%)
January 8, 2019	SAP version 3.0	38 (5%)	12 (1%)
August 25, 2020	SAP Version 3.1	538 (74%)	246 (66%)
September 2, 2020	Sample size re-estimation [1]	551 (76%)	249 (67%)
January 4, 2021	SAP version 4.0	724 (100%)	368 (99%)
January 22, 2021	Interim Efficacy Look	724 (100%)	371 (100%)
November 19, 2024	Final Database Lock	724 (100%)	371 (100%)

1 Unblinded interim efficacy look based on the first 50 randomized subjects who completed Week 60 visit.
Abbreviations: SAP, statistical analysis plan.
Source: Statistical Review Team

Sample Size

The sample size for the proportion of subjects achieving FPRE was based on the results at Week 8 of the phase 2 DUET study. Assuming a response rate of 20% and 50%, in the irbesartan and sparsentan arms, respectively, the SAP specified that using the Pearson chi-square test for two proportions and a 2-sided α level of 0.05, a total of 190 subjects (95 per treatment arm) would provide at least 90% power to detect a difference in response proportions between sparsentan and irbesartan on the relative scale.

Sample size calculations were specified for eGFR chronic slope. In SAP version 3.1 (prior to sample size re-estimation), it was assumed that the difference in eGFR slopes between FPRE responders and non-responders would be approximately 8.4 mL/min/1.73 m^2 per year. With the assumed treatment difference in response proportions of 30%, the treatment difference in eGFR slopes was expected to be approximately 2.52 mL/min/1.73 m^2 per year and the residual standard deviation was assumed to be 10.80 mL/min/1.73 m^2 per year. Using these assumptions, a 2-sided α of 0.05, a sample size of 300 subjects (approximately 150 per treatment arm) would have at least 90% power to detect a slope difference of at least 2.5 mL/min/1.73 m^2 per year. The study would have at least 80% power if the underlying difference in eGFR slope was at least 2.0 mL/min/1.73 m^2 per year. With 300 subjects, the minimum treatment difference in eGFR slope would be at least approximately 1.40 mL/min/1.73 m^2 per year. Power calculations followed the approach described in Dupont and Plummer (Dupont WD, 1998).

The total slope sample size calculations were only included in SAP version 4.0 after the sample size re-estimation. According to the SAP, for the eGFR total slope, the study would have at least 90% power to detect an eGFR total slope difference of at least 2.1 mL/min/1.73 m^2 per year, assuming a standard deviation of 5.5 mL/min/1.73 m^2 per year obtained from the blinded interim data for DUPLEX.

Interim Analysis for Sample Size Re-assessment

A sample size reassessment (SSRE) procedure, conducted by the Data Monitoring Committee (DMC), was planned when the first 50 randomized subjects completed the Week 60 visit. The

SAP specified the methodology described by Mehta and Pocock (Mehta CR, 2011) for SSRE and the conditional power was computed based on the observed estimate of the eGFR over the treatment period. If the conditional power was 50% to 80%, the sample size would be increased accordingly to increase power, to a maximum sample size of 300*1.35 (405 subjects). If the conditional power was outside the range, the trial would continue without an increase in sample size.

Data Monitoring Committee

An independent DMC oversaw the safety and overall conduct of this study. The DMC consisted of four members with expertise in nephrology, hypertension, clinical pharmacology, and statistics. An independent clinical research organization (CRO) was responsible for the open and closed session reports and had access to unblinded data. An independent CRO reporting biostatistician performed the SSRE at the interim analysis.

Inadvertent Increase in the Sample Size of DUPLEX Based on Comparative Interim eGFR Data

The planned sample size for DUPLEX was 300 subjects. On September 2, 2020, an SSRE using comparative interim eGFR data was conducted as prespecified in the SAP when the first 50 randomized subjects completed the Week 60 visit; the data cut off for the SSRE was August 12, 2020. According to the prespecified plan, if the conditional power at SSRE was 50 to 80%, the sample size could be increased from 300 to a maximum of 405 subjects. On September 2, 2020, the DMC recommended "No increase in sample size" after the SSRE.[5] However, the study continued enrollment and randomized 371 subjects, i.e., 24% more subjects than originally planned. This was inconsistent with the DMC recommendation and as well as the SAP. Since this interim look was based on comparative interim eGFR data, it was unclear whether unblinded interim eGFR results could have been inadvertently communicated or inferred based on the DMC recommendation.

During the review of the application, the Agency requested information on the larger than planned sample size of 371. The Applicant stated that "Upon receipt of the DMC's SSR recommendation, Travere notified the sites that screening would close soon."

- According to the Applicant's submission,[6] the Applicant emailed study sites on October 8, 2020, stating that 761 subjects had been screened (the review team noted only 609 subjects had been screened based on the number who had signed an informed consent by October 8, 2020), 267 subjects had been randomized (confirmed by statistical review team), and that screening would close when 820 subjects had been screened globally.

[5] According to the DMC recommendation form.

[6] "\\CDSESUB1\evsprod\NDA216403\0141\m5\53-clin-stud-rep\535-rep-effic-safety-stud\fsgs\5351-stud-rep-contr\021fsgs16010\duplex-site-comms.pdf"

- When close to 300 subjects had been randomized, the Applicant had notified the sites/investigators by email on November 6, 2020, that subjects who had signed an informed consent on or before November 6, 2020, would be eligible for randomization.
- Based on the review of the database, the Agency noted that a total of 720 subjects had been screened and 290 had been randomized as of November 6, 2020.
- In response to an information request , the Applicant stated that with the large number of subjects in screening, "in the best interest of the subjects, Travere made the decision that any patient who signed an informed consent form and started screening before the deadline, and met all study criteria, would be allowed to participate if they had consented prior to the deadline."
- This led to 724 subjects being screened and 371 subjects being randomized.

Based on review of the submitted documents, the statistical review team noted that at the time of the unblinded SSRE, the amount of statistical information based on 50 subjects was small and few subjects had one year or more of eGFR data. Thus, the risk of potential unblinding of interim eGFR efficacy data was minimal. Based on the explanation provided by the Applicant, the review team did not disagree with the Applicant's decision regarding over-enrollment.

Of note, this sample size increase resulted in higher study power than originally planned for the eGFR endpoint (assuming the other assumptions in the power calculation were valid). As such, the study was adequately sized to have enough power to detect a treatment effect on eGFR that might be smaller than the minimum treatment effect specified in the sample size calculations (assuming the other assumptions in the power calculation were valid).

In summary, despite the DMC's recommendation not to increase the sample size based on the prespecified plan for SSRE, given the rapid rate of enrollment, the Applicant permitted the enrollment of additional subjects who had already signed an informed consent and had been screened, to be enrolled, resulting in the enrollment of at least 24% more subjects than planned. The statistical review team concluded that there was limited statistical information at the interim to infer any trends in eGFR even if by arm results were available to the Applicant. Further, the statistical review team agrees that enrollment was more rapid after the Applicant announced the deadline to cease enrollment following the interim efficacy look and that it was not reasonable to exclude the screened subjects at the specified date. However, from an operational perspective, the statistical team does not consider this to be appropriate study conduct following a planned interim SSRE.

Efficacy Analysis Set

The full analysis set (FAS) included all subjects who were randomized and took at least one dose of randomized therapy.

Multiplicity Testing

The study was originally designed to support accelerated approval based on effects on FPRE at the interim analysis, with confirmation of the clinical benefit based on effects on eGFR at the final analysis. The alpha control strategy for the US is described below.

At the interim analysis, the proportion of subjects achieving FPRE at Week 36 was evaluated using a 2-sided α of 0.05. If the test was significant, the study would continue to the final time-point when all subjects completed Week 112. Otherwise, the study would be stopped.

The hierarchical testing for the US was to be performed sequentially at a 2-sided α of 0.05 in the following order and testing would be stopped if an endpoint was not statistically significant:

1. eGFR total slope over 2 years at the final analysis
2. eGFR chronic slope over 2 years at the final analysis
3. Change in eGFR from baseline of the double-blind period to 4 weeks post-cessation of randomized treatment at Week 112

Handling of Intercurrent Events

General considerations

For the planned statistical analysis of the efficacy endpoints specified in the SAP, any data collected after treatment discontinuation were to be excluded from the statistical analysis model. Per the assumptions of the statistical model, these "missing data" (including missing data following death, or missing data due to incomplete outcome assessment) were assumed to be missing at random (MAR) according to the statistical model and their future outcomes were "imputed" according to the remaining subjects who did not discontinue randomized treatment.

Of note, such an approach is generally more in line with a hypothetical strategy. Generally, the Division does not recommend such a strategy for handling treatment discontinuations and generally prefers a treatment policy strategy for handling subjects who discontinue treatment prematurely, as this strategy best preserves the intent of randomization.

This scenario has limited clinical interest because the expectation in clinical practice is that patients who permanently discontinue treatment for a clinical reason(s) would not resume treatment. Moreover, the assumption that the future outcomes in subjects who discontinue treatment prematurely would be similar to those who remain in the trial does not seem plausible (i.e., subjects who discontinue treatment prematurely are likely different from those who remain in the trial on study medication).

For these reasons, using a MAR assumption for estimation of the hypothetical estimand is not considered appropriate.

Analysis of change from baseline to Week 112

Both sparsentan and irbesartan can cause a reversible pharmacodynamic effect on eGFR. Generally speaking, when there is concern that a treatment can have a large reversible pharmacodynamic effect on eGFR, the Division advises Sponsors to take all study subjects off of the study medication at the end of the study and assess eGFR in all subjects after an adequate washout period (i.e., a period that is long enough for the pharmacodynamic effect to reverse). The efficacy of the drug in slowing kidney disease progression is then assessed using the change in eGFR from baseline to that timepoint. In DUPLEX, Week 112 (i.e., a timepoint 4weeks post-treatment cessation) was used for this assessment. However, the Applicant uses a principal

stratum strategy in the analysis, which limits the statistical analysis to only those on treatment completers and is dependent on unverifiable assumptions.

Planned Statistical Analysis Model for the Primary and Key Secondary Endpoints

The statistical analysis for the estimation of the rate of eGFR decline from baseline (Day 1) through Week 108 was to use a random coefficient model using random slope and random intercept. The model included baseline continuous eGFR, continuous analysis visit week, treatment group, treatment by continuous analysis visit week, and randomization stratification factors (combination of screening eGFR categories and nephrotic status based on UPCR). Specifically, screening eGFR was categorized as ≥30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2. Screening UPCR was categorized as non-nephrotic for UPCR ≤3.5 g/g and nephrotic for UPCR >3.5 g/g for subjects ≥18 years of age. For subjects aged <18 years of age, screening UPCR was categorized as non-nephrotic for UPCR ≤2 g/g and nephrotic for UPCR >2 g/g.

For the chronic slope analysis (defined from Week 6 through Week 108), the piece-wise random coefficient model (with cut-point defined at Week 6) allowing for random slopes and random intercepts, was to be used. The model included baseline eGFR, treatment group, continuous time from baseline, continuous time from the change point at Week 6, treatment group by continuous time from baseline interaction, treatment group by continuous time from the change point at Week 6 interaction, and randomization stratification factors.

The change from baseline in eGFR on the absolute scale and the change from baseline in log UPCR were to be evaluated using a mixed model repeated measures (MMRM) regression. Both models included the continuous baseline measurement (or continuous log UPCR for the UPCR endpoint), categorical analysis visit week, treatment group, treatment by categorical analysis visit week, and randomization stratification factors.

For the change in eGFR from baseline to 4-weeks post cessation of randomized treatment at Week 112, an analysis of covariance model based only on the subset of subjects who had not discontinued randomized treatment at Week 108 was to be used.

For both the random coefficient and MMRM models (Sabanes BD,2025), the unstructured variance covariance was to be used to model the within subject errors. The method of Kenward-Roger was to be used to estimate the denominator degrees of freedoms. If convergence issues arose, the autoregressive-1 covariance structure would be used.

For binary responder endpoints, the Applicant had specified a repeated measures generalized linear model with logit link function adjusting for randomization stratification factors, treatment, categorical analysis visit, and interaction of treatment with categorical analysis visit. The proposed methodology generally addresses a conditional quantity and does not target a marginal risk difference interpretation. See Additional Statistical Analysis section for further discussion.

Planned Subgroup Analysis

As specified in the SAP, subgroup analyses were planned for the following baseline subgroups of interest:

- Age categories: <18, ≥18 years
- Age categories at FSGS diagnosis: <18, ≥18 years
- Sex: Male, Female
- Race: White, Black, Asian, Others
- Baseline body mass index (BMI) (kg/m^2): <27, ≥27
- Randomization strata:
    - Screening eGFR 30 to <60 mL/min/1.73m^2 and non-nephrotic (screening UPCR ≤3.5 g/g for subjects ≥18 years of age and ≤2 g/g for subjects <18 years of age)
    - Screening eGFR 30 to <60 mL/min/1.73m^2 and nephrotic (screening UPCR >3.5 g/g for subjects ≥18 years of age and >2 g/g for subjects <18 years of age)
    - Screening eGFR ≥60 mL/min/1.73 m^2 and non-nephrotic (screening UPCR ≤3.5 g/g for subjects ≥18 years of age and ≤2 g/g for subjects <18 years of age)
    - Screening eGFR ≥60 mL/min/1.73 m^2 and nephrotic (screening UPCR >3.5 g/g for subjects ≥18 years of age and >2 g/g for subjects <18 years of age)
- Baseline eGFR (mL/min/1.73 m^2):
    - <60, 60 to <120, ≥120
    - <120, ≥120
- Baseline UPCR (g/g):
    - Non-nephrotic (≤3.5 for subjects ≥18 years of age and ≤2 for subjects <18 years of age)
    - Nephrotic (>3.5 for subjects ≥18 years of age and >2 for subjects <18 years of age)
- Prior use of the following RAAS inhibitors: Yes, No
    - ACE inhibitors
    - Angiotensin II receptor blockers (ARBs)
    - Aldosterone blockers
    - Aliskiren
    - Any RAAS inhibitors
- Baseline use of the following medications: Yes, No
    - Any immunosuppressive agents
    - Steroids
    - Other immunosuppressive agents including CNIs, MMF, azathioprine, ACTH
    - Antihypertensive medications (except RAAS inhibitors) including diuretics
    - Diuretics
    - Statins and other hypolipidemic drugs
- Years since FSGS diagnosis: ≤10, >10
- Geographic region: North America, Europe, Asia Pacific, South America
- Baseline cardiovascular history: Yes, No
- History of hypertension: Yes, No

- Known mutation in podocyte proteins: Yes, No

For the relevant continuous efficacy endpoints included in this review (eGFR and UPCR), subgroup analyses using the primary statistical analysis model were conducted within each subgroup level. Some analyses were not conducted by the review team because the number of subjects in a subgroup was too small. Additional subgroup analyses were also conducted based on ethnicity (defined by Hispanic, not Hispanic), and region (US vs outside of US), and documented nephrotic syndrome at baseline (Yes vs No).

Post-hoc Exploratory Endpoints/Analyses

The Applicant's Summary of Efficacy document included numerous post-hoc exploratory analyses of proteinuria. Examples include proportion of subjects achieving FPRE at each visit from Week 6 to Week 108, complete remission (defined as UPCR <0.3 g/g) at any time, and the proportion of subjects achieving UPCR cutoffs of <0.5, <0.7, <1.0, and <1.5 g/g at any time. Most of these endpoints lacked a clear definition. For example, the Applicant's "analysis of the proportion of subjects who achieved complete proteinuria remission at any time on treatment over the course of the double-blind period" did not specify how this endpoint was defined. Some of these exploratory analyses are discussed in this review.

Sensitivity Analyses of the Primary and Key Secondary Endpoints

The Applicant pre-specified the following sensitivity analyses in the SAP:

- Multiple imputation using MAR assumption
- Analysis of the endpoint using only subjects who completed the blinded treatment (non-randomized subgroup)
- Analyses including local laboratory data
- A tipping point analysis based on MAR assumption

None of the sensitivity analyses included all the observed data collected regardless of adherence to randomized treatment. In addition, all these analyses assumed missing data were implicitly MAR according to the MMRM model, which is not reasonable. There were no specific strategies to handle missing data, whether excluded due to the occurrence of an intercurrent event or not.

Exploratory Endpoints and Post-hoc Analyses Conducted by the Review Team

Given concerns that the approaches prespecified in the SAP to analyze the data relied on an implicit missing at random assumption, the review team conducted additional analyses to address intercurrent events as discussed below.

<u>Handling of Intercurrent Events</u>

Table 7 shows the intercurrent events that were identified during the review and how they were addressed for continuous and binary endpoints.

Table 7. Handling of Intercurrent Events by the Statistical Review Team by Endpoint Type

No	Intercurrent Event	Continuous	Binary
1	Treatment discontinuation	Treatment policy	Treatment policy
2	Receipt of kidney transplant or initiation of chronic dialysis	Hypothetical strategy	Failure for the endpoint
3	Death	Hypothetical strategy	Failure for the endpoint

Source: Statistical Team

For intercurrent events 2 or 3, the following strategies were considered when evaluating continuous eGFR or UPCR endpoints.

A. The subject outcome would continue to be predicted based on the remaining subjects with future data according to the regression model (what the Applicant had implicitly considered in their framework).
B. The subjects' trajectory following these events would likely be similar to the mean observed trajectory in the irbesartan arm from that time point onward.
C. The trajectory would be like some worst percentage of all observed data.

All the above strategies require untestable assumptions. In this review, for simplicity, strategies A and B were used to handle intercurrent events 2 and 3 for continuous endpoints.

Handling of Residual Missing Data

The SAP assumed that any missing data regardless of the occurrence of intercurrent events 1-3 could be implicitly estimated from the MMRM or random coefficient model, which may not be reasonable. In general, for subjects who had missing data due to intercurrent event 1 only, we have considered retrieved dropout multiple imputation (i.e., an approach that may best approximate a treatment policy estimand). If the number of such retrieved dropouts was small, other approaches were considered, such as a copy reference approach. In general, for subjects with missing data who have not had any of the above intercurrent events, imputation based on completers may be a reasonable approach as long as the missing rate is low. This approach was used in FDA's analyses. Tipping point sensitivity analyses were planned to be conducted given that the imputation approaches for missing data rely on unverifiable assumptions.

For the change from baseline in eGFR to 4-weeks post cessation of randomized treatment at Week 112, FDA analyses included all observed data regardless of adherence to treatment and handled ICEs as in Table 7. FDA re-fit the MMRM model by including data at Week 112 and reported the analogous results.

Non-responder imputation was used to impute subjects with missing values for responder endpoints at specific visits, and sustained response across visits. For sustained response across visits, non-responder imputation was used when subjects were missing intermittent values across study visits.

Additional Statistical Analyses

For responder endpoints, to address a difference in risk interpretation, the review team reported results using a difference in proportions with 95% confidence intervals using a normal approximation to the difference in binomial proportion. In addition, the review team included a

Mantel-Haenszel weighted difference in proportions to adjust for stratification factors, and a covariate adjusted logistic regression targeting the marginal difference in proportions with robust errors (Li L, 2025).

Exploratory Endpoints Considered by Review Team

The review team focused on proteinuria responder endpoints that were considered more readily interpretable or clinically meaningful because they included a sustained response over a duration of time.

- Proportion of subjects achieving complete remission at Week 48 and continuing to be in complete remission across subsequent visits.
- Proportion of subjects achieving complete remission at Week 60 and continuing to be in complete remission across subsequent visits.

For the above endpoints, the review team also explored the proportion of subjects achieving other possible UPCR thresholds that the Applicant had included in the CSR, e.g., 0.7 g/g, 1.0 g/g, and 1.5 g/g. In addition, the review team also reported the proportion of subjects achieving complete remission (defined as UPCR <0.3) at landmark visits (from Week 48 onwards). The time point of Week 48 was used as a starting point to reflect close to 1 year of randomized treatment.

For responder endpoints (i.e., endpoints capturing favorable outcomes), subjects who experienced intercurrent events related to death, receipt of kidney transplant, or initiation of chronic dialysis were considered to be non-responders for the endpoint, as were subjects with missing data for the endpoint.

7.1.1.4. Protocol Amendments

According to the Applicant, the protocol for the DUPLEX study was amended nine times (6 global and 3 country-specific) after the original protocol was finalized on January 19, 2018. Notable global changes in the protocol were as follows:

Amendment 1, dated June 26, 2018

- Harmonized with the PROTECT protocol and addressed comments from regulatory agencies. PROTECT was the phase 3 trial in subjects with IgAN that supported approval of sparsentan for IgAN.

Amendment 2, dated January 7, 2019

- Streamlined endpoints and statistical methods, added guidance and testing related to safety monitoring.

Amendment 3, dated June 6, 2019

- Removed mandate for contraception in male subjects.
- Added a minimum weight requirement to inclusion criteria.
- Harmonized with PROTECT Protocol Amendment 2.

Amendment 5, dated January 23, 2020

- Added OLE Period to protocol.

Amendment 6, dated December 1, 2020 (After sample size re-estimation)

- Clarified the timing for discontinuing standard-of-care treatment.
- Added guidance for working with restrictions related to COVID-19.
- Updated study endpoints per FDA recommendation.
- Added the residual standard deviation of eGFR total slope estimated from the unblinded interim efficacy look

Amendment 7, dated November 2, 2021

- Updated to include information on recording of SAEs during the OLE period.
- Added that SGLT2i use was allowed in the OLE period because of increased use of these drugs following "positive" results of large clinical studies with SGLT2i in nondiabetic subjects with proteinuric kidney diseases.

Amendment 8, dated March 31, 2023

- Extended the OLE by 2 years with study visits every 6 months.
- Changed COVID SAE reporting procedure to follow "normal" SAE reporting procedure

Amendment 9, dated January 18, 2024

- Removed the extension of the OLE period that was added in Protocol Amendment 8 because of a business decision to not extend the study.

In all versions of the study protocol (including amendments 8 and 9), all key efficacy analyses were specified to use post-baseline assessments for each subject during the double-blind period. This differs from what was specified in the SAP.

7.1.2. DUPLEX Results

7.1.2.1. Study Subjects

7.1.2.1.1. Subject Disposition

The disposition of all randomized subjects is shown in Table 8. Of the 724 subjects screened, 371 subjects were randomized and took at least one dose of randomized therapy.

During the double-blind period, 29% of the randomized subjects discontinued treatment, with a similar proportion of subjects across arms. The most common reasons for treatment discontinuation were adverse events and withdrawal by the subject. The overall trial discontinuation rate was 9%. The time to treatment discontinuation curve is shown in Figure

Table 8. Participant Disposition, FAS, DUPLEX Double-Blind Period

Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Total N=371 n (%)
Completed Randomized Treatment During DB Period			
Completed	129 (70%)	136 (73%)	265 (71%)
Discontinued	55 (30%)	51 (27%)	106 (29%)
Reason for Treatment Discontinuation During DB Period			
Adverse Event	24 (13%)	19 (10%)	43 (12%)
Withdrawal by Subject	14 (8%)	18 (10%)	32 (9%)
Physician Decision	9 (5%)	6 (3%)	15 (4%)
Receipt of Kidney Transplant or Initiation of Chronic Dialysis	4 (2%)	4 (2%)	8 (2%)
Lost to Follow-up	2 (1%)	0	2 (1%)
Pregnancy	0	2 (1%)	2 (1%)
Protocol Deviation	1 (1%)	1 (1%)	2 (1%)
Death	0	1 (1%)	1 (<1%)
Diagnosis of Class II-IV CHF	1 (1%)	0	1 (<1%)
Study Completion Status			
Completed	168 (91%)	171 (91%)	339 (91%)
Discontinued	16 (9%)	16 (9%)	32 (9%)
Reason for Study Discontinuation			
Withdrawal of Consent	7 (4%)	11 (6%)	18 (5%)
Death	4 (2%)	3 (2%)	7 (2%)
Lost to Follow-up	3 (2%)	2 (1%)	5 (1%)
PI Decision	2 (1%)	0	2 (1%)

Source: Review Team
Abbreviations: CI, confidence interval; n, number of subjects in specified population or group; N, number of subjects in treatment arm; NA, not applicable; DB, double blind, CHF, chronic heart failure; PI, primary investigator

Intercurrent Events and Missing Data

Intercurrent events that were observed during the double-blind period in DUPLEX included treatment discontinuation, receipt of kidney transplant, initiation of chronic dialysis, and death. Table 9 shows the available eGFR data at Week 108 according to treatment completion status. Overall, 25% of randomized subjects did not have an eGFR assessment at Week 108, including 2% who died prior to Week 108, 4% who had received a kidney transplant/dialysis, 15% who had discontinued treatment prematurely but did not have another event prior to Week 108, and 5% who remained on therapy at Week 108.

Table 9. Proportion of Subjects with eGFR Assessment at Week 108, DUPLEX

	Sparsentan (N=184)	Irbesartan (N=187)	Total (N=371)
Available eGFR at Week 108	134 (73%)	144 (77%)	278 (75%)
Completed Treatment	119 (65%)	129 (69%)	248 (67%)
Discontinued Treatment	15 (8%)	15 (8%)	30 (8%)
No Additional intercurrent events	13 (7%)	12 (6%)	25 (7%)
Receipt of kidney transplant/dialysis [1]	2 (1%)	3 (2%)	5 (1%)
Missing eGFR at Week 108	50 (27%)	43 (23%)	93 (25%)
Completed Treatment	10 (5%)	7 (4%)	17 (5%)
Discontinued Treatment	40 (22%)	36 (19%)	76 (20%)
No additional intercurrent events	30 (16%)	26 (14%)	56 (15%)
Died prior to Week 108	4 (2%)	2 (1%)	6 (2%)
Receipt of kidney transplant/dialysis	6 (3%)	8 (4%)	14 (4%)

Source: Statistical Review Team
1 Data collected after receipt of kidney transplantation or initiation of chronic dialysis were excluded from efficacy analyses.
Abbreviations: eGFR, estimated glomerular filtration rate

Table 10 shows the available UPCR data at Week 108 according to treatment completion status. Overall, 28% of randomized subjects did not have a UPCR assessment at Week 108, including 2% who died prior to Week 108, 4% who had received a kidney transplant/dialysis, 17% who had discontinued treatment prematurely but did not have another event prior to Week 108, and 5% who remained on therapy at Week 108.

Table 10. Proportion of Subjects with UPCR Assessment at Week 108, DUPLEX

	Sparsentan (N=184)	Irbesartan (N=187)	Total (N=371)
Available UPCR at Week 108	128 (70%)	140 (75%)	268 (72%)
Completed Treatment	119 (65%)	128 (68%)	247 (67%)
Discontinued Treatment	9 (5%)	12 (6%)	21 (6%)
No additional intercurrent events	9 (5%)	9 (5%)	18 (5%)
Receipt of kidney transplant/dialysis[1]	0 (0%)	3 (2%)	3 (1%)
Missing UPCR at Week 108	56 (30%)	47 (25%)	103 (28%)
Completed Treatment	10 (5%)	8 (4%)	18 (5%)
Discontinued Treatment	46 (25%)	39 (21%)	85 (23%)
No additional events	34 (18%)	29 (16%)	63 (17%)
Died prior to Week 108	4 (2%)	2 (1%)	6 (2%)
Receipt of kidney transplant/dialysis[1]	8 (4%)	8 (4%)	16 (4%)

Source: Statistical Review Team
Abbreviations: ICE, intercurrent event
1 Data collected after receipt of kidney transplantation or initiation of chronic dialysis were excluded from efficacy analyses.
Abbreviations: UPCR, urine protein to creatinine ratio

Missing eGFR and UPCR assessments prior to Week 108 are reported in Table 42 and Table 43 respectively.

In summary, the protocol “encouraged” subjects who permanently discontinued study medication during the double-blind period to continue study visits through Week 112 for continued collection of safety and efficacy data despite stopping study medication. Excluding subjects who died, initiated dialysis or had a kidney transplant, approximately 20% of

randomized subjects had missing eGFR data at Week 108 and approximately 23% of subjects had missing proteinuria data. In general, it can be challenging to interpret the result of analyses when there is a significant amount of missing data, since the analyses rely on assumptions about the missing data which may or may not be valid.

7.1.2.1.2. Demographics and Baseline Characteristics

Baseline demographic characteristics were generally well-balanced between the two treatment groups (Table 11). The median age at baseline was 42 years. Most subjects were White. Few subjects (7%) self-identified as Black/African American. In contrast, the proportion of patients with FSGS who are Black/African American in the US is reported to be approximately 24 to 53% (Munis 2025, Tuttle 2023, Rydel 1995). Approximately 10% of subjects were 8 to <18 years of age.

Baseline clinical characteristics were generally similar between the two groups. The median eGFR was 55 mL/min/1.73 m^2 and median UPCR was 3 g/g. The distribution of subjects across the different eGFR and UPCR categories between the two arms were also balanced including the number of subjects with nephrotic range proteinuria and with a history of nephrotic syndrome.

Table 11. Baseline Demographics and Clinical Characteristics, FAS, DUPLEX

Characteristic	Sparsentan N=184	Irbesartan N=187
Sex, n (%)		
Male	101 (55)	99 (53)
Female	83 (45)	88 (47)
Race, n (%)		
White	134 (73)	135 (72)
Other	5 (3)	12 (6)
Asian	23 (12)	27 (14)
Black or African American	16 (9)	9 (5)
Multiple	3 (2)	4 (2)
American Indian or Alaska Native	1 (1)	0 (0)
Native Hawaiian or Other Pacific Islander	2 (1)	0 (0)
Age, years		
Mean (SD)	42 (17)	42 (17)
Median (min, max)	42 (9, 74)	42 (9, 75)
Age Category, n (%)		
≥18	168 (91)	168 (90)
<18	16 (9)	19 (10)
US, n (%)		
US	73 (40)	68 (36)
Outside of US	111 (60)	119 (64)
Body Mass Index (kg/m2)		
Mean (SD)	28 (6)	28 (6)
Median (min, max)	27 (16, 47)	27 (15, 45)
Strata Used for Randomization,[1] n (%)		
Screen eGFR 30 to <60 mL/min/1.73 m^2 and Non-nephrotic	70 (38)	71 (38)
Screen eGFR ≥ 60 mL/min/1.73 m^2 and Non-nephrotic	56 (30)	57 (30)
Screen eGFR 30 to <60 mL/min/1.73 m^2 and Nephrotic	28 (15)	29 (16)
Screen eGFR ≥ 60 mL/min/1.73 m^2 and Nephrotic	30 (16)	30 (16)

Characteristic	Sparsentan N=184	Irbesartan N=187
eGFR, mL/min/1.73 m^2		
Mean (SD)	63 (29)	64 (32)
Median (min, max)	56 (25, 172)	55 (21, 208)
eGFR Category (mL/min/1.73 m^2), n (%)		
≥60	82 (45)	86 (46)
≥30 to <60	94 (51)	87 (47)
<30	8 (4)	14 (7)
UPCR, g/g		
Mean (SD)	3.7 (2.3)	3.7 (2.7)
Median (min, max)	3.1 (0.8, 13.2)	3.0 (0.1, 27.1)
UPCR Category 1 (g/g), [1] n (%)		
Non-Nephrotic	104 (57)	109 (58)
Nephrotic	80 (43)	78 (42)
UPCR Category 2 (g/g),[1] n (%)		
Nephrotic Adult	64 (35)	60 (32)
Non-Nephrotic Adult	104 (57)	108 (58)
Nephrotic Pediatric	16 (9)	18 (10)
Non-Nephrotic Pediatric	0 (0)	1 (1)
Years Since Diagnosis, n (%)		
≤10	163 (89)	166 (89)
>10	21 (11)	21 (11)
Baseline Steroid Use, n (%)		
Yes	23 (13)	31 (17)
No	161 (87)	156 (83)
Baseline Immunosuppressants Use, n (%)		
Yes	50 (27)	46 (25)
No	134 (73)	141 (75)
Baseline Antihypertensive Use*, n (%)		
Yes	120 (65)	114 (61)
No	64 (35)	73 (39)
Genetic Testing		
Yes	15 (8)	20 (11)
No	169 (92)	167 (89)
Documented Nephrotic Syndrome-Baseline,[2] n (%)		
Yes	55 (30)	62 (33)
No	129 (70)	125 (67)
UPCR Category,[1] n (%)		
Nephrotic Adult	64 (35)	60 (32)
Non-Nephrotic Adult	104 (57)	108 (58)
Nephrotic Pediatric	16 (9)	18 (10)
Non-Nephrotic Pediatric	0 (0)	1 (1)
Serum Creatinine (mg/dL)		
Mean (SD)	1.4 (0.6)	1.4 (0.6)
Median	1.4	1.3
Min, Max	0.3, 3.0	0.3, 3.3
Urine Albumin (g/L)		
Mean (SD)	2212 (1343)	2238 (1549)
Median	1946	1888
Min, Max	185, 7252	20, 11206
Urine Albumin/Creatinine Ratio (g/g)		
Mean (SD)	2.7 (1.5)	2.7 (1.5)
Median	2.4	2.4

Characteristic	Sparsentan N=184	Irbesartan N=187
Min, Max	0.3, 10.0	0.0, 8.2

Source: Review team
1 Non-nephrotic: UPCR ≤3.5 g/g for subjects ≥18 years of age and ≤2 g/g for subjects <18 years of age; Nephrotic: UPCR >3.5 g/g for subjects ≥18 years of age and >2 g/g for subjects <18 years of age.
2 Documented history of nephrotic syndrome is defined as follows: If the term "nephrotic syndrome" was present in medical history or if all of the following conditions were met at any of the visits prior to the first dose of randomized treatment: UP/C >3.5 g/g (adults) or UP/C >2 g/g (pediatrics), serum albumin <3.0 g/dL, and abnormal edema from physical examination.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation; FAS, full analysis set

7.1.2.1.3. Concomitant Medications and Rescue Medication Use

The most commonly used concomitant medications (≥30% of all subjects) were lipid-modifying agents (76%), diuretics (56%), vaccines (50%), vitamins (50%), analgesics (49%), antibacterials for systemic use (45%), calcium channel blockers (44%), drugs for acid-related disorders (43%), agents acting on the RAS (58%), antithrombotic agents (35%), corticosteroids for systemic use (33%), and beta blocking agents (31%).

Notable Concomitant Medications

Immunosuppressive therapies:

- At baseline, 30% of subjects in the sparsentan group and 25% of subjects in the irbesartan group received immunosuppressive therapies (ISTs).
- During the double-blind period, the proportion of subjects treated with concomitant ISTs was higher in the sparsentan group (49%) compared with the irbesartan group (40%).
- The proportion of subjects treated with concomitant ISTs but who had no baseline use was similar in the sparsentan (29%) versus the irbesartan (27%) treatment group.

Antihypertensive medications:

- At baseline, a similar number of subjects in the sparsentan group (65%) were treated with antihypertensive agents compared to the irbesartan group (62%).
- During the double-blind period, the proportion of subjects treated with concomitant antihypertensive medications were similar in the sparsentan group compared to the irbesartan group (91% and 89%, respectively).
- The proportion of subjects treated with concomitant antihypertensive medication but who had no baseline use was higher in the sparsentan (78%) versus irbesartan (67%) group. The difference was mainly due to higher use of diuretics in the sparsentan group.

Lipid-modifying medications:

- At baseline, treatment with lipid-modifying drugs was similar in both the sparsentan and irbesartan groups (60% and 61%, respectively).
- During the double-blind period, 79% of the sparsentan group and 73% of the irbesartan group were treated with concomitant lipid-modifying drugs.
- The proportion of subjects treated with concomitant lipid-modifying drugs but who had no baseline use was similar in the sparsentan (31%) versus the irbesartan (27%) group.

7.1.2.2. Efficacy Results

At the Week 36 interim analysis, the Applicant reported the conditional probability of FPRE was 42.5% and 26% in the sparsentan and irbesartan arm, respectively. Conditional on the stratification factors and log baseline proteinuria, the adjusted difference was 16% higher in the sparsentan compared to the irbesartan arm (95% CI: 4%, 28%; p=0.009) according to the Applicant's clinical study report (CSR).

The FDA review team also analyzed this endpoint using all available UPCR data and handling missing UPCR outcomes as non-responders. In this analysis, the marginal probability of FPRE was 42% (n=78) and 26% (n=49) in subjects randomized to the sparsentan and irbesartan arms, respectively. The FDA review team concluded that the marginal difference in probability of FPRE response at Week 48 was significant and this difference was 17% higher (95% CI: 8% to 26%; p<0.001) in favor of sparsentan compared to irbesartan.

7.1.2.2.1. Primary Endpoint: eGFR

Because the "interim surrogate endpoint" (FPRE) was statistically significant, the remaining secondary endpoints in the testing hierarchy for the US (see Section 7.1.1.3) were sequentially evaluated. The Applicant's prespecified primary endpoint for the US was based on an annualized on-treatment 2-year eGFR total slope, with data after treatment discontinuation implicitly imputed as missing at random based on the regression model. Per the Applicant's CSR, the estimated on-treatment eGFR results did not show a statistically significant improvement in the sparsentan arm (-5.4 mL/min/1.73 m^2 per year) compared to the irbesartan arm (-5.7 mL/min/1.73 m^2 per year). The estimated annualized on-treatment eGFR "total slope of eGFR assessed from Day 1 to Week 108 – full analysis set" was 0.3 mL/min/1.73 m^2 per year (95% CI: -1.7, 2.4; p=0.7) comparing sparsentan with irbesartan.

As discussed in Section 7.1.1.3, the FDA review team does not agree that the Applicant's estimand strategy for handling treatment discontinuations is appropriate. In addition, based on the submitted program files, the Applicant estimated eGFR slope for the primary endpoint using only eGFR assessments from Week 2 to Week 108 (as opposed to Day 1 to Week 108) in the longitudinal data analysis, which does not reflect a "total slope analysis" consistent with the primary endpoint description.

Given the presented findings did not estimate a total slope from Day 1 through Week 108, and concerns with the methodologic approaches used by the Applicant to analyze the data, and because of sparsentan's acute effect on eGFR, the statistical review team conducted additional analyses of the eGFR data, which are summarized below.

Analyses of total and chronic slope including all observed data

When including all observed data collected and handling the intercurrent events of initiation of renal replacement therapy (kidney transplant or initiation of chronic dialysis), or death as missing at random according to the regression model, there was no nominally significant difference in the annualized rate of linear decline in eGFR from baseline through Week 108 comparing the sparsentan with irbesartan arms. Subjects randomized to the sparsentan arm averaged an annualized eGFR decline of 6.1 mL/min/1.73 m^2 and subjects randomized to

irbesartan averaged an annualized eGFR decline of 6.3 mL/min/1.73 m^2. The estimated difference in the annualized rate of linear decline through the study was 0.1 mL/min/1.73 m^2 per year (95% CI: -1.9, 2.1; p=0.89) and not significantly different between sparsentan and irbesartan arms (Table 12).

Table 12. Annualized eGFR Rate of Linear Decline Excluding Data Collected After Occurrence of Intercurrent Events, FAS, DUPLEX

	Sparsentan N=184	Irbesartan N=187
Results from a RC model From Baseline Through Week 108 [1]		
Est. Annualized Rate, LSM (SE)	-6.1 (0.73)	-6.3 (0.72)
Diff in Annualized Rate, LSM (95% CI)	0.1 (-1.9, 2.1)	
P-Value	0.89	
From Week 2 Through Week 108 [2]		
Est. Annualized Rate, LSM (SE)	-5.8 (0.75)	-6.3 (0.74)
Diff in Annualized Rate, LSM (95% CI)	0.5 (-1.5, 2.6)	
P-Value	0.61	

Source: Statistical Team
1: The random coefficient model was fit to all eGFR data including baseline (Day 1) as outcomes, adjusting for baseline eGFR, stratification factors, treatment, continuous visit week, interaction of continuous visit week with treatment, allowing for random intercept and random slope. Data excluded after occurrence of receipt of kidney transplant, initiation of chronic dialysis, or missing data were assumed to be missing at random according to the model. Baseline is defined as Day 1 in the study.
2: Analogous analysis consistent with the Applicant specification in the SAS programs as the primary analysis of total slope, which was reported in NEJM. The result from the Applicant's specification estimates the rate of decline starting from Week 2 and is not a total slope interpretation.
Abbreviations: LSM, least squares means; SE, standard error; CI, confidence interval; RC, random coefficient; Est, estimated; Diff, difference; FAS, full analysis set

The FDA review team conducted an analogous analysis for the total slope based on the piece-wise random coefficient model used to report the results of chronic slope excluding data after the occurrence of intercurrent events of renal replacement therapy, and handling missing data (including death) as MAR (Table 13). The estimated difference in annualized chronic slope from Week 6 through Week 108 was 1.1 mL/min/1.73 m^2 (95% CI: -1.1, 3.3; p=0.33) favoring the sparsentan arm. Using the same model, the estimated total slope from Day 1 through Week 108 was -11.5 mL/min/1.73 m^2 for the sparsentan arm and -10.5 mL/min/1.73 m^2 for the irbesartan arm, with an estimated difference in total slope from Day 1 through Week 108 of -1.0 mL/min/1.73 m^2 (95% CI: -5.0, 3.0), favoring the irbesartan arm.

Table 13. Annualized eGFR Chronic Rate of Linear Decline from Week 6 through 108 and Total Slope After Excluding Data Collected After Occurrence of Intercurrent Events, FAS, DUPLEX

	Sparsentan N=184	Irbesartan N=187
Chronic Slope from Week 6 Through Week 108		
Est. Annualized Rate, LSM (SE)	-5.3 (0.8)	-6.4 (0.8)
Diff in Annualized Rate, LSM (95% CI)	1.1 (-1.1, 3.3)	
P-Value	0.33	
Total Slope from Baseline through Week 108		
Est. Difference, LSM (SE)	-11.5 (1.7)	-10.5 (1.7)
Diff in Total Slope, LSM (95% CI)	-1.0 (-5.0, 3.0)	
P-Value	0.62	

Source: Statistical Team

The above results are estimated from the same piece-wise linear spline random coefficient model with a knot at Week 6. Baseline is referred to as Day 1 for the study. Missing data (including death) and after occurrence of kidney transplant, or initiation of dialysis are assumed missing at random according to the regression model.
Abbreviations: LSM, least squares means; SE, standard error; CI, confidence interval; RC, random coefficient; Est, estimated; Diff, difference

The FDA review team also conducted sensitivity analyses that assumed the acute effect lasted for different durations to address the uncertainty in the timing of the change point from the acute to chronic slope (Table 14). For the chronic annualized slope analyses, regardless of the week specified for the change point, the estimated rate of decline was numerically lower for sparsentan as compared to irbesartan arm.

The estimates of the "total slope" using different change points from the respective models accounting for the timing of the acute effect, were numerically lower in the irbesartan arm. These findings for total slope using a piece-wise spline model differed numerically (i.e., were numerically better for irbesartan) from the findings using a single slope-based analysis (see Table 12), which were numerically better for sparsentan.

Table 14. Estimates for Annualized Chronic eGFR Slope and Total Slope at 2 years using a Linear Piece-wise Regression Model Assuming the Various Changepoints, FAS, DUPLEX

	Annualized Chronic Slope			Total Slope From Baseline through Week 108		
Change-points	Sparsentan (N=184)	Irbesartan (N=187)	Annualized Difference (95% CI)	Sparsentan (N=184)	Irbesartan (N=187)	Adjusted Difference (95% CI)
Week 2[1]	-5.8 (0.7)	-6.3 (0.7)	0.5 (-1.4, 2.4)	-10.5 (1.8)	-9.0 (1.8)	-1.5 (-5.3, 2.3)
Week 4	-5.4 (0.8)	-6.4 (0.8)	0.9 (-1.4, 3.2)	-11.4 (1.7)	-10.3 (1.7)	-1.1 (-5.2, 3.0)
Week 6	-5.3 (0.8)	-6.4 (0.8)	1.1 (-1.1, 3.3)	-11.5 (1.7)	-10.5 (1.7)	-1.0 (-5.0, 3.0)
Week 8	-5.1 (0.8)	-6.4 (0.8)	1.2 (-0.9, 3.4)	-11.2 (1.6)	-10.3 (1.6)	-0.9 (-4.8, 3.0)
Week 12	-5.1 (0.8)	-6.4 (0.8)	1.3 (-0.8, 3.4)	-10.6 (1.6)	-9.7 (1.6)	-0.9 (-4.8, 2.9)

Source: Statistical Review Team
[1] Two-slope model assumed an unstructured variance covariance matrix except for the analysis with change point at Week 2 where an autoregressive (1) variance covariance matrix was used.
Abbreviations: CI, confidence interval; FAS, full analysis set

In conclusion, statistical analyses based on all data collected from Day 1 to 2 years (Week 108) do not indicate that sparsentan slowed the decline in kidney function compared to irbesartan over two years.

Change from baseline in eGFR across scheduled visits up to end of double-blind period

The random coefficient models assume a linear decline in kidney function, which may not be a reasonable assumption. The Agency also analyzed the difference in the change from baseline in eGFR to different time points in the study using a MMRM regression model, which does not rely on a strong linearity assumption. At Week 108, subjects randomized to sparsentan had an estimated mean change from baseline of -13.9 mL/min/1.73 m^2 and subjects randomized to irbesartan had an estimated mean change from baseline of -12.2 mL/min/1.73 m^2 (Table 15). The difference in the mean change from baseline comparing sparsentan with irbesartan at Week 108 was not nominally significant (adjusted difference: -1.7 mL/min/1.73 m^2; 95% CI: -

5.4, 2.0; p=0.36), and the adjusted change from baseline was numerically smaller in the irbesartan arm than the sparsentan arm.

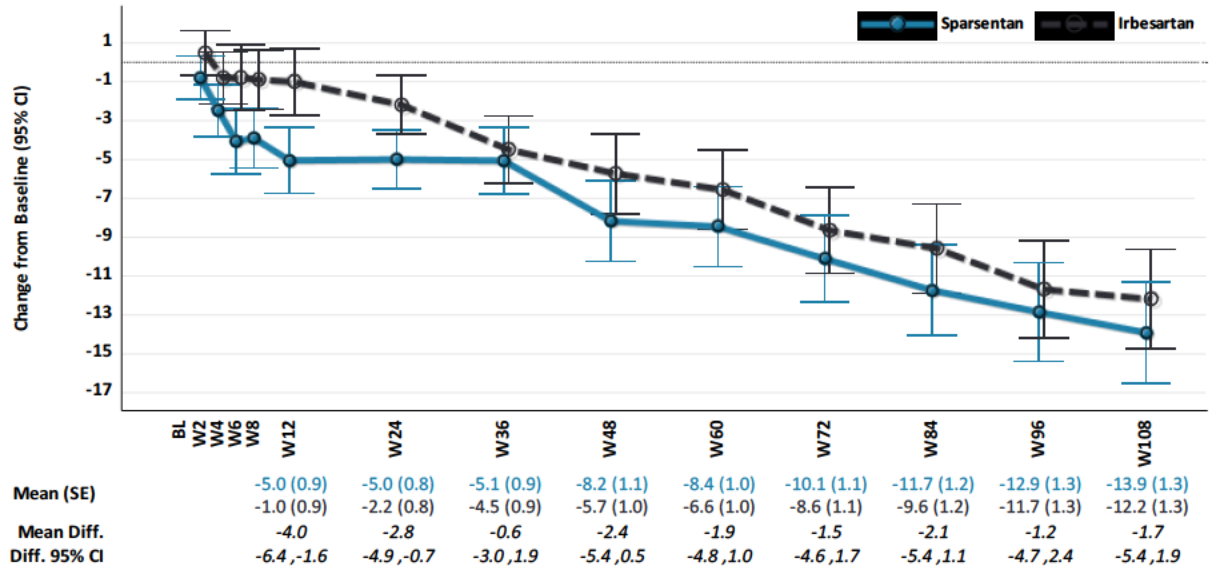
Table 15. Estimates of Change from Baseline in eGFR Based on All Data Collected with ICE Handling in MMRM analysis, FAS, DUPLEX

eGFR (mL/min/1.73 m^2)	Sparsentan N=184	Irbesartan N=187
Baseline (Day 1), mean (SD)	63 (29)	64 (32)
Change from baseline at Week 108, LSM (SE)	-13.9 (1.3)	-12.2 (1.3)
Adj Diff from Irbesartan, Est (95% CI)	-1.7 (-5.4, 2.0)	
p-value	0.36	

Source: Statistical Review Team
Data collected after ICE due to receiving kidney transplant or initiation of chronic dialysis are excluded and treated as missing at random according to the MMRM regression model.
Abbreviations: SD, standard deviation; LSM, least squares mean; SE, standard error; Adj, adjusted; Diff, difference; ICE, intercurrent events

Figure 4 presents the estimated eGFR trajectory based on the regression model for both the sparsentan and irbesartan arms. The adjusted mean decrease from baseline in eGFR was larger in the sparsentan as compared to irbesartan arm at all study visits until Week 24. From Week 60 onward, the adjusted least squares mean change in eGFR appeared to decline in a similar fashion in the two treatment arms. For all scheduled visits, the adjusted mean decrease from baseline in eGFR was numerically greater in the sparsentan arm compared to the irbesartan arm. Of note, based on the trajectory of the decline shown in the figure, there does not appear to be an obvious change point in the slope (i.e., single time point that can be used to define an acute vs chronic slope). It is also unclear how to interpret the plateau in the point estimates of the change from baseline in the sparsentan arm from Weeks 12 through 36 and subsequent acute decline from Week 36 to Week 48.

Figure 4. Estimated Trajectory in the Change from Baseline in eGFR across Study Visits through Week 108, DUPLEX



Source: Statistical review team

Data collected after ICE due to receiving kidney transplant or initiation of chronic dialysis are excluded. Missing data were implicitly imputed as missing at random according to the MMRM regression model.
Abbreviations: eGFR, estimated glomerular filtration rate; Diff, difference; CI, confidence interval; BL, baseline; MMRM, mixed model repeated measures.

In summary, the absolute change from baseline in eGFR at various timepoints appeared to be numerically smaller in the irbesartan arm. The analyses do not indicate that sparsentan reduce the decline in kidney function compared to irbesartan over two years.

Analysis of the Change in eGFR from Baseline to Post Treatment at Week 112

As discussed in Section 7.1.1.3, pharmacodynamic effects on eGFR can make it challenging to interpret on-treatment changes in eGFR and to distinguish the pharmacodynamic effects of a drug on eGFR from effects on disease progression. In the CSR, the Applicant reported that the estimated change from baseline to 4-weeks post-cessation for sparsentan treatment completers (n=124) was -10.4 mL/min/1.73 m^2 and irbesartan treatment completers (n=125) was -12.1 mL/min/1.73 m^2. Based on the completers of randomized treatment, the estimated difference in the change from baseline to 4-weeks post-cessation was 1.8 (95% CI: -1.4, 4.9) mL/min/1.73 m^2 higher for sparsentan compared to irbesartan. In general, analyses conditioned on subjects completing randomized treatment (a post-baseline variable) can produce bias estimates.

To address the issue, the statistical review team conducted an analysis based on all the randomized subjects with eGFR data collected through Week 112. The estimates of the change from baseline in eGFR to Week 112 were similar in the irbesartan and sparsentan arms (-13.0 and -13.2 mL/min/1.73 m^2, respectively) (Table 16).

Table 16. Estimates Based on Change from Baseline in eGFR Using All Data Collected with ICE Handling as Missing at Random according to MMRM analysis Including Week 112, DUPLEX

	Sparsentan N=184	Irbesartan N=187
Baseline, mean (SD)	63 (29)	64 (32)
Change from baseline at Week 112, LSM(SE)	-13.2 (1.3)	-13.0 (1.3)
Adj Diff from Irbesartan, Est (95% CI)	-0.2 (-3.8, 3.4)	
p-value	0.92	

Source: Statistical Review Team
Based on all observed data up to Week 112 excluding data after ICE and missing at random assumption based on the mixed model repeated measures. Differs from Applicant where analysis was conditioned on a completers analysis of subjects who had Week 108 on treatment data.
Abbreviations: SD, standard deviation; LSM, least squares mean; SE standard error; CI, confidence interval; Adj, adjusted; Diff, difference.

Missing Data

As shown in Table 9, the proportion of subjects with missing eGFR assessments at Week 108 was high, with 25% of subjects missing data; the majority of subjects with missing data had discontinued randomized treatment prematurely. Because the results for both the change from baseline in eGFR and total slope analyses were not statistically significant, no tipping point analyses were conducted on the imputed results in Table 17 (and Table 18 respectively for total slope analyses)Table 9 to address the robustness of the results to the missing data assumptions. In general, it is challenging to interpret the results of imputation analyses when

there is a significant amount of missing data, since the analyses rely on assumptions about the missing data which may or may not be valid. Figure 5 shows the preferred multiply imputed results using copy reference with worst 5% sampling for intercurrent events of RRT, or death. However, as discussed earlier, regardless of missing data, analyses of eGFR (whether as a change from baseline or linear slope) did not suggest that sparsentan reduce or slow the loss of kidney function as compared to irbesartan.

Table 17. Summary of Adjusted Change from Baseline in eGFR After Accounting for Multiple Imputation, FAS, DUPLEX

Change from baseline in eGFR at Week 108	Sparsentan (N=184) Est (SE)	Irbesartan (N=187) Est (SE)	Est Diff (95% CI)
Implicit MAR			
On Treatment	-12.8 (1.3)	-11.2 (1.3)	-1.6 (-5.3, 2.0)
All Observed	-14.0 (1.4)	-11.9 (1.3)	-2.1 (-5.9, 1.7)
All Observed (Exc ICE)	-13.9 (1.3)	-12.2 (1.3)	-1.7 (-5.4, 2.0)
Multiple Imputation			
Copy Reference[1]	-13.8 (1.3)	-12.0 (1.3)	-1.8 (-5.4, 1.8)
Copy Reference MI + Worst 5%[2]	-13.9 (1.4)	-12.8 (1.3)	-1.1 (-4.8, 2.7)
Applicant's (Copy Reference MI + Worst 5%) [3]	-14.3 (1.4)	-13.3 (1.4)	-1.0 (-4.9, 2.8)
MAR MI[4]	-13.3 (1.3)	-11.9 (1.3)	-1.5 (-5.0, 2.1)
MAR MI + Worst 5%[5]	-13.7 (1.3)	-12.7 (1.3)	-1.0 (-4.7, 2.8)
MAR (PMM)[6]	-13.6 (1.3)	-12.4 (1.3)	-1.3 (-4.9, 2.3)
Applicant's[7] (ADMIREF5)	-14.4 (1.2)	-13.2 (1.5)	-1.2 (-5.0, 2.6)
Applicant's[8] (PMM/ ADMIREF7)	-14.2 (1.4)	-13.3 (1.2)	-0.9 (-4.5, 2.7)

Source: Statistical Review Team, Applicant's response to IR12 dated January 06, 2026 (Seq #0181), Applicant's response to IR15 (Seq #0191)

1: Non retrieved dropouts from sparsentan arm (including those who died, or had initiated renal replacement therapy) were imputed according to eGFR data from irbesartan completers and retrieved dropouts. Subjects who remained on randomized treatment and were missing outcome at Week 108 had their trajectory imputed according to respective subjects have no missing outcome at Week 108 and same randomized treatment.

2, 3: Approach described in 1 was used to first address all missing data regardless of intercurrent event of death, or initiation of renal replacement therapy. After which, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data. Preferred imputation by the Agency. The Applicant reported their version of the results according to the Agency's approach with bounds on the range of eGFR (5, 180) in Seq #0191, using a different starting seed. Review team reproduced Applicant's results submitted.

4: Subjects with any missing data are imputed according to the subjects without missing data per randomized treatment assignment.

5: Approach described in 3 was used to first address all missing data regardless of intercurrent event of death, or initiation of renal replacement therapy. After which, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data.

6: Method of predictive mean matching multiple imputation was applied under the missing at random assumption.

7: Applicant's imputation results using monotone regression approach, maximum value of eGFR was set to 180, worst 1% sampling for death and initiation of renal replacement therapy, and imputation was conducted separately for eGFR < 60 and eGFR ≥60. Results are based on an ANCOVA model on the change from baseline in eGFR at each visit with treatment, baseline eGFR, and randomization strata as fixed effects, with Huber-White sandwich errors. See ADMIREF5 results in Table 8.6.1_IR12 in Seq #0181 dated January 06, 2026.

8: Applicant's imputation results using predictive mean matching algorithm, no bounds on imputed eGFR, worst 1% sampling for death and initiation of renal replacement therapy, and imputation was conducted separately for eGFR < 60 and eGFR ≥60. Results are based on an ANCOVA model on the change from baseline in eGFR at each visit with treatment, baseline eGFR, and randomization strata as fixed effects, with Huber-White sandwich errors. See ADMIREF7 results in Table 8.7.1_IR12 in Seq #0181 dated January 06, 2026.

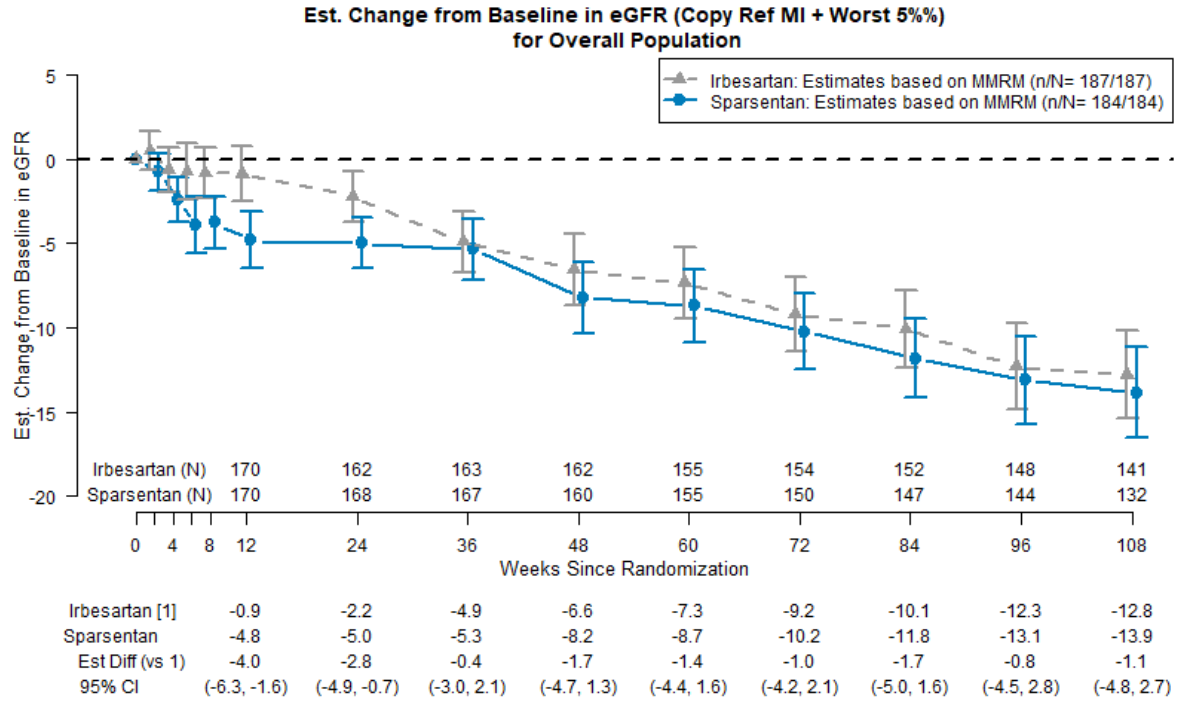
Abbreviations: FAS, full analysis set; eGFR, estimated glomerular filtration rate; Exc, exclude; ICE, intercurrent events; CI, confidence interval; MAR, missing at random; MI, multiple imputation; PMM, predictive mean matching; Reg, regression.

Table 18. Summary of Annualized Rate of Change in eGFR From Baseline Through Week 108 After Accounting for Multiple Imputation, FAS, DUPLEX

Estimated Rate of Change	Sparsentan (N=184) Ann. Rate (SE)	Irbesartan (N=187) Ann. Rate (SE)	Est Diff in Annualized Rate (95% CI)	Nominal P-value
Implicit MAR				
On Treatment	-5.7 (0.7)	-5.8 (0.7)	0.0 (-2.0, 2.0)	0.99
All Observed	-6.1 (0.7)	-6.0 (0.7)	-0.2 (-2.2, 1.9)	0.88
All Observed (Exc ICE)	-6.1 (0.7)	-6.3 (0.7)	0.1 (-1.9, 2.2)	0.88
Multiple Imputation				
Copy Reference[1]	-5.9 (0.7)	-6.1 (0.7)	0.2 (-1.6, 2.1)	0.8
Copy Reference MI + Worst 5%[2]	-6.0 (0.7)	-6.6 (0.7)	0.6 (-1.4, 2.6)	0.57
MAR (Monotone Reg)[3]	-5.6 (0.7)	-6.1 (0.7)	0.4 (-1.4, 2.3)	0.66
MAR + Worst 5%[4]	-5.8 (0.7)	-6.2 (0.7)	0.5 (-1.4, 2.3)	0.63
MAR (PMM)[5]	-5.9 (0.7)	-6.5 (0.7)	0.7 (-1.3, 2.6)	0.52
Applicant's[6] (ADMIREF5)	-6.3	-6.7	0.5 (-1.6, 2.5)	0.66
Applicant's[7] (PMM/ADMIREF7)	-6.2	-6.7	0.5 (-1.5, 2.5)	0.62

Source: Statistical Review Team and Applicant's response to IR12 dated January 06, 2026 (Seq #0181)
1: Non retrieved dropouts from sparsentan arm (including those who died, or had initiated renal replacement therapy) were imputed according to eGFR data from irbesartan completers and retrieved dropouts. Subjects who remained on randomized treatment and were missing outcome at Week 108 had their trajectory imputed according to respective subjects have no missing outcome at Week 108 and same randomized treatment, minimum value of eGFR was set to 5, maximum value of eGFR was set to 150.
2: Approach described in 1 was used to first address all missing data regardless of intercurrent event of death, or initiation of renal replacement therapy. After which, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data. Minimum value of eGFR was set to 5, maximum value of eGFR was set to 180.
3: Subjects with any missing data are imputed according to the subjects without missing data per randomized treatment assignment.
4: Approach described in 3 was used to first address all missing data regardless of intercurrent event of death, or initiation of renal replacement therapy. After which, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data.
5. Method of predictive mean matching multiple imputation was applied under the missing at random assumption.
6: Applicant's imputation results with monotone regression modelling, maximum value of eGFR was set to 180, worst 1% sampling for death and initiation of renal replacement therapy, and imputation was conducted separately for eGFR < 60 and eGFR ≥60. See ADMIREF5 results in Table 4.6_IR12 in Seq #0181 dated January 06, 2026. SE was not reported by the Applicant.
7: Applicant's imputation results using predictive mean matching algorithm, no bounds on eGFR imputed values, worst 1% sampling for death and initiation of renal replacement therapy, and imputation was conducted separately for eGFR < 60 and eGFR ≥60. See ADMIREF7 results in Table 4.7_IR12 in Seq #0181 dated January 06, 2026. SE was not reported by the Applicant.
Abbreviations: FAS, full analysis set; eGFR, estimated glomerular filtration rate; Exc, exclude; ICE, intercurrent events; CI, confidence interval; MAR, missing at random; PMM, predictive mean matching; Reg, regression; MI, multiple imputation.

Figure 5 Estimated Trajectory for Change from Baseline in eGFR Based on Copy Reference Multiple Imputation with Worst 5% Sampling for ICE, FAS, DUPLEX



Source: Statistical Review Team
Non retrieved dropouts from sparsentan arm (including those who died, or had initiated renal replacement therapy) were imputed according to eGFR data from irbesartan completers and retrieved dropouts. Subjects who remained on randomized treatment and were missing outcome at Week 108 had their trajectory imputed according to respective subjects have no missing outcome at Week 108 and same randomized treatment.
After which, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data.
Abbreviations: FAS, full analysis set; eGFR, estimated glomerular filtration rate; Exc, exclude; ICE, intercurrent events; CI, confidence interval; MAR, missing at random; MI, multiple imputation.

7.1.2.2.2. Proteinuria as Continuous Endpoint

The Applicant specified evaluating UPCR as a continuous endpoint as an exploratory endpoint. Similar to the eGFR endpoint, the Applicant specified an analysis using only on treatment data with a hypothetical strategy for treatment discontinuation. As reported by the Applicant, the ratio of the geometric mean ratio of UPCR with baseline at Week 108 based on an on-treatment comparison was 0.74 (95% CI: 0.58, 0.93; p=0.01). Given concerns with the Applicant's approach to analyzing the data, and specifically the use of an on-treatment analysis, the review team conducted additional analyses.

In an analysis using all available data collected regardless of adherence to randomized treatment or occurrence of intercurrent events related to kidney transplant, chronic dialysis and assuming data are missing at random (including death) according to the MMRM model, the ratio of the geometric mean ratio of UPCR with baseline at Week 108 was 0.86 (95% CI: 0.68, 1.09; p=0.22) in the sparsentan arm as compared to the irbesartan arm.

The review team conducted an additional analysis excluding UPCR data after the intercurrent event of receipt of kidney transplant and initiation of chronic dialysis. Assuming missing data as well as data occurring after this intercurrent event are missing at random and using the regression model to implicitly imputed the data, the geometric mean ratio (GMR) of 24-hour UPCR to baseline UPCR was 0.5 and 0.7 in the sparsentan and irbesartan groups, respectively at week 108 (Table 19). At Week 108, the ratio of the geometric mean ratio in 24-hour UPCR to baseline was 0.80 (95% CI: 0.64, 1.00, p=0.054) in the sparsentan as compared to irbesartan arm. Compared to the Applicant's on-treatment analysis results, the relative percent reduction in this analysis is lower (20% vs a relative percent reduction of 26% in the Applicant's on-treatment analysis).

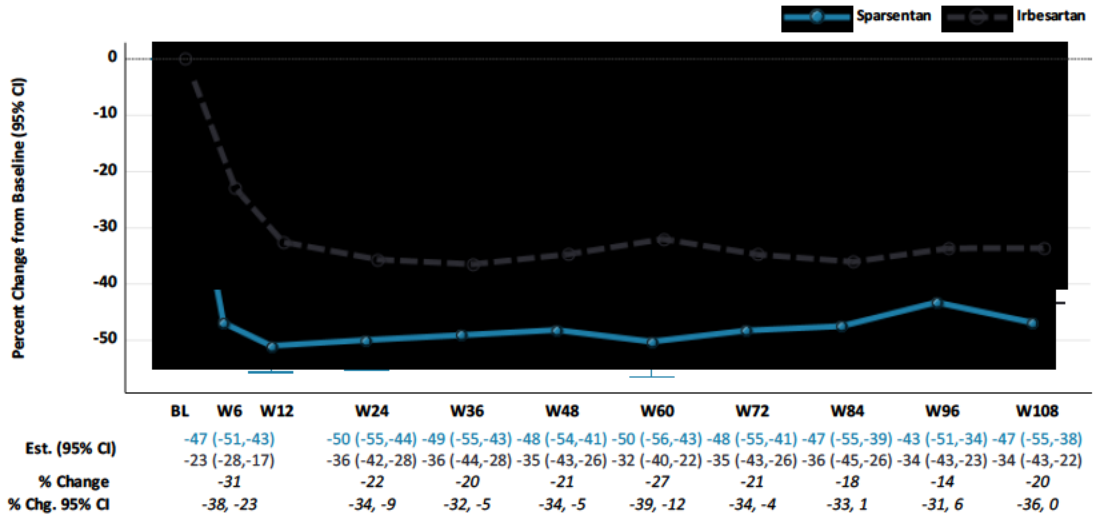
Table 19. Estimated Percent Change from Baseline for UPCR at Week 48 and 108 excluding data after kidney transplant, or chronic dialysis, and implicit MAR assumption based on MMRM model, FAS, DUPLEX

Description	Sparsentan (N=184)	Irbesartan (N=187)
Baseline (g/g): Geometric Mean (log SD)	3.2 (0.6)	3.1 (0.7)
Week 48		
n (%)	157 (85)	158 (85)
GMR with Baseline, Est (SE)	0.5 (0.1)	0.8 (0.1)
Ratio of GMR with Irbesartan, Est (95% CI)	0.80 (0.68, 0.95)	
Relative % Change Between Arms, Est (95% CI)	-21 (-34%, -5%)	
Week 108		
n (%)	128 (70)	137 (73)
GMR with Baseline, Est (SE)	0.5 (0.08)	0.7 (0.08)
Ratio of GMR with Irbesartan, Est (95% CI)	0.80 (0.64, 1.00)	
Relative % Change with Irbesartan, Est (95% CI)	-20% (-36%, 0%)	
p-value, vs Irbesartan	0.054	

Source: Statistical Team
The mixed model repeated measures (MMRM) was fit to all UPCR data collected excluding data due to ICE (kidney transplant, chronic dialysis) and assuming MAR according to the MMRM model per the Applicant's analysis for continuous endpoint.
Abbreviation: UPCR, urine protein to creatinine ratio; FAS, full analysis set; SD, standard deviation; LSM, least squares mean; SE, standard error; CI, confidence interval; %, percentage; GMR, geometric mean ratio MAR, missing at random; FAS, full analysis set; MMRM mixed model repeated measures

Figure 6 shows the estimated trajectory for the percent change from baseline in 24-hour UPCR (g/g) for each arm over 108 weeks based on all data collected after excluding data observed after the intercurrent event of renal replacement therapy. Across the visit weeks, the estimated geometric mean percent reduction from baseline for the sparsentan arm ranged from 14% to 31% (Week 6).

Figure 6 Relative Percent Change from Baseline (95% CI Error Bars) in 24-Hour UPCR and Excluding Data Collected after ICE, FAS, DUPLEX



Source: Statistical Review Team
The mixed model repeated measures (MMRM) was fit to all UPCR data collected excluding data after ICE (kidney transplant, chronic dialysis). Missing data were imputed under an implicit MAR assumption according to the MMRM model per the Applicant's analysis for continuous endpoint.
Abbreviations: Est, estimates; CI, confidence intervals; UPCR, urine protein to creatinine ratio, FAS, full analysis set; BL, baseline; %, percent; Chg, change; W, week; BL, baseline; ICE, intercurrent events; MMRM, mixed model repeated measures; MAR, missing at random.

Analysis of the Change in UPCR from Baseline to Post Treatment at Week 112

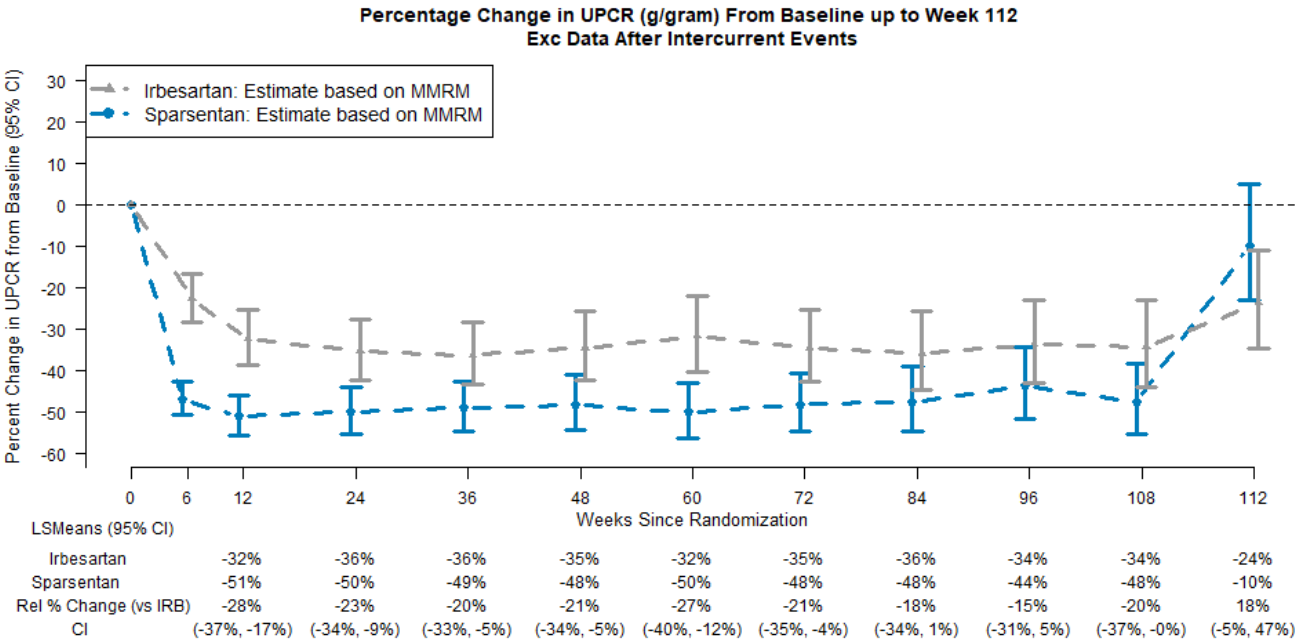
The statistical review team conducted an analysis based on all the randomized subjects with UPCR data collected through Week 112 after excluding data due to initiation of renal replacement therapy. The estimates of the geometric mean ratio of UPCR with baseline to Week 112 were 0.8 and 0.9 respectively in sparsentan and irbesartan arm respectively (Table 20, Figure 7). The relative ratio of GMR compared to irbesartan was 1.2 (95% CI 0.9, 1.5), which translates to an 18% numerically higher (95% CI: -5%, 47%) on sparsentan arm. The observed relative percentage change between sparsentan and irbesartan was smaller than the Applicant's reported findings based on all available data (Estimated relative % change: 27% higher on sparsentan; 95% CI: 1%, 59%).

Table 20. Estimates Based on Change from Baseline in logarithm UPCR to Week 112 Based on MMRM Analysis Assuming Missing Data are Missing at Random, DUPLEX

UPCR at Week 112	Sparsentan N=184	Irbesartan N=187
All available data (exc data after initiation of renal replacement therapy)[1]		
GMR with Baseline, Est (SE)	0.9 (0.1)	0.8 (0.1)
Ratio of GMR with Irbesartan, Est (95% CI)	1.2 (0.9, 1.5)	
Relative % Change with Irbesartan, Est (95% CI)	18 (-5, 47)	
All available data[2]		
GMR with Baseline, Est (SE)	0.9 (0.1)	0.7 (0.1)
Ratio of GMR with Irbesartan, Est (95% CI)	1.3 (1.0, 1.6)	
Relative % Change with Irbesartan, Est (95% CI)	27 (1, 59)	

The mixed model repeated measures (MMRM) was fit to all logarithm UPCR data collected up until Week 112 adjusting for baseline log UPCR, stratification variables, treatment, visit, interaction of treatment and visit. Missing data were implicitly handled as missing at random according to the MMRM model.
[1] Data after intercurrent events of initiation of renal replacement therapy were excluded.
[2] Reproduced analyses according to the Applicant's reported findings in table 14.2.1.2.2 of the CSR, with minor differences in the decimal.
Abbreviations: UPCR, urine protein to creatinine ratio; GMR, geometric mean ratio; Est, estimates; CI, confidence interval; SE, standard error; exc, exclude.

Figure 7. Relative Percent Change from Baseline (95% CI Error Bars) in 24-Hour UPCR up to Week 112 and Excluding Data Collected after ICE, FAS, DUPLEX



Source: Statistical Review Team
The mixed model repeated measures (MMRM) was fit to all available logarithm UPCR data collected up until Week 112 adjusting for baseline log UPCR, stratification variables, treatment, visit, interaction of treatment and visit. Data after intercurrent events of initiation of renal replacement therapy were excluded. Missing data were implicitly handled as missing at random according to the MMRM model.
Point estimates and CI can differ from previous analysis since data at Week 112 were not included in the model.
X-axis for Week 112 is not drawn to scale.
Abbreviations: UPCR, urine protein to creatinine ratio; Rel, relative; CI, confidence interval; MMRM mixed model repeated measures

Missing Data

As shown in Table 10, a significant number of subjects did not have UPCR data at Week 108. The statistical review team conducted sensitivity analysis to assess the impact of missing data using multiple imputation. Depending on the multiple imputation approach used to handle the missing data, estimates of the relative percent reduction in UPCR in the sparsentan as compared to irbesartan arm ranged from 20 to 26 percent (Table 21). Although the results of the different analyses using multiple imputation are all nominally significant based on the MMRM analyses model, the findings are not robust to deviations of assumptions of the multiple imputation (See 15.3 for Tipping Point Analyses and Figure 17).

The estimated UPCR trajectory based on copy reference multiple imputation, with worst 5% sampling for intercurrent events of RRT and death, is shown in Figure 8. The point estimates are

consistent with the observed analysis after excluding data due to intercurrent events of initiation of renal replacement therapy.

Table 21. Summary of 24-Hour UPCR Findings at Week 108 Addressing Missing Data, FAS, DUPLEX

Description	Sparsentan (N=184) GMR (SE)	Irbesartan (N=187) GMR (SE)	Est GMR (vs Irbesartan) (95% CI)	Relative % Change [8] (95% CI)	Nominal p-value
Implicit MAR according to MMRM					
On Treatment (Applicant's)	0.50 (0.09)	0.68 (0.08)	0.74 (0.58, 0.93)	-26% (-42%, -7%)	0.01
All Observed	0.54 (0.09)	0.62 (0.08)	0.87 (0.68, 1.10)	-13% (-32%, 10%)	0.2
All Observed (Exc ICE)	0.53 (0.08)	0.66 (0.08)	0.80 (0.64, 1.00)	-20% (-36%, 0%)	0.05
With Multiple Imputation					
Copy Reference[1]	0.53 (0.08)	0.66 (0.08)	0.80 (0.64, 1.00)	-20% (-36%, -0%)	0.046
Copy Reference+ Worst 5%) [2]	0.54 (0.08)	0.70 (0.08)	0.78 (0.63, 0.98)	-22% (-37%, -2%)	0.03
Applicant's (Copy Reference + Worst 5%) [3]	0.54 (0.08)	0.70 (0.08)	0.78 (0.62, 0.98)	-22% (-38%, -2%)	0.03
Return to Baseline[4]	0.54 (0.08)	0.73 (0.08)	0.74 (0.59, 0.92)	-26% (-41%, -8%)	0.008
Return to Baseline (Worst 5%) [5]	0.55 (0.08)	0.74 (0.08)	0.74 (0.59, 0.93)	-26% (-41%, -7%)	0.009
MAR [6]	0.51 (0.08)	0.66 (0.08)	0.77 (0.61, 0.97)	-23% (-39%, -3%)	0.02
MAR (Worst 5%) [7]	0.54 (0.08)	0.70 (0.08)	0.77 (0.61, 0.96)	-23% (-39%, -4%)	0.02
Applicant's (ADMIREF6) [8]	0.56 (0.08)	0.71 (0.08)	0.78 (0.62, 0.99)	-22% (-38%, -1%)	0.04
Applicant's (PMM/ ADMIREF8) [9]	0.55 (0.08)	0.70 (0.08)	0.78 (0.63, 0.97)	-22% (-37%, -3%)	0.03

Source: Statistical Review Team, Applicant's response to IR12 dated January 06, 2026 (Seq #0181), Applicant's response to IR15 (Seq #0191)

1: Non retrieved dropouts from sparsentan arm (including those who died, or had initiated renal replacement therapy) were imputed according to UPCR data from irbesartan completers and retrieved dropouts. Subjects who remained on randomized treatment and were missing outcome at Week 108 had their trajectory imputed according to respective subjects have no missing outcome at Week 108 and same randomized treatment.

2, 3: Approach described in 1 was used to first address all missing data regardless of intercurrent event of death, or initiation of renal replacement therapy. After which, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data. Preferred imputation by the Agency. Applicant reported their version of the results according to the Agency's approach with upper bounds of 30 for UPCR in Seq #0191, and using a different starting seed. Review team reproduced Applicant's results submitted.

4, 5: Subjects with missing outcomes following treatment discontinuation are imputed according to the baseline distribution under the assumption the benefit is reverted to baseline. Maximum value of UPCR was set to 30. In 5, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data.

6, 7: Subjects with any missing data are imputed according to the subjects without missing data per randomized treatment assignment. Maximum value of UPCR was set to 30. Subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data.

8: Applicant's approach used monotone regression modelling, maximum value of UPCR was set to 75, worst 5% sampling for death and initiation of renal replacement therapy, and imputation was conducted separately for UPCR ≤ 3.5 g/g for subjects ≥ 18 years or ≤ 2.0 g/g for subjects < 18 years vs UPCR >3.5 g/g for subjects ≥ 18 years or > 2.0 g/g for subjects < 18 years. See ADMIREF6 results in Table 9.6.1_IR12 in Seq #0181 dated January 06, 2026. SE was not reported by the Applicant.

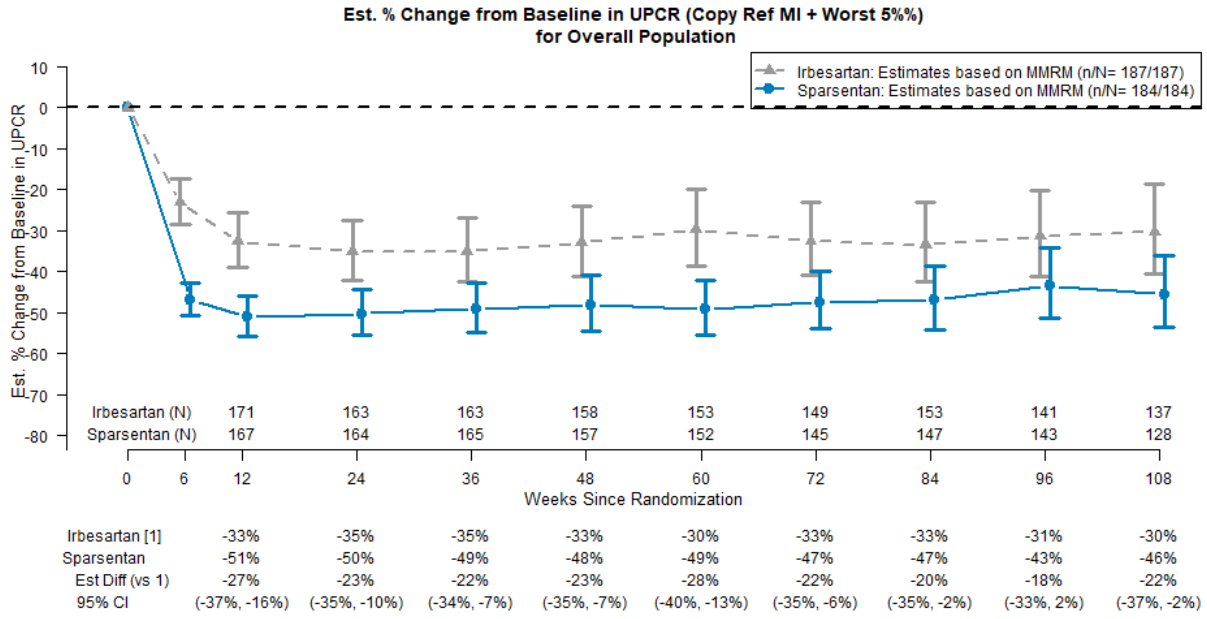
9: Applicant's approach used predictive mean matching algorithm, no bounds on UPCR imputed values, worst 5% sampling for death and initiation of renal replacement therapy, and imputation was conducted separately for UPCR ≤ 3.5 g/g for subjects ≥ 18 years or ≤ 2.0 g/g for subjects < 18 years vs UPCR >3.5 g/g for subjects ≥ 18 years or > 2.0 g/g for subjects < 18 years. See ADMIREF8 results in Table 9.7_IR12 in Seq #0181 dated January 06, 2026. SE was not reported by the Applicant.

8: Relative percent change between arms was converted from using (Est GMR -1)*100.

The mixed model repeated measures (MMRM) was fit to all UPCR data imputed as the primary statistical analysis model for 1-3. Applicant used ANCOVA model on the change from baseline in log UPCR at each visit with treatment, baseline log UPCR, and randomization strata as fixed effects, with Huber-White sandwich errors

Abbreviations: Est, estimated; Diff, difference; CI, confidence interval; ICE; intercurrent events; MAR, missing at random; MMRM, mixed model repeated measures; PMM, predictive mean matching; Reg, regression; FAS, full analysis set; UPCR, urine protein to creatinine ratio; GMR, geometric mean ratio.

Figure 8. Estimated UPCR Trajectory Based on Copy Reference Multiple Imputation with Worst 5% Sampling for ICE, FAS, DUPLEX



Source: Statistical Review Team
Non retrieved dropouts from sparsentan arm (including those who died, or had initiated renal replacement therapy) were imputed according to UPCR data from irbesartan completers and retrieved dropouts. Subjects who remained on randomized treatment and were missing outcome at Week 108 had their trajectory imputed according to respective subjects have no missing outcome at Week 108 and same randomized treatment.
After which, subjects who had died or initiated renal replacement therapy, had their outcome were sampled based on the worst 5% of the observed data
Abbreviations: UPCR, urine protein to creatinine ratio; Diff, different; CI, confidence interval; MMRM, mixed model repeated measures; MI, multiple imputation; %, percentage; FAS, full analysis set; MI, multiple imputation.

7.1.2.2.3. Proteinuria as Responder Type Endpoints

In practice guidelines (KIDIGO 2021), the currently accepted definition of complete remission of FSGS includes a UPCR <0.3 g/g; however, the Division has indicated openness to accepting other thresholds because some patients may have residual proteinuria due to irreversible glomerular scarring. The Applicant, based on the findings from PARASOL, evaluated other responder definitions of UPCR to provide support for efficacy.

The statistical team conducted responder analyses at Week 108 for selected UPCR cut-offs (Table 22). Acknowledging lack of multiplicity control, the estimated difference in the probability of UPCR <0.7 (a value chosen by the Applicant in the Summary of Clinical Efficacy) was 8% higher on the absolute scale in the sparsentan compared with the irbesartan arm. At higher values of UPCR thresholds of 1.0 or 1.5, the estimated differences in responders in the sparsentan compared to irbesartan arm was similar.

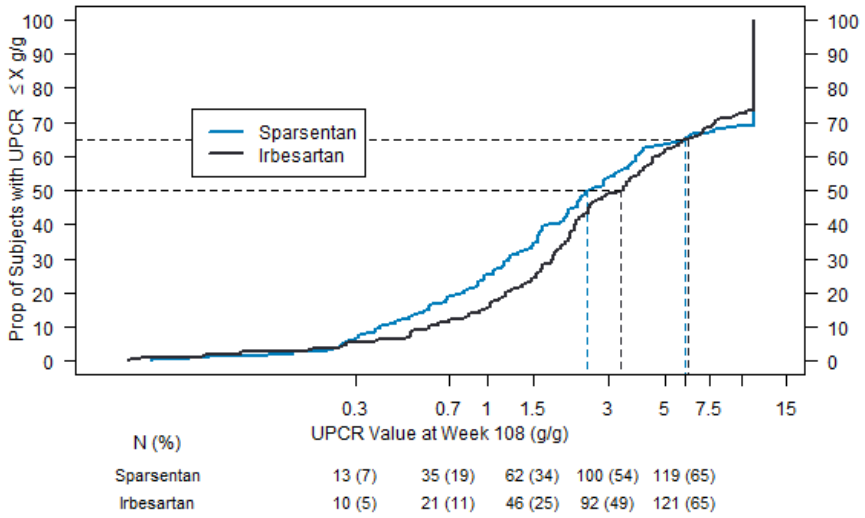
Table 22. Probability of UPCR Less Than Various Cut-offs at Week 108, FAS, DUPLEX

UPCR (g/g) <	Sparsentan (N=184)	Irbesartan (N=187)	Est Diff (95% CI)	Regression Diff (95% CI)
0.3	13 (7%)	10 (5%)	2% (-3%, 7%)	2% (-3%, 7%)
0.5	24 (13%)	16 (9%)	4% (-2%, 11%)	5% (-2%, 11%)
0.7	35 (19%)	21 (11%)	8% (1%, 15%)	8% (1%, 15%)
1.0	47 (26%)	30 (16%)	10% (1%, 18%)	10% (2%, 18%)
1.5	62 (34%)	46 (25%)	9% (0%, 18%)	10% (1%, 18%)

Source: Statistical Review Team
Missing UPCR data as well as UPCR data collected after occurrence of renal replacement therapy were handled as failures for the thresholds.
Abbreviations: UPCR, urine protein to creatinine; CI, confidence interval; Diff, difference, FAS, full analysis set

As shown in the cumulative distribution function for UPCR at Week 108 (Figure 9, the proportion of subjects with a value less than or equal to the threshold value was greater in the sparsentan arm compared to irbesartan arm for UPCR threshold values ranging from 0.3 to approximately 6 g/g, with smaller differences between arms at values greater than 3 g/g. Above UPCR values of 6 g/g, there was a numerical trend towards irbesartan.

Figure 9. Cumulative Distribution Function of UPCR at Week 108, FAS, DUPLEX



Source: Statistical Review Team
Subjects with missing UPCR are assigned the worst or largest observed value across arm for the cumulative distribution function. Percentages are with respect to the total randomized subjects in each arm. Data collected after occurrence of intercurrent event of initiation of renal replacement therapy are handled as missing.
Abbreviations: UPCR, urine protein to creatinine ratio; FAS, full analysis set; N, number of subjects meeting the definition of UPCR ≤X.

The difference in the adjusted probability of subjects meeting a given UPCR threshold between 0.7 to 1.5 g/g in the sparsentan compared to the irbesartan arm was, as a whole, similar across earlier and later time points. At Week 60, the difference in the adjusted probability was nominally significant for all the UPCR thresholds evaluated (Table 23).

Table 23. Cross-Sectional Responder Analysis for UPCR Less than Various Thresholds at Weeks 48 up to Week 108, FAS, DUPLEX

	Sparsentan (N=184)	Irbesartan (N=187)	Regression Diff (95% Robust CI)
Week 48			
UPCR < 0.3	10 (5%)	5 (3%)	3% (-1%, 7%)
UPCR < 0.5	24 (13%)	10 (5%)	8% (2%, 14%)
UPCR < 0.7	36 (20%)	22 (12%)	8% (1%, 15%)
UPCR < 1.0	50 (27%)	35 (19%)	9% (1%, 17%)
UPCR < 1.5	80 (43%)	56 (30%)	14% (5%, 23%)
Week 60			
UPCR < 0.3	17 (9%)	8 (4%)	5% (0%, 10%)
UPCR < 0.5	26 (14%)	13 (7%)	8% (2%, 14%)
UPCR < 0.7	38 (21%)	18 (10%)	12% (5%, 18%)
UPCR < 1.0	55 (30%)	32 (17%)	13% (5%, 21%)
UPCR < 1.5	79 (43%)	49 (26%)	17% (8%, 26%)
Week 72			
UPCR < 0.3	15 (8%)	7 (4%)	5% (0%, 9%)
UPCR < 0.5	30 (16%)	14 (7%)	9% (3%, 16%)
UPCR < 0.7	38 (21%)	23 (12%)	9% (1%, 16%)
UPCR < 1.0	49 (27%)	36 (19%)	8% (-0%, 16%)
UPCR < 1.5	69 (38%)	49 (26%)	12% (3%, 21%)
Week 96			
UPCR < 0.3	12 (7%)	7 (4%)	3% (-2%, 7%)
UPCR < 0.5	24 (13%)	13 (7%)	7% (1%, 13%)
UPCR < 0.7	37 (20%)	23 (12%)	8% (1%, 15%)
UPCR < 1.0	41 (22%)	31 (17%)	6% (-2%, 14%)
UPCR < 1.5	68 (37%)	51 (27%)	10% (1%, 19%)
Week 108			
UPCR < 0.3	13 (7%)	10 (5%)	2% (-3%, 7%)
UPCR < 0.5	24 (13%)	16 (9%)	5% (-2%, 11%)
UPCR < 0.7	35 (19%)	21 (11%)	8% (1%, 15%)
UPCR < 1.0	47 (26%)	30 (16%)	10% (2%, 18%)
UPCR < 1.5	62 (34%)	46 (25%)	10% (1%, 18%)

Source: Statistical Review Team
Subjects who did not have UPCR assessments, or had receipt of kidney replacement therapy, initiation of chronic dialysis or death were considered as failures for the above endpoint.
Risk differences were estimated from a logistic regression fit to the response adjusting for treatment and stratification factors, with robust estimators following Li et al 2025.
Abbreviations: UPCR, urine protein to creatinine ratio; Diff, difference; CI, confidence interval; FAS, full analysis set

According to a post-hoc exploratory analysis conducted by the Applicant, 34 subjects in the sparsentan arm and 14 in the irbesartan arm achieved "UPCR <0.3 g/g at any time" while on randomized treatment. Per the Applicant, using the first timepoint when UPCR was <0.3 g/g, a total of 19 sparsentan and 9 irbesartan subjects, respectively, achieved "sustained complete remission (UPCR <0.3 g/g) by Repeated Consecutive Measures Through Week 108."

The Applicant's analyses used on-treatment data, which, as discussed earlier in the review, is not considered appropriate. The review team conducted the analyses using all available UPCR data, excluding data after intercurrent event of renal replacement therapy, and had assessments evaluated up to Week 108. The following findings were noted:

- A total of 34 subjects randomized to sparsentan and 15 randomized to irbesartan achieved a UPCR < 0.3 g/g at any time. Of these subjects, a total of 17 subjects randomized to sparsentan and 9 randomized to irbesartan had a subsequent UPCR assessment meeting the criteria of <0.3 g/g.
- Of the subjects who achieved a UPCR <0.3 g/g, a total of six sparsentan and four irbesartan subjects continued to have a UPCR <0.3 g/g at subsequent visits until Week 108, and did not initiate renal replacement therapy or die.

The results indicate that few subjects in either treatment arm remained in complete remission from the first time point of achieving a UPCR <0.3 g/g through all subsequent visits to Week 108 and that the numbers were similar in the two arms.

Of note, the Applicant's assessment of the proportion of subjects achieving a sustained UPCR < 0.3 g/g at any time was only confirmed by one repeat measurement and was not necessarily sustained through Week 108. Acknowledging that patients can transiently exceed a threshold and that thresholds other than 0.3 g/g should also be considered, the team evaluated the proportion of subjects who achieved a given UPCR threshold at a timepoint such as Week 48 or Week 60 (given that these timepoints are close to 1 year), and were able to continue to maintain this UPCR threshold at each subsequent visit through Week 108. Subjects with missing data, including those who died prior to Week 108, or had received a kidney transplant, or initiated chronic dialysis were considered as non-responders for this definition.

At Week 48, the probability of achieving the UPCR threshold ranged from 5% versus 3% (sparsentan vs. irbesartan, respectively) at the most stringent threshold (UPCR <0.3 g/g) to 43% versus 30% (sparsentan vs. irbesartan, respectively) at the least stringent threshold (UPCR <1.5 g/g) (Table 24 The proportion of subjects achieving the UPCR threshold at Week 48 and continuing to meet the same UPCR threshold through Week 108 was similar or only slightly numerically higher in the sparsentan as compared to the irbesartan arm.

Table 24. Proportion of Responders at Week 48 and continue to be a responder after Week 48 up to Week 108, FAS, DUPLEX

	Week 48	Sustained Through Week 60	Sustained Through Week 72	Sustained Through Week 84	Sustained Through Week 96	Sustained Through Week 108
UPCR <0.3						
Sparsentan, Responders (%)	10 (5)	8 (4)	5 (3)	3 (2)	3 (2)	2 (1)
Irbesartan, Responders (%)	5 (3)	3 (2)	2 (1)	2 (1)	2 (1)	2 (1)
Difference (95% CI)	2.8 (-1.2, 6.8)	2.7 (-0.7, 6.2)	1.6 (-1.1, 4.4)	0.6 (-1.8, 2.9)	0.6 (-1.8, 2.9)	0
UPCR <0.5						
Sparsentan, Responders (%)	24 (13)	17 (9)	15 (8)	13 (7)	13 (7)	10 (5)
Irbesartan, Responders (%)	10 (5)	9 (5)	7 (4)	6 (3)	5 (3)	5 (3)
Difference (95% CI)	7.7 (1.9, 13.5)	4.4 (-0.8, 9.6)	4.4 (-0.4, 9.2)	3.9 (-0.6, 8.3)	4.4 (0, 8.8)	2.8 (-1.2, 6.8)
UPCR <0.7						
Sparsentan, Responders (%)	36 (20)	26 (14)	24 (13)	18 (10)	17 (9)	14 (8)
Irbesartan, Responders (%)	22 (12)	16 (9)	14 (7)	12 (6)	12 (6)	11 (6)
Difference (95% CI)	7.8 (0.4, 15.2)	5.6 (-0.9, 12)	5.6 (-0.6, 11.7)	3.4 (-2.2, 8.9)	2.8 (-2.6, 8.3)	1.7 (-3.4, 6.8)
UPCR <1.0						
Sparsentan, Responders (%)	50 (27)	39 (21)	34 (18)	29 (16)	26 (14)	22 (12)
Irbesartan, Responders (%)	35 (19)	25 (13)	22 (12)	19 (10)	16 (9)	14 (7)
Difference (95% CI)	8.5(-0.1, 17.0)	7.8 (0.2, 15.5)	6.7 (-0.6, 14)	5.6 (-1.2, 12.4)	5.6 (-0.9, 12)	4.5 (-1.5, 10.5)
UPCR <1.5						
Sparsentan, Responders (%)	80 (43)	63 (34)	56 (30)	48 (26)	43 (23)	36 (20)

	Week 48	Sustained Through Week 60	Sustained Through Week 72	Sustained Through Week 84	Sustained Through Week 96	Sustained Through Week 108
Irbesartan, Responders (%)	56 (30)	38 (20)	37 (20)	32 (17)	28 (15)	26 (14)
Difference (95% CI)	13.5 (3.8, 23.2)	13.9 (5, 22.9)	10.6 (1.9, 19.4)	9 (0.6, 17.3)	8.4 (0.4, 16.4)	5.7 (-1.9, 13.2)

Source: Statistical Review Team
Missing data are handled as non-responders to the treatment. Estimated difference in probability of response and 95% CI using a normal approximation to the difference in binomial proportion are presented.
Subjects who died, or have kidney transplant, or chronic dialysis have their UPCR outcome set as non-responders to the treatment
Abbreviations: UPCR, urine protein to creatinine ratio, FAS full analysis set; CI, confidence intervals.

The review team also used Week 60 to evaluate the probability of sustained UPCR less than various thresholds from Week 60 through Week 108. The difference between arms was generally small for the various thresholds through Week 108 (Table 25).

Table 25. Proportion of Responders at Week 60 and continue to be a responder after Week 60 up to Week 108, FAS, DUPLEX

	Week 60	Sustained Through Week 72	Sustained Through Week 84	Sustained Through Week 96	Sustained Through Week 108
UPCR < 0.3					
Sparsentan, Responders (%)	17 (9)	10 (5)	7 (4)	5 (3)	4 (2)
Irbesartan, Responders (%)	8 (4)	4 (2)	3 (2)	3 (2)	3 (2)
Difference (95% CI)	5 (-0.1, 10)	3.3 (-0.6, 7.2)	2.2 (-1.1, 5.5)	1.1 (-1.8, 4.1)	0.6 (-2.2, 3.3)
UPCR <0.5					
Sparsentan, Responders (%)	26 (14)	19 (10)	16 (9)	15 (8)	12 (7)
Irbesartan, Responders (%)	13 (7)	9 (5)	8 (4)	7 (4)	7 (4)
Difference (95% CI)	7.2 (1, 13)	5.5 (0.2, 10.9)	4.4 (-0.6, 9.4)	4.4 (-0.4, 9.2)	2.8 (-1.7, 7.3)
UPCR <0.7					
Sparsentan, Responders (%)	38 (21)	30 (16)	24 (13)	23 (13)	18 (10)
Irbesartan, Responders (%)	18 (10)	14 (7)	12 (6)	12 (6)	11 (6)
Difference (95% CI)	11 (3.8, 18)	8.8 (2.3, 15.4)	6.6 (0.6, 12.6)	6.1 (0.2, 12)	3.9 (-1.6, 9.4)
UPCR <1.0					
Sparsentan, Responders (%)	55 (30)	43 (23)	38 (21)	33 (18)	28 (15)
Irbesartan, Responders (%)	32 (17)	27 (14)	24 (13)	21 (11)	19 (10)
Difference (95% CI)	12.8 (4.2, 21)	8.9 (1, 16.9)	7.8 (0.3, 15.4)	6.7 (-0.5, 13.9)	5.1 (-1.7, 11.8)
UPCR <1.5					
Sparsentan, Responders (%)	79 (43)	65 (35)	54 (29)	48 (26)	41 (22)
Irbesartan, Responders (%)	49 (26)	42 (22)	36 (19)	32 (17)	29 (16)
Difference (95% CI)	16.7 (7.2, 26)	12.9 (3.7, 22)	10.1 (1.4, 18.8)	9 (0.6, 17.3)	6.8 (-1.2, 14.7)

Source: Statistical Review Team
Missing data are handled as non-responders to the treatment. Estimated difference in probability of response and 95% CI using a normal approximation to the difference in binomial proportion are presented.
Subjects who died, or have kidney transplant, or chronic dialysis have their UPCR outcome set as non-responders to the treatment
Abbreviations: UPCR, urine protein to creatinine; FAS, full analysis set; CI, confidence interval

7.1.2.2.4. Subgroup Analyses

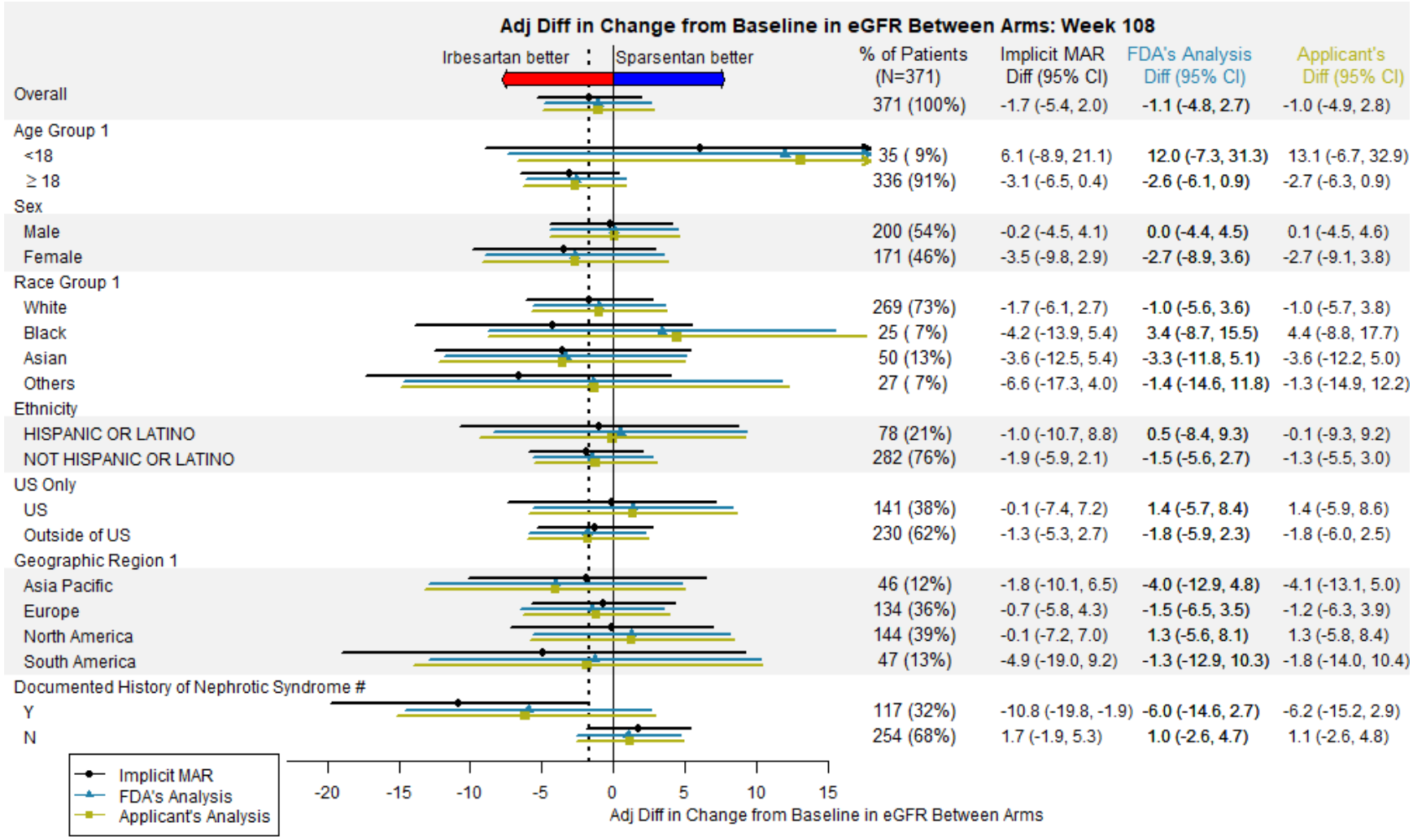
Subgroup analyses were conducted for the change from baseline in eGFR at Week 108 and for the change from baseline in proteinuria at Week 108.

Change from Baseline in eGFR Endpoint

Figure 10 and Figure 11 shows the adjusted change from baseline in eGFR to Week 108 for various subgroups of interest. Positive numbers in the figure (see blue arrow) indicate that sparsentan is better than irbesartan; negative numbers in the figure (see red arrow) indicate that irbesartan is better than sparsentan. The analyses indicate some observed heterogeneity in the subgroups; however, in general caution should be exercised when interpreting subgroup analyses but particularly in a case such as this, since the eGFR endpoint was not met. Selected

eGFR trajectories (age, sex, US, eGFR (<60 vs ≥ 60 to <120 mL/min/1.73 m^2), documented history of nephrotic syndrome) are included in Section 15.3.

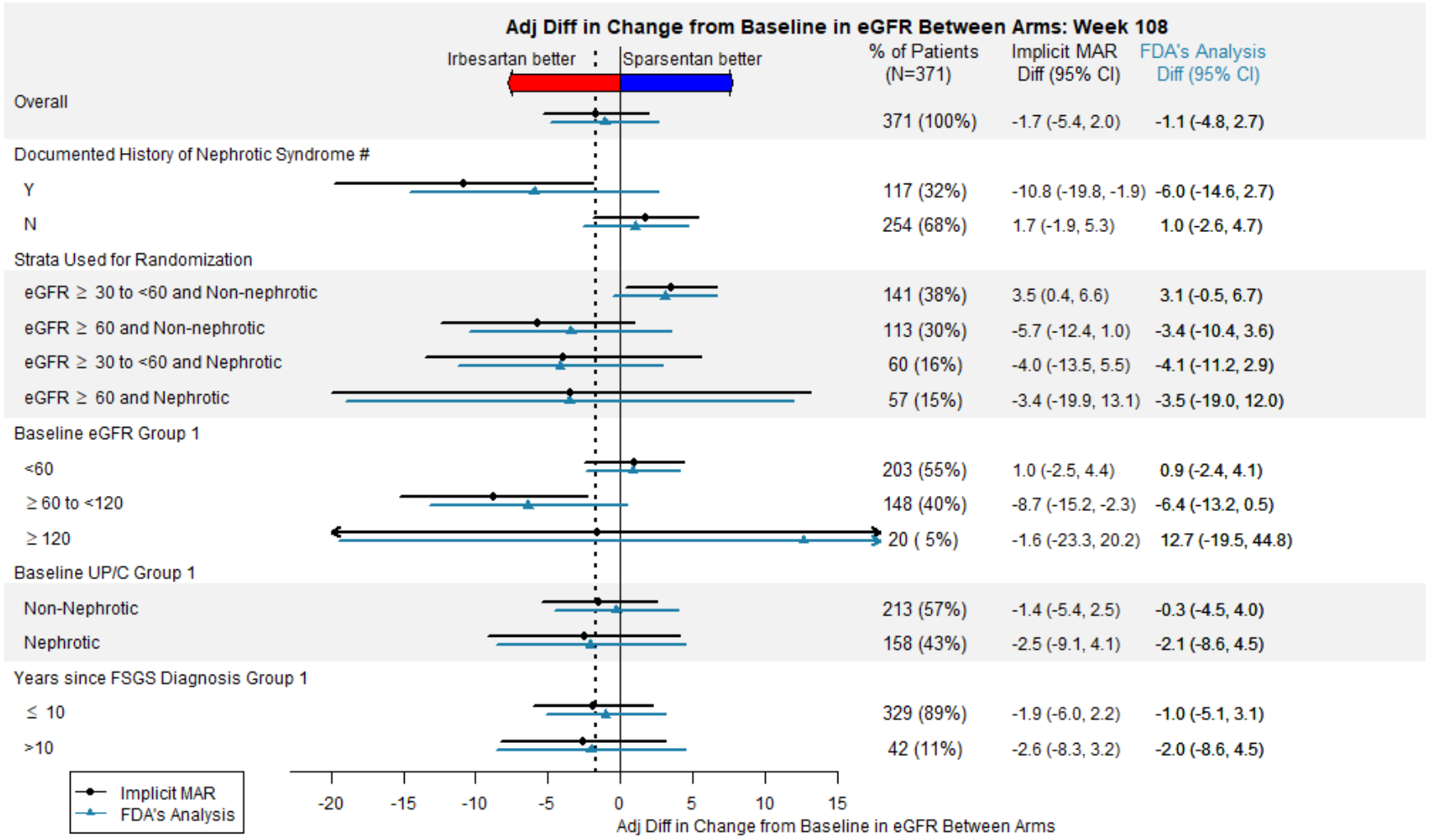
Figure 10. Forest Plot for the Change from Baseline in eGFR at Week 108 Between Arms (Figure 1 of 2), FAS, DUPLEX



Source: Statistical Review Team, Reproduced results from s006-ir15-resp-part1-biostats.pdf in Seq 0191 submitted by Applicant.
The MMRM was used to analyze the change from baseline in eGFR post-baseline adjusting for baseline eGFR, treatment, visit, stratification factors, visit by treatment interaction. The vertical dotted line at -1.7 is the observed estimate in the overall population after excluding data due to intercurrent event of renal replacement therapy and under an implicit MAR for missing data.

Implicit MAR (Black line): Observed data excluding data collected after ICE and implicit MAR assumption based on MMRM model.
FDA's Analysis (Blue line and 95% CI): Copy reference with worst 5% sampling for intercurrent event of initiation of renal replacement therapy and death. Rubin's rule is used to combine the 500 multiple imputation results.
Applicant's Analysis (Golden line and 95% CI): Similar copy reference multiple imputation (500 times) with worst 5% sampling for intercurrent event of initiation of renal replacement therapy and death based on Agency's request in IR15. Different simulation seed was used compared to the blue lines. Rubin's rule is used to combine the 500 multiple imputation results.
The Agency included the following exploratory subgroups for Ethnicity, US only, and Documented History of Nephrotic Syndrome. Large uncertainties about the point estimates are observed when there are <10% randomized in the subgroup categories.
Abbreviations: Adj, adjusted; Diff, difference; eGFR, estimated glomerular filtration rate; Diff, difference; CI, confidence interval; MI, multiple imputation; FSGS, Focal Segmental Glomerulosclerosis; Y, Yes; N, No; UP/C, urine protein to creatinine ratio; MMRM, mixed model repeated measures; MAR, missing at random; Copy Ref, copy reference.

Figure 11. Forest Plot for the Change from Baseline in eGFR at Week 108 Endpoint Between Arms (Figure 2 of 2), FAS, DUPLEX



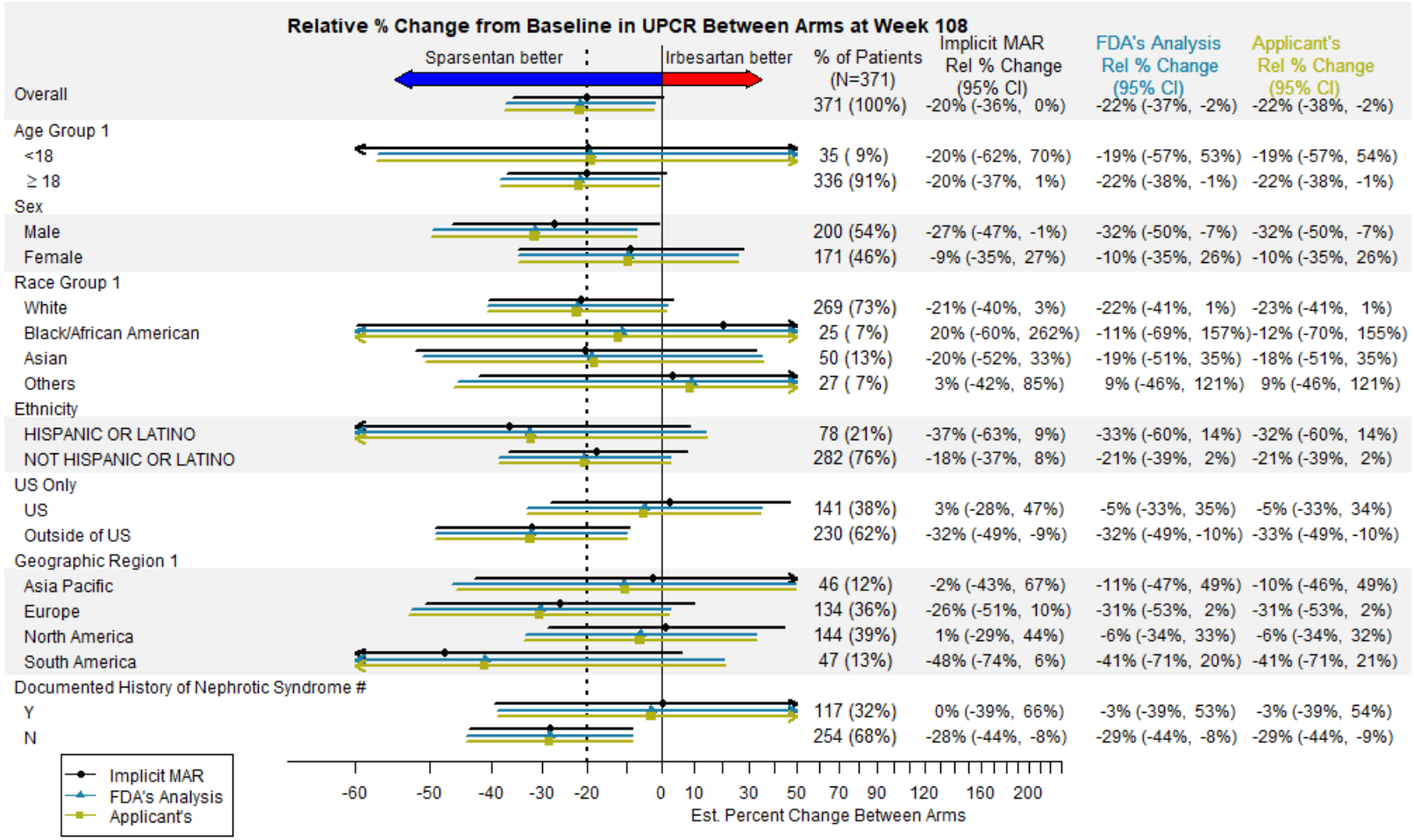
Source: Statistical Review Team
#: Documented history of nephrotic syndrome is defined as follows: If the term "nephrotic syndrome" was present in medical history or if all of the following conditions were met at any of the visits prior to the first dose of randomized treatment: UP/C >3.5 g/g (adults) or UP/C >2 g/g (pediatrics), serum albumin <3.0 g/dL, and abnormal edema from physical examination.
Non-Nephrotic UPCR is defined by screening UPCR ≤3.5 g/g for subjects ≥18 years of age and ≤2 g/g for subjects <18 years of age.

Nephrotic UPCR is defined by screening UPCR >3.5 g/g for subjects ≥18 years of age and >2 g/g for subjects <18 years of age.
FDA's Analysis (Blue line): Copy reference with worst 5% sampling for intercurrent event of initiation of renal replacement therapy and death. MMRM was used to analyze the change from baseline in eGFR post-baseline adjusting for baseline eGFR, treatment, visit, stratification factors, and visit by treatment interaction. Rubin's rule is used to combine the 500 multiple imputation results.
The Agency included the following exploratory subgroups for Ethnicity, US only, and Documented History of Nephrotic Syndrome. Large uncertainties about the point estimates are observed when there are <10% randomized in the subgroup categories.
Abbreviations: Adj, adjusted; Diff, difference; eGFR, estimated glomerular filtration rate; Diff, difference; CI, confidence interval; MI, multiple imputation; FSGS, Focal Segmental Glomerulosclerosis; Y, Yes; N, No; UP/C, urine protein to creatinine ratio; MMRM, mixed model repeated measures; MAR, missing at random; Copy Ref, copy reference

Change from Baseline in Proteinuria Endpoint

Figure 12 and Figure 13 show the results of subgroup analyses for the change from baseline in UPCR at Week 108, assuming implicit MAR according to the MMRM model with copy reference multiple imputation combined with worst 5% sampling for intercurrent events of initiation of renal replacement therapy and death. The analyses indicate some observed heterogeneity in the subgroups. In general caution should be exercised when interpreting subgroup analyses but particularly in a case such as this, since the eGFR endpoint was not met and the UPCR results at Week 108 are only nominally significant after multiple imputation. Selected subgroups are presented in 15.3.

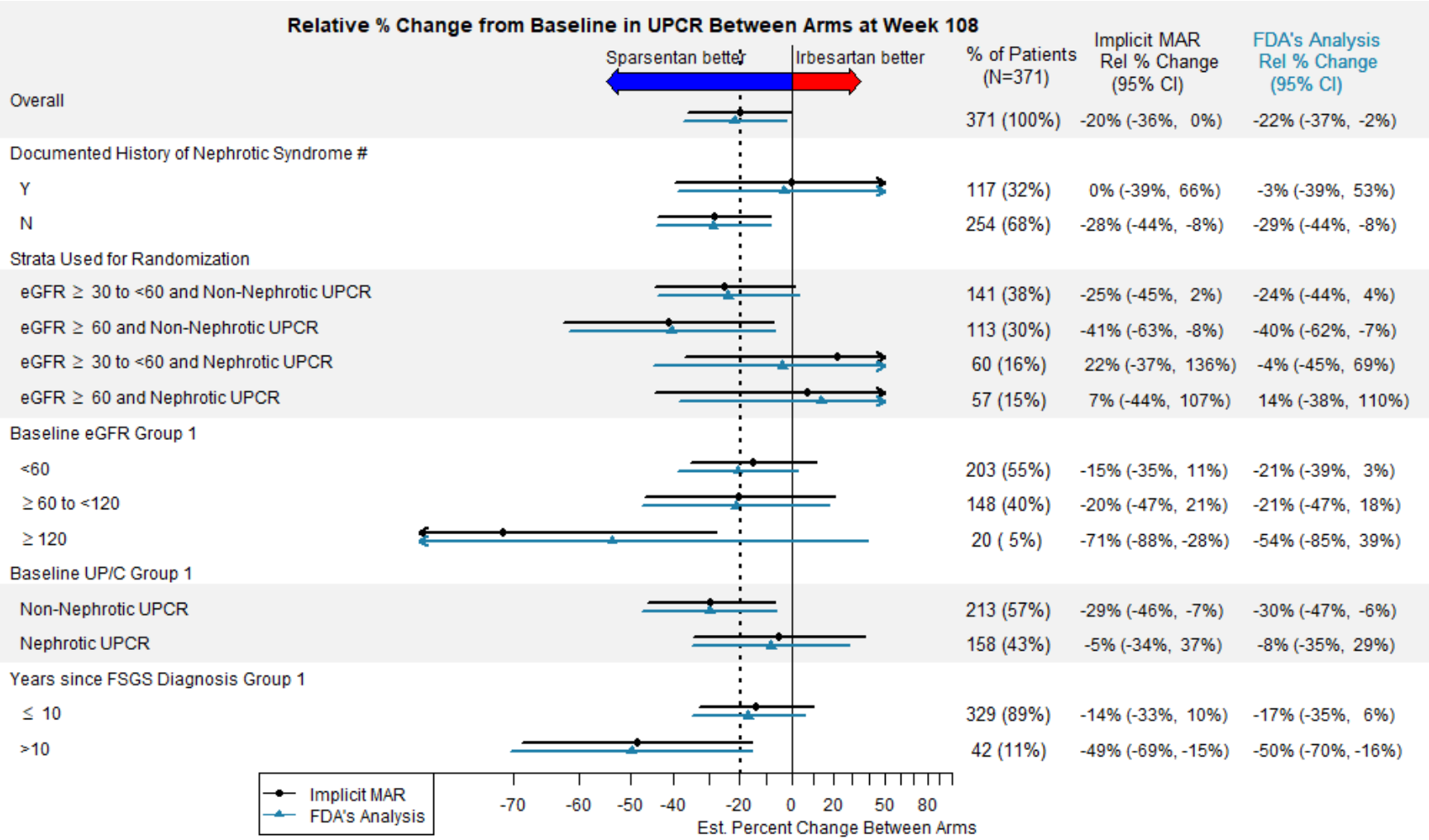
Figure 12. Forest Plot for the Relative % Change from Baseline in UPCR at Week 108 Between Arms (Figure 1 of 2), FAS, DUPLEX



Source: Statistical Review Team; See response for IR15 of s006-ir15-resp-part1-biostats.pdf in Seq 0191 from Applicant
Negative values of percentage change indicate sparsentan is better than irbesartan; Positive values of percentage change indicates irbesartan is better than sparsentan.
Implicit MAR (Black line): Observed data excluding data collected after ICE and implicit MAR assumption based on MMRM model. MMRM was used to analyze the change from baseline in log UPCR post-baseline adjusting for baseline log UPCR, treatment, visit, stratification factors, visit by treatment interaction. The vertical dotted line at ~ -20% is the observed estimate in the overall population.

FDA's Analysis (Blue line): Copy reference multiple imputation (1000 times) with worst 5% sampling for intercurrent event of initiation of renal replacement therapy and death. MMRM was used to analyze the change from baseline in log UPCR post-baseline adjusting for baseline log UPCR, treatment, visit, stratification factors, and visit by treatment interaction. Rubin's rule is used to combine the 1000 multiple imputation results.
Applicant's (Golden line): Applicant conducted copy reference multiple imputation (500 times) with worst 5% sampling for intercurrent event of initiation of renal replacement therapy and death based on Agency's request in IR15. Different simulation seed was used compared to the blue lines. MMRM was used to analyze the change from baseline in log UPCR post-baseline adjusting for baseline log UPCR, treatment, visit, stratification factors, and visit by treatment interaction. Rubin's rule is used to combine the 500 multiple imputation results. Results in columns are presented in the USPI.
Large uncertainties about the point estimates are observed when there are <10% randomized in the subgroup categories.
Abbreviations: Adj, adjusted; Diff, difference; eGFR, estimated glomerular filtration rate; Diff, difference; CI, confidence interval; MI, multiple imputation; FSGS, Focal Segmental Glomerulosclerosis; Y, Yes; N, No; UPCR/UP/C, urine protein to creatinine ratio; MAR, missing at random; Ref, reference; Rel, relative; %, percentage; MMRM, mixed model repeated measures; Copy Ref, copy reference

Figure 13. Forest Plot for the Relative % Change from Baseline in UPCR at Week 108 Between Arms (Figure 2 of2), FAS, DUPLEX



Source: Statistical Review Team
Negative values of percentage change indicate sparsentan is better than irbesartan; Positive values of percentage change indicates irbesartan is better than sparsentan.
#: Documented history of nephrotic syndrome is defined as follows: If the term “nephrotic syndrome” was present in medical history or if all of the following conditions were met at any of the visits prior to the first dose of randomized treatment: UP/C >3.5 g/g (adults) or UP/C >2 g/g (pediatrics), serum albumin <3.0 g/dL, and abnormal edema from physical examination.

Non-Nephrotic UPCR is defined by screening UPCR ≤3.5 g/g for subjects ≥18 years of age and ≤2 g/g for subjects <18 years of age.
Nephrotic UPCR is defined by screening UPCR >3.5 g/g for subjects ≥18 years of age and >2 g/g for subjects <18 years of age.
Implicit MAR (Black line): Observed data excluding data collected after ICE and implicit MAR assumption based on MMRM model. MMRM was used to analyze the change from baseline in log UPCR post-baseline adjusting for baseline log UPCR, treatment, visit, stratification factors, visit by treatment interaction. The vertical dotted line at ~ -20% is the observed estimate in the overall population.
Copy Ref + Worst 5% (Blue line): Copy reference with worst 5% sampling for intercurrent event of initiation of renal replacement therapy and death. MMRM was used to analyze the change from baseline in log UPCR post-baseline adjusting for baseline log UPCR, treatment, visit, stratification factors, and visit by treatment interaction. Rubin's rule is used to combine the 1000 multiple imputation results.
Large uncertainties about the point estimates are observed when there are <10% randomized in the subgroup categories.
Abbreviations: Adj, adjusted; Diff, difference; eGFR, estimated glomerular filtration rate; Diff, difference; CI, confidence interval; MI, multiple imputation; FSGS, Focal Segmental Glomerulosclerosis; Y, Yes; N, No; UPCR/UP/C, urine protein to creatinine ratio; MAR, missing at random; Ref, reference; Rel, relative; %, percentage; MMRM, mixed model repeated measures; Copy Ref, copy reference

7.1.2.2.5. Composite Renal Events

The Applicant also conducted exploratory analyses assessing effects on clinical outcomes and surrogate endpoints for progression to kidney failure that are commonly used in trials of CKD. Of note, when these endpoints are used as key efficacy endpoints in clinical trials, the definition of what constitutes an endpoint event is prespecified and measures are put in place to ensure the systematic capture of these events. For example, for eGFR-based endpoints, for subjects reaching the prespecified threshold (e.g., eGFR <15 mL/min/1.73 m^2 or ≥40% reduction in eGFR), confirmatory samples are obtained within some window of reaching the threshold (e.g., 4 weeks after the date of the first eGFR assessment meeting the threshold) to confirm the endpoint event has occurred. In DUPLEX, such measures were not instituted. In addition, DUPLEX was not designed to address differences in kidney outcomes.

The Applicant's analyses of the proportion of subjects who died, initiated renal replacement therapy or experienced a confirmed eGFR <15 mL/min/1.73 m^2 or a confirmed decrease in eGFR ≥40% mL/min/1.73 m^2 is shown in the table below (Table 26). For these analyses, the Applicant defined a "confirmed event" as one that was confirmed by an assessment at least 14 days after the initial event and limited the analysis to an on-treatment analysis. For this review, the review team focused on confirmed eGFR <15 mL/min/1.73 m^2, or initiation of RRT, or death.

Table 26. Applicant's Analysis of Composite Kidney Endpoints and Composite Endpoint Components, FAS, DUPLEX

	Sparsentan (N = 184) n (%)	Irbesartan (N = 187) n (%)	Sparsentan versus Irbesartan
Confirmed 40% Reduction in eGFR, ESRD, or Death	37 (20.1)	43 (23.0)	RR: 0.87 (0.60, 1.26)
Confirmed 40% Reduction in eGFR	30 (16)	36 (19)	
ESRD	12 (6.5)	21 (11.2)	RR: 0.58 (0.31, 1.07)
Confirmed eGFR <15 mL/min/1.73 m^2	5 (3)	11 (6)	
RRT Initiated	10 (5)	13 (7)	
Confirmed eGFR <15 mL/min/1.73 m^2 OR RRT Initiated	12 (7)	21 (11)	
Death	4 (2)	3 (2)	
Renal Death	0	0	
Confirmed 40% Reduction in eGFR, ESRD, or Renal Death	35 (19.0)	42 (22.5)	RR: 0.84 (0.58, 1.23)
Confirmed 50% Reduction in eGFR, ESRD, or Death	23 (12.5)	33 (17.6)	RR: 0.70 (0.45, 1.11)
Confirmed 50% Reduction in eGFR, ESRD, or Renal Death	21 (11.4)	31 (16.6)	RR: 0.68 (0.43, 1.10)

Abbreviations: CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CMH = Cochran-Mantel-Haenszel; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FAS = Full Analysis Set; n = number of subjects; RR = relative risk; RRT = renal replacement therapy
Notes: Percentages are based on all patients in the FAS within each group. eGFR is determined using the CKD-EPI equation for patients ≥16 years of age at screening, and the Modified Schwartz formula for patients <16 years of age at screening. ESRD is defined as initiation of RRT or sustained eGFR <15 mL/min/1.73^2 during the study (confirmed after repeat assessment of at least 14 days after initial assessment). Patients with events are those who met the indicated criteria. The relative risks and their corresponding 95% CIs are obtained from a CMH test controlling for randomization factors.
Source: Table 14.2.4.1 (Program: T14.2.4.1-RespEffend.sas); Table 14.2.4.1.1 (Program: T14.2.4.1.1-RespEffend.sas); Table 14.2.4.1.2 (Program: T14.2.4.1.2-RespEffend.sas); Table 14.2.4.1.3 (Program: T14.2.4.1.3-TTEEffend.sas); Table 14.2.4.1.4 (Program: T14.2.4.1.4-ESRD.sas); Table 14.2.4.1.6 (Program: T14.2.4.1.6-RespEffend.sas); Table 14.2.4.1.11 (Program: T14.2.4.1.11-RespESRD.sas); and Table 14.3.2.1.1 (Program: T14.3.2.1.1-Deaths.sas).

Source: Table 14.2.4.1 of the Applicant's CSR

Of note, the Applicant's results are based on on-treatment eGFR data only and included some events collected after the end of Week 108 double-blind period. In addition, the Applicant did not report the number of subjects who did not complete the study and therefore had incomplete eGFR assessments prior to Week 108; in the Applicant's analyses, these subjects are considered a "success," i.e., not an event for the eGFR-based endpoints.

Given concerns with the methodology used by the Applicant, including using only on-treatment eGFR values to determine a confirmed sustained eGFR ≤15 mL/min/1.73 m^2, the FDA review team conducted additional analyses using the scheduled visits collected after treatment discontinuation to determine whether participants had a confirmed eGFR ≤15 mL/min/1.73 m^2.

The review team also varied the timing of the repeat assessment, using an assessment obtained at least 28 days after the initial assessment (instead of at least 14 days) to define a "confirmed" eGFR ≤15 mL/min/1.73 m^2. For reporting the amount of missing data, the team determined the number of participants who did not have a Week 108 assessment (but may have had an assessment at Week 96 or Week 112), as well as the number of participants who did not have an assessment at Week 108 and also did not have an assessment at Week 96 and 112.

The table below shows the number of subjects who had a confirmed eGFR <15 mL/min/1.73 m^2 based on two consecutive measurements made at least 14 days apart, or initiated RRT based on data up to Week 108 (i.e., Day ≤771 of the study) (Table 27). Approximately 8% of subjects randomized to sparsentan and 10% randomized to irbesartan had a confirmed eGFR <15 mL/min/1.73 m^2 based on two consecutive assessment visits, initiated RRT, or died at week 108. The adjusted difference in the probability of an event at Week 108 was 2.6% lower (95% robust CI: -8.1%, 2.9%) in the sparsentan as compared to irbesartan arm. The proportion of subjects with a given component of the composite (e.g., proportion of subjects who died, proportion who initiated RRT) was similar in the two arms. Approximately 21% of subjects randomized to sparsentan and 17% randomized to irbesartan did not have a Week 108 assessment.

The Applicant also conducted a sensitivity analysis using unscheduled visits to determine if a subject had a confirmed eGFR <15 mL/min/1.73 m^2. Using this approach, a total of 20 subjects in the irbesartan arm and 14 in the sparsentan arm had a confirmed eGFR <15 mL/min/1.73 m^2, initiated RRT, or died. In a sensitivity analysis using a window of at least 28 days after the initial assessment to define a confirmed eGFR, 18 subjects in the irbesartan arm and 14 in the sparsentan met the endpoint at Week 108.

In conclusion, there were few events in either arm. Given the limited number of events and post-hoc nature of these analyses, it is challenging to draw reliable conclusions about sparsentan's effect on these outcomes.

Table 27. Total Number of Subjects Who Had Received Kidney Transplant, or Initiated Chronic Dialysis, Confirmed eGFR <15 mL/min/1.73 m^2 on Two Assessments Made at Least 14 Days Apart by Week 108 (Day 771), and Missing Any Weeks 96 Or 108 eGFR Assessments, FAS, DUPLEX

Description	Sparsentan (N=184)	Irbesartan (N=187)	Adj Risk Diff (95% Robust CI)
Alive and did not have confirmed eGFR <15, and RRT	170 (92)	168 (90)	
Missing Week 108 assessments	38 (21)	32 (17)	
Without eGFR assessments between Weeks 96 – 112 [1]	22 (12)	20 (11)	
Number with confirmed eGFR <15, or RRT, or death	14 (8)	19 (10)[2]	-2.6 (-8.1, 2.9)
Age <18 years	2 (1)	6 (3)	
Documented history of nephrotic syndrome (Yes)	11 (6)	11 (6)	
Documented history of nephrotic syndrome (No)	3 (2)	8 (4)	
Number of Participants with components[2, 3]	14 (8)	19 (10)[1]	
Any confirmed eGFR <15	6 (3)	9 (5)	
RRT	9 (5)	12 (6)	
Death	4 (2)	2 (1)	

1: Subjects' eGFR assessments were counted as missing for Week 108 assessments if they did not have either Week 96, 108, or 112 assessments.
2: A participant can have more than one of the components.
3: The Applicant reported 20 events in the irbesartan arm based on unscheduled eGFR data that was collected that was not adequately flagged in the submitted dataset to be used without additional data manipulation. The eGFR data used in the FDA analysis were based on ANL06FL = "Y". In addition, the events for RRT and death reported by the Applicant included data collected beyond Day 771, end of the double-blind period, and during the open label period for some subjects.
Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set; RRT, renal replacement therapy; Adj, adjusted; Diff, difference; CI, confidence intervals.

7.1.3. Key Efficacy Review Issues

7.1.3.1. Clinical Significance of the Treatment Effect on Proteinuria

Issue

Pre-specified and post hoc analyses demonstrate that sparsentan reduces proteinuria in subjects with FSGS; however, the magnitude of reduction varies depending on the analytic method used to handle missing data. A key review issue was whether the magnitude of the reduction in proteinuria relative to irbesartan will translate to a clinically meaningful effect on progression to kidney failure.

Background

Data supporting the use of proteinuria as a surrogate endpoint for a treatment's effect on progression to kidney failure include a strong understanding of the pathophysiology of FSGS, and the role of proteinuria in the pathophysiology of FSGS, as well as epidemiologic evidence. In an analysis of patient-level data from over 1,600 patients with FSGS across more than 25 registries and datasets, 84-month kidney failure-free survival rate was higher for patients achieving a UPCR below various thresholds at 24 months (i.e., 0.3, 0.5, 0.7, 1.0, 1.5 g/g)

compared to patients who had not achieved those UPCR thresholds.[7] While these observational data support an association between proteinuria and the risk of kidney failure, data from randomized controlled trials indicating that treatment effects on proteinuria above some magnitude reliably predict treatment effects on outcomes are currently lacking.

Assessment

The review team acknowledges that the proteinuria endpoint (FPRE) at Week 36, which was intended to support accelerated approval, was prespecified, alpha-protected and statistically significant. At interim analysis, according to FDA's analysis (and consistent with the Applicant's analysis), the marginal probability of FPRE was 42% (n=78) and 26% (n=49) in the sparsentan and irbesartan arms, respectively. The marginal difference in probability was 17% higher (95% CI: 8% to 26%; p<0.001) on sparsentan compared to irbesartan.

However, because the magnitude of proteinuria reduction at interim analysis was smaller than the assumed reduction used to power the confirmatory eGFR endpoint (and given concerns with the interim eGFR findings), the Division recommended that the Applicant complete the ongoing trial in lieu of submitting an application for accelerated approval based on the results of the interim analysis.

Apart from the FPRE at interim analysis all additional analyses of proteinuria in DUPLEX were post hoc and exploratory. These additional analyses were conducted to better understand the treatment effect of sparsentan on proteinuria and included an evaluation of proteinuria as a continuous endpoint and various responder analyses.

Analyses of proteinuria as a continuous endpoint showed that the relative percent change from baseline in UPCR between the sparsentan and irbesartan arms ranged from 20% to 26% depending on the assumptions of the multiple imputation used to handle the missing data (overall, 28% of randomized subjects did not have a UPCR assessment at Week 108) (Table 21).

For sustained responder type analyses, various proteinuria cutoffs ranging from a UPCR of <0.3 g/g (CR) to <1.5 g/g were used. These analyses showed that for CR, there was no difference between treatment arms in the proportion of subjects who achieved CR at Week 48 or Week 60 and maintained CR through to Week 108. For higher UPCR thresholds (<0.5, <0.7, <1.0, <1.5 g/g), a slightly numerically higher proportion of subjects on sparsentan achieved those thresholds and maintained them through to Week 108 compared to subjects on irbesartan (Table 24 and Table 25).

[7] The PARASOL-FSGS workgroup presented these data at a workshop titled "Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis" on October 7 and 8, 2024. PARASOL (Proteinuria and Other Biomarkers as Endpoints for Clinical Trials in Kidney Disease) is a project that is co-sponsored by the International Society of Glomerular Disease, NephCure, the Kidney Health Initiative, and the National Kidney Foundation. The purpose of the PARASOL-FSGS project is to build on what is known from published work on FSGS to advance the understanding of quantitative relationships between potential surrogate endpoints and long-term outcomes in FSGS to support regulatory drug approval.

Sparsentan and irbesartan can have acute hemodynamic effects leading to proteinuria reduction while on the drug and a rebound in proteinuria after discontinuation of the drug. To evaluate whether the effect on proteinuria likely reflected an effect on the underlying disease, an evaluation was conducted of change from baseline to Week 112 (i.e., after being off study drug for 4 weeks and being restarted on standard of care, which included ACEi or ARBs other than irbesartan). In an analysis excluding data due to intercurrent events and using similar model assumptions as the Applicant's primary analysis, the geometric LS mean percent change from baseline to Week 112 in UPCR was -10% in the sparsentan arm and -24% in the irbesartan arm. These results are difficult to interpret because subjects were allowed to take ACEi/non-irbesartan ARBs during the "off treatment" period from Week 108 to 112, and these medications also have an acute hemodynamic effect on proteinuria and eGFR. However, based on these results, sparsentan's effect on proteinuria seems to reflect a reversible pharmacodynamic effect (as opposed to an effect on the underlying disease).

Blood pressure trajectories from baseline to Week 112 (Figure 14) track with the proteinuria trajectories during the same timeframe. This observation further supports that sparsentan's effect on proteinuria may be a reversible hemodynamic effect, rather than an effect on the underlying disease.

Conclusion

The effect on proteinuria in the overall DUPLEX population, after appropriately addressing missing data to target an ITT estimand, ranged between 20% to 26%, and can be tipped when assumptions were varied. There was also no clear sustained responder population across the range of UPCR thresholds from 0.3 g/g to 1.5 g/g. Further, off-treatment analyses suggest that sparsentan's effect on proteinuria appears to be a reversible pharmacodynamic effect rather than an effect on the underlying disease. Given the limitations of the data supporting the use of proteinuria as a surrogate endpoint and the size of the treatment effect, it is uncertain whether the size of the treatment effect on proteinuria relative to irbesartan will translate into a clinically meaningful effect on progression to kidney failure in the overall trial population. To further understand the clinical significance of the proteinuria findings, the review team also evaluated the eGFR and other exploratory data in DUPLEX (see Section 7.1.3.2).

7.1.3.2. Sparsentan's Effect on the Rate of Loss of Kidney Function (eGFR) and Kidney Failure Events

Issue

Given the limitations of the data supporting the use of proteinuria as a surrogate endpoint and the size of the treatment effect on proteinuria, a key review issue was whether other findings in the trial provide reassurance that sparsentan's effect on proteinuria will translate into a clinically meaningful effect on progression to kidney failure.

Background

The primary efficacy endpoint at the final analysis was the rate of change in eGFR from baseline to Week 108 and was not statistically significant. However, analyses of the PARASOL

observational data suggest that although changes in eGFR are associated with kidney failure in patients with FSGS, it may be challenging to demonstrate efficacy using eGFR-based endpoints in clinical trials of FSGS because of the high variability in eGFR in patients with FSGS and the size of the affected population.

The Applicant asserts that total eGFR slope (assessed from Day 1 to Week 108) favored sparsentan and that based on the findings from PARASOL, the high variability in eGFR in patients with FSGS would make it infeasible to assess eGFR as an endpoint in a randomized controlled trial in this population because it would require "too large a sample size and too long a timeframe." The Applicant also asserts that various post hoc analyses related to kidney outcomes were in favor of sparsentan.

Assessment

Effects on eGFR

The endpoint intended to support traditional approval was eGFR slope from Day 1 to Week 108. According to the Applicant, the "total slope of eGFR assessed from Day 1 to Week 108 – full analysis set" at Week 108 in the sparsentan and irbesartan arms was -5.4 and -5.7 mL/min/1.73 m^2 per year, respectively. The slope difference (sparsentan-irbesartan) was 0.3 mL/min/1.73 m^2 per year (95% CI: -1.7, 2.4; p=0.75).

The statistical team noted, however, that the Applicant's eGFR slope for the primary endpoint was estimated using only on-treatment data. In the Applicant's primary analysis of the endpoint, up to 33% of the randomized subjects were excluded from their analysis, and 25% of randomized subjects did not have an eGFR assessment at Week 108. In addition, the analysis only included eGFR assessments from Week 2 to Week 108 (as opposed to the prespecified analysis from Day 1 to Week 108), which is more consistent with a chronic slope interpretation.

When including all observed eGFR data and handling the intercurrent events of renal replacement therapy or death as missing at random according to the regression model (i.e., the Applicant's primary statistical analysis model), the annualized eGFR slope from Day 1 to Week 108 was -6.1 and -6.3 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively, resulting in a difference (sparsentan-irbesartan) of 0.1 mL/min/1.73 m^2 per year (95% CI: -1.9, 2.1; p=0.89).

eGFR slope-based analyses make strong assumptions that the eGFR decline over time is linear. To relax this assumption, the change from baseline to Week 108 in eGFR was assessed using all data and handling the intercurrent events of kidney transplant, renal replacement therapy, or death as missing at random according to the regression model. When excluding data collected after ICEs of RRT and treating those data as MAR according to the Applicant's MMRM regression model, the adjusted mean change from baseline in eGFR at Week 108 was -13.9 and -12.2 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively, resulting in a difference (sparsentan-irbesartan) of -1.7 mL/min/1.73 m^2 (95% CI: -5.4, 2.0; p=0.36) (Table 15).

When incorporating imputation to address missing data, at Week 108, the mean change from baseline in eGFR was -13.9 and -12.8 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively, resulting in a difference (sparsentan-irbesartan) of -1.1 mL/min/1.73 m^2 (95%

CI: -4.8, 2.7) (Table 17). Across all study visits, the adjusted mean decrease from baseline in eGFR was numerically greater (i.e., worse) in the sparsentan arm compared to the irbesartan arm (Figure 4).

Acute hemodynamic effects on eGFR can make it challenging to interpret on-treatment changes in eGFR because the pharmacodynamic effects of a drug on eGFR cannot be distinguished from true effects on disease progression. As such, an analysis of change from baseline to a reasonable timepoint after study treatment discontinuation can be an important analysis because it assesses the residual effect on eGFR assuming the acute effect on eGFR has reversed/resolved.

According to the Applicant, the least squares mean change from baseline to Week 112 (4 weeks after discontinuation of randomized treatment) in eGFR in subjects who completed blinded treatment was -10.4 and -12.1 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively, resulting in a difference (sparsentan-irbesartan) of 1.8 mL/min/1.73 m^2 (95% CI -1.39, 4.93). Given concern about bias related to including only subjects who completed the double-blind period, the statistical team conducted an analysis based on all randomized subjects with eGFR data collected through Week 112.

Given the amount of missing eGFR data at Week 112 (25%), it is challenging to obtain a reliable estimate of the difference between treatment arms for that timepoint. However, using all eGFR data and handling intercurrent events and missing data as missing at random (MAR), the least squares mean change from baseline to Week 112 in eGFR was similar between the treatment arms, i.e., -13.2 and -13.0 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively, resulting in a difference (sparsentan-irbesartan) of -0.2 mL/min/1.73 m^2 (95% CI -3.8, 3.4).

According to analyses of observational data conducted as part of the PARASOL project, it may be challenging to detect a treatment effect on eGFR in a feasible clinical trial because of the variability in eGFR in this population. However, as shown in Table 28, the statistical team's analysis indicated that the observed residual variability in eGFR in the overall DUPLEX population (approximately 46 mL/min/1.73 m^2) was much smaller than that reported in the observational PARASOL data (overall residual variability approximately 203-232 mL/min/1.73 m^2).

In their sample size calculations for DUPLEX, the Applicant assumed a residual annualized variability for chronic slope of 10.8 mL/min/1.73 m^2 per year. Based on an observed annualized residual variability for total slope at interim analysis of 5.5 mL/min/1.73 m^2 per year, DUPLEX was adequately powered to detect a 2.1 mL/min/1.73 m^2 per year difference between treatment arms. Further, DUPLEX randomized 71 more subjects (24% more) than originally planned (n=300). Thus, with a larger sample size, the study was more than adequately powered to detect a treatment effect of 2.1 mL/min/1.73 m^2 per year difference between treatment arms.

Table 28. Estimated Residual Variability, Variability of Intercept, and Slope from Random Coefficient Model, DUPLEX

Subgroups	N (%)	Residual Variability	Intercept Variability	Slope Variability
Overall	371 (100%)	46	36	80
Age <18	35 (9%)	90	102	204
Age ≥18	336 (91%)	39	24	54
Nephrotic Syndrome: No	254 (68%)	34	28	45
Nephrotic Syndrome: Yes	117 (32%)	73	48	167
eGFR ≥30 to <60 mL/min/1.73 m^2 and Nephrotic[1]	141 (38%)	25	6	89
eGFR ≥30 to <60 mL/min/1.73 m^2 and Non-nephrotic [2]	60 (16%)	15	9	18
eGFR ≥60 mL/min/1.73 m^2 and Nephrotic[1]	57 (15%)	117	121	234
eGFR ≥60 mL/min/1.73 m^2 and Non-nephrotic [2]	113 (30%)	61	33	66
eGFR: 30 to <60 mL/min/1.73 m^2	201 (54%)	18	8	41
eGFR: ≥ 60 mL/min/1.73 m^2	170 (46%)	80	66	128

Nephrotic: Screening UPCR >3.5 for subjects >=18 years of age and >2 for subjects <18 years of age
Non-Nephrotic: Screening UPCR <=3.5 for subjects >=18 years of age and <=2 for subjects <18 years of age
Abbreviations: N, number of randomized subjects

Effects on Kidney Failure Event Rates

Although DUPLEX was not designed or adequately powered to evaluate kidney composite outcomes, the Applicant conducted exploratory analyses assessing effects on clinical outcomes and surrogate endpoints for progression to kidney failure that are commonly used in trials of chronic kidney disease. Based on the statistical team's analyses using all observed eGFR data based on scheduled visits, numerically fewer subjects in the sparsentan arm (14 [8%]) compared to the irbesartan arm (19 [10%]) had a confirmed eGFR <15 mL/min/1.73 m^2 on two assessments at least 14 days apart, initiated RRT, or died. However, there were few events and missing data (approximately 12% of subjects did not have eGFR assessments collected during Weeks 96 through to 112).

Irbesartan as an Active Control

The review team considered whether to consider DUPLEX as an active control trial and whether a non-inferiority analysis could be used to assess the effectiveness of sparsentan in reducing progression to kidney failure. However, data on irbesartan's effect on slowing the loss of kidney function (eGFR) and/or reducing the risk of kidney failure in an FSGS population similar to the population enrolled in the trial are lacking. Absent such information, it is not feasible to interpret the results in the context of a non-inferiority study.

Conclusion

Both treatment arms experienced a rapid rate of loss of kidney function during the trial. Analyses of eGFR data in DUPLEX are challenging to interpret given the amount of missing eGFR data and the hemodynamic effects of sparsentan and irbesartan on eGFR. Nonetheless, there is no consistent numerical trend favoring sparsentan across various analytical models, and in fact, in some analyses, eGFR may, on average, be worse in the sparsentan arm compared with irbesartan.

The high variability of eGFR in FSGS, as highlighted by PARASOL, is an important consideration for trial design; however, the observed variability in DUPLEX was lower than that reported in

the observational PARASOL data. Considering the observed trial variability in DUPLEX as well as the inadvertent sample size increase (by 24%), DUPLEX was adequately powered to detect a difference in eGFR slope of 2.1 mL/min/1.73 m^2 according to their revised sample size calculations after the unblinded interim sample size re-estimation look.

In post hoc analyses, numerically fewer subjects in the sparsentan as compared to irbesartan arm had a confirmed eGFR <15 mL/min/1.73 m^2 on two assessments at least 14 days apart, initiated RRT, or died, however data regarding effects on kidney outcomes should be interpreted with caution given the small number of events, missing data, and results of analyses evaluating treatment effects on eGFR as a continuous variable. Given the available data, there is uncertainty regarding whether sparsentan's effect on proteinuria will translate into a clinically meaningful effect on progression to kidney failure in the overall trial population.

7.1.3.3. Impact of Missing Data on Interpretation of the Efficacy Findings

Issue

There was a significant amount of missing data in DUPLEX. The impact of missing data on the interpretation of the efficacy findings was a key review issue.

Background

Missing data impair the reliability and interpretability of clinical trial results by introducing bias in estimates of the treatment effect and increasing the chance of erroneous conclusions. As such, the National Research Council (NRC) report "The Prevention and Treatment of Missing Data in Clinical Trials" recommends (1) careful design and conduct to limit the amount and impact of missing data, and (2) analyses that makes full use of information on all randomized subjects and are based on careful attention to the assumptions about the nature of the missing data underlying estimates of treatment effects.

In DUPLEX, the primary estimand of interest as prespecified in the protocol targeted an ITT estimand. However, the SAP targeted a hypothetical strategy for treatment discontinuation for all key efficacy analyses. During the double-blind period, 29% of randomized subjects discontinued treatment, with a similar proportion of subjects across arms. In the Applicant's analyses, the data for these subjects was treated as "missing" and assumed to be MAR according to the regression model. In addition, a significant proportion of subjects who discontinued treatment prematurely had missing data for UPCR and/or eGFR at Week 108.

As noted in Section 7.1.1.3, the statistical review team did not agree with the approaches used by the Applicant to analyze the data, and thus performed analyses that included all data collected regardless of adherence to randomized treatment with consideration of intercurrent events. The review team also conducted additional sensitivity analyses to assess the robustness of the findings to different assumptions about the missing data.

Assessment

For multiple imputation, we generally consider imputation according to the randomization stratification factors to ensure similar precision. During the review, when we considered stratifying the imputation process according to baseline stratification factors, there were convergence issues noted due to small number of subjects in certain strata. Thus, the imputation procedure was revised to only consider imputation by treatment arm.

Thus, to address these challenges, for the continuous endpoints, the statistical team considered analyses based on all the observed data collected regardless of intercurrent events, and observed data collected excluding data collected after RRT (i.e., receipt of kidney transplantation, or initiation of chronic dialysis). Missing data were primarily handled as MAR according to the regression model. We then considered analyses around the MAR assumption based on copy reference, copy reference with worst 5% sampling for ICE due to RRT or death, return to baseline, return to baseline with worst 5% sampling for ICE due to RRT or death. For eGFR, return to baseline is not a reasonable assumption due to the progressive nature of the disease. Acknowledging that the missing rate was high, these imputations attempt to address the precision and bias of the treatment effect in the overall population.

As noted in Section 7.1.3.1, depending on the analyses method used, the point estimate of the treatment effect on proteinuria ranged between 20% to 26%, and can be tipped when assumptions were varied (See 15.3 for Tipping Point Analyses and Figure 17). As noted in Section 7.1.2.2.1, the eGFR findings were not statistically significant even when imputing the missing data. Thus, no further sensitivity analyses were conducted.

Conclusion

Different methodologies can be used as sensitivity analyses to address missing data in clinical trials. However, when there is a significant amount of missing data, none of these methodologies can adequately address potential bias in the estimate of the treatment effect. In DUPLEX, after excluding missing data due to intercurrent events of death, receipt of kidney transplantation, or initiation of chronic dialysis, approximately 20% and 22% of subjects had missing eGFR and UPCR assessments at Week 108, respectively. The amount of missing data is considered substantial from the statistical review team's perspective and limits the ability to reliably estimate the treatment effect on proteinuria and eGFR at Week 108.

7.1.3.4. Efficacy in Subjects without Nephrotic Syndrome

Issue

There is uncertainty regarding whether the size of treatment effect on proteinuria seen in the overall trial population will translate into a clinically meaningful effect on progression to kidney failure. Additional analyses were conducted to assess for a greater response in a subgroup that might be expected to have a greater response to sparsentan given its mechanism of action, i.e., subjects without nephrotic syndrome.

Background

FSGS is not a single disease but is a heterogeneous condition due to different etiologies and disease processes. While key drivers of disease progression are thought to depend on the underlying pathophysiology, the ability to sub-divide the population based on key drivers of disease progression is currently limited. To qualify for enrollment in DUPLEX, subjects were required to have biopsy-proven FSGS or a genetic mutation known to cause FSGS and UPCR ≥1.5 g/g; subjects with FSGS secondary to another condition and kidney transplant recipients were to be excluded.

In primary FSGS associated with the nephrotic syndrome, an immune-mediated process (attributed to a circulating permeability factors) is thought to be a key driver of disease progression and the disease is typically treated with immunosuppressive therapy. In contrast, in subjects without nephrotic syndrome, other processes, such as maladaptive glomerular hemodynamics (chronic glomerular hypertension and hyperfiltration), and activation of pro-inflammatory and pro-fibrotic pathways leading to podocyte injury and loss may play a more important role (De Vriese AS, 2021). Given its mechanism of action as a dual ETAR and AT1R antagonist, sparsentan might be expected to have a greater treatment effect in subjects without the nephrotic syndrome.

Assessment

Analyses were conducted in subjects with and without nephrotic syndrome. For the purposes of these analyses, nephrotic syndrome was defined as (a) documentation of nephrotic syndrome in the medical history, or (b) the concurrent presence of proteinuria >3.5 g/24 hours (adults) or UPCR >2.0 g/g (pediatric subjects <18 years of age), serum albumin <3.0 g/dL, and edema at baseline. In DUPLEX, 68% of subjects did not have nephrotic syndrome, i.e., did not meet both criteria (a) and (b).

Table 29 shows the findings for the percent UPCR reduction from baseline at Week 108 and mean change from baseline in eGFR at Week 108 for the overall population, and subjects with and without nephrotic syndrome.

In the subgroup of subjects without nephrotic syndrome, UPCR reduction at Week 108 relative to baseline was 48% in the sparsentan arm compared to 27% in the irbesartan arm. Compared to irbesartan, after addressing for missing data, subjects in the sparsentan arm had a 29% larger reduction (95% CI: 8%, 44%; nominal p=0.008) in the ratio of adjusted mean of log-transformed UPCR at Week 108 from baseline. Sensitivity analyses using tipping point analyses show that the findings in this subgroup are robust to deviations of assumptions of missing data (Figure 18). In contrast, there was no difference between treatment arms in UPCR reduction from baseline to Week 108 (estimated reduction: 3%; 95% CI: -53%, 39%; nominal p=0.9) in the subgroup of subjects with nephrotic syndrome.

In the subgroup of subjects without nephrotic syndrome, the mean change from baseline in eGFR at Week 108 was -11.2 and -12.4 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively. The difference in the estimated adjusted mean change from baseline in eGFR was

1.0 mL/min/1.73 m^2 (95% CI: -4.6, 2.7) and numerically better in the sparsentan arm compared to the irbesartan arm.

In the subgroup with nephrotic syndrome, the mean change from baseline in eGFR at Week 108 was -20 and -14 .1 mL/min/1.73 m^2 in the sparsentan and irbesartan arms, respectively. As shown in Table 29, the average difference between arms was 6.0 mL/min/1.73 m^2 and numerically better for the irbesartan arm instead; however, there is considerable uncertainty around this point estimate as reflected by the wide 95% CI that crosses zero.

Table 29 Summary of Change from Baseline in Log UPCR and eGFR at Week 108 after Addressing Missing Data for Overall Population and Subgroup defined by Documented History of Nephrotic Syndrome, FAS, DUPLEX

	Overall Population		Without Nephrotic Syndrome		With Nephrotic Syndrome	
	Sparsentan	Irbesartan	Sparsentan	Irbesartan	Sparsentan	Irbesartan
N	184	187	129	125	55	62
FDA's Analysis						
% Reduction in UPCR at Week 108 relative to baseline (95% CI)	46% (36%, 54%)	30% (19%, 41%)	48% (38%, 56%)	27% (13%, 39%)	39% (15%, 56%)	37% (14%, 54%)
% Reduction in UPCR (vs Irbesartan) [1] (95% CI)	22% (2%, 37%)		29% (8%, 44%)		3% (-53%, 39%)	
Applicant's (Label)						
% Reduction in UPCR at Week 108 relative to baseline (95% CI)	46% (36%, 54%)	30% (18%, 40%)	48% (38%, 56%)	27% (13%, 39%)	39% (14%, 56%)	37% (13%, 54%)
% Reduction in UPCR (vs Irbesartan) [1] (95% CI)	22% (2%, 38%)		29% (9%, 44%)		3% (-54%, 39%)	
FDA's Analysis						
Adjusted change in eGFR at Week 108 from baseline (SE)	-13.9 (1.4)	-12.8 (1.3)	-11.2 (1.3)	-12.2 (1.3)	-20.0 (3.2)	-14.1 (3.0)
Adj Diff (vs Irbesartan) [2] (95% CI)	-1.1 (-4.8, 2.7)		1.0 (-2.6, 4.7)		-6.0 (-14.6, 2.7)	
Applicant's (Label)						
Adjusted change in eGFR at Week 108 from baseline (SE)	-14.3 (1.4)	-13.3 (1.4)	-11.3 (1.3)	-12.4 (1.3)	-21.3 (3.4)	-15.1 (3.2)
Adj Diff (vs Irbesartan) [2]	-1.0 (-4.9, 2.8)		1.1 (-2.6, 4.8)		-6.2 (-15.2, 2.9)	

(95% CI)						

Source: Statistical Review Team; See Table 29.1, Table 29.2, Table 28.1_IR15, Table 28.2_IR15 of s006-ir15-resp-part1-biostats.pdf from Seq 0191
[1] Positive values of % reduction indicates favoring sparsentan; Negative values of % reduction indicates favoring irbesartan.
[2] Positive values of adjusted difference (vs irbesartan) indicates numerical better for sparsentan; Negative values of adjusted difference (vs irbesartan) indicates numerically better for irbesartan.
Missing data were handled using copy reference multiple imputation and worst 5% percent of the data were used to impute outcome after intercurrent event due to renal replacement therapy, or death.
FDA Analysis for UPCR used different starting seeds from the Applicant and 1000 multiple imputation were conducted. For eGFR, different starting seeds were used and 500 multiple imputation were conducted .
Applicant's (Label): 500 multiple imputation runs were requested to verify Agency's imputation procedures using different starting seeds results. Differences are due to Monte-Carlo simulations. Statistical reviewer verified the submitted multiple imputed data and the results reported in Seq #0191.
Abbreviations: UPCR, urine protein to creatinine ratio; eGFR, estimated glomerular filtration rate; CI, confidence intervals; Adj, adjusted; Diff, difference; %, percent; SE, standard error

In the subgroup of subjects without nephrotic syndrome, based on scheduled visits, there were three and eight subjects in the sparsentan and irbesartan arms, respectively, who had a confirmed eGFR <15 mL/min/1.73 m^2 based on two consecutive measurements made at least 14 days apart, or initiated RRT based on data up to Week 108 (i.e., Day ≤771 of the study). In the subgroup of subjects with nephrotic syndrome, based on scheduled visits, 11 subjects in each arm met the same criteria. Because of the small number of events, it is challenging to draw reliable conclusions about sparsentan's effect on these outcomes.

The results of analyses of UPCR conducted by the Applicant in subjects without nephrotic syndrome using data from the phase 2 trial, DUET, were generally consistent with the subgroup findings in subjects without nephrotic syndrome in DUPLEX. Effects on eGFR could not be assessed in DUET because of the short duration of the double-blind period (8 weeks).

Conclusion

Post hoc subgroup findings in a study that failed to meet its primary endpoint are generally unreliable. DUPLEX did not meet its eGFR-based primary endpoint. However, based on pathophysiologic and epidemiologic evidence, the review team acknowledges that a robust treatment effect on a proteinuria-based endpoint could, in principle, support traditional approval in FSGS. However, absent a compelling treatment effect on sustained complete remission or near-normalization of proteinuria, data on 2-year eGFR are needed to understand the clinical significance of the proteinuria finding (see Section 7.1.3.1).

In DUPLEX, sparsentan reduced proteinuria compared to irbesartan in the overall trial population and the results trended consistently across analytic methods to address missing data. However, the clinical significance of the proteinuria reduction is unclear (Sections 7.1.3.1 and 7.1.3.2). Sparsentan, based on its mechanism of action, might be expected to be more effective in patients without an immune-mediated etiology of FSGS (generally, patients without nephrotic syndrome). As such, a study evaluating both population groups (with and without nephrotic syndrome) would lead to conclusions closer to the null.

The review team, therefore, conducted additional subgroup analyses in subjects without nephrotic syndrome. These analyses show a larger treatment effect on proteinuria reduction in the sparsentan arm compared to the irbesartan arm in subjects without nephrotic syndrome as compared to the treatment effect on proteinuria reduction in the overall trial population. In

contrast, there was no difference between treatment arms in proteinuria reduction in the subgroup of subjects with nephrotic syndrome.

The review team believes that considering sparsentan's mechanism of action, these subgroup results are reliable because (1) the size of this subgroup is reasonably large in relation to the overall trial population, (2) the magnitude of the treatment effect on proteinuria is large and the results are robust to missing data assumptions, and (3) analyses of effects on the loss of kidney function (eGFR) and kidney failure outcomes in this subgroup provide additional reassurance that the effect on proteinuria is likely to translate to benefit.

8. Safety Evaluation

8.1. Safety Experience and Current Sparsentan US Prescribing Information (PI)

Sparsentan is an endothelin type A receptor and angiotensin II receptor antagonist indicated for the treatment of IgAN.

The current PI for sparsentan includes a boxed warning for embryofetal toxicity and hepatotoxicity. Sparsentan is only available through a Risk Evaluation and Mitigation Strategies (REMS) program because of the risk of hepatotoxicity. Warnings and Precautions include hepatotoxicity, embryo-fetal toxicity, hypotension, acute kidney injury, hyperkalemia, and fluid retention. The most common adverse reactions include hyperkalemia, hypotension (including orthostatic hypotension), peripheral edema, dizziness, anemia, acute kidney injury, and elevated liver transaminases.

8.2. Safety Review Approach

The safety of sparsentan in subjects with FSGS was primarily assessed by analyses of safety data from the double-blind treatment period of the DUPLEX trial (Table 4). Given the differences in the design, doses, and populations of the pooled datasets from DUPLEX, DUET and PROTECT clinical trials, the safety reviewer did not present the safety findings from the pooled datasets.

The safety evaluation included a review of data quality and integrity, as well as adverse events and laboratory datasets. In general, there were no concerns regarding submission quality or conduct of the studies with respect to the safety assessment.

The FDA safety review focused on the known and potential risks of sparsentan. Treatment-emergent adverse events (TEAEs) were analyzed based on Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 preferred terms (PTs), the Applicant's predefined queries, and by pooling similar AEs (referred to as the Office of New Drugs custom medical queries [OCMQs]). The OCMQ analysis is like a customized MedDRA query. No major issues were identified with respect to data quality, recording, coding, and categorizing AEs.

In the sections that follow, AEs are treatment-emergent and generally presented as a risk difference (RD), which was calculated as the difference in the percentage of subjects with AEs

between the sparsentan and irbesartan: negative RD values indicate a lower risk in the sparsentan arm and positive RD values indicate a higher risk.

8.3. Review of the Safety Database

In DUPLEX, 184 subjects were exposed to sparsentan for a median duration of 108 weeks during the double-blind period (Table 30). The submitted safety data, along with the known experience with sparsentan, were considered adequate to assess the safety in the FSGS population.

Table 30. Duration of Exposure, Safety Population, DUPLEX Double-Blind Period

Parameter	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)
Duration of treatment, weeks		
Mean (SD)	88.2 (34.9)	91 (32.9)
Median (Q1, Q3)	108 (71.1, 108.3)	108 (100, 108.4)
Min, Max	0.6, 112	1, 111.7
Total exposure (person weeks)	16228	17010
Subjects treated, by duration, n (%)		
<12 weeks	12 (6.5)	9 (4.8)
12 to <26 weeks	9 (4.9)	10 (5.3)
26 to <50 weeks	12 (6.5)	10 (5.3)
50 to <100 weeks	20 (10.9)	18 (9.6)
≥100 weeks	131 (71.2)	140 (74.9)

Reviewer's analysis. Source: adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation.

8.4. Safety Results

8.4.1. Overview of Treatment-Emergent Adverse Events and Adverse Reactions

Table 31 provides an overview of the TEAEs observed in the double-blind period of DUPLEX. The overall incidence of TEAEs, including both serious and non-serious events, was similar between the two treatment groups. While the proportion of subjects who experienced a serious adverse event (SAE) was numerically higher in the irbesartan as compared to the sparsentan group, the proportion who experienced an TEAE resulting in treatment discontinuation or dose modification, or an TEAE classified as severe was slightly numerically greater in the sparsentan group.

Table 31. Overview of Treatment-Emergent Adverse Events, Safety Population, DUPLEX Double-Blind Period

Event Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
SAE	68 (37.0)	82 (43.9)	-6.9 (-16.9, 3.1)
SAEs with fatal outcome	4 (2.2)	3 (1.6)	0.6 (-2.2, 3.3)
Life-threatening SAEs	5 (2.7)	2 (1.1)	1.6 (-1.1, 4.4)

Event Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
SAEs requiring hospitalization	42 (22.8)	49 (26.2)	-3.4 (-12.1, 5.4)
SAEs resulting in disability	3 (1.6)	1 (0.5)	1.1 (-1.0, 3.2)
Congenital anomaly or birth defect	0	1 (0.5)	-0.5 (-1.6, 0.5)
Other	37 (20.1)	48 (25.7)	-5.6 (-14.1, 3.0)
AE leading to permanent discontinuation of study drug	26 (14.1)	22 (11.8)	2.4 (-4.5, 9.2)
AE leading to dose modification of study drug	59 (32.1)	57 (30.5)	1.6 (-7.9, 11.0)
AE leading to interruption of study drug	31 (16.8)	33 (17.6)	-0.8 (-8.5, 6.9)
AE leading to reduction of study drug	34 (18.5)	29 (15.5)	3.0 (-4.7, 10.6)
Any AE	172 (93.5)	174 (93.0)	0.4 (-4.7, 5.5)
Severe and worse	44 (23.9)	41 (21.9)	2.0 (-6.6, 10.5)
Moderate	79 (42.9)	80 (42.8)	0.2 (-9.9, 10.2)
Mild	49 (26.6)	53 (28.3)	-1.7 (-10.8, 7.4)

Reviewer's analysis. Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of the study drug.
Duration is a median of 108 weeks.
Coded as MedDRA version 23.0 preferred terms.
Severity as assessed by the investigator. Rows with severe and worse, moderate, and mild show maximum severity.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

8.4.2. Deaths

During the double-blind period, 4 subjects in the sparsentan group and 3 subjects in the irbesartan group died due to TEAEs (Table 32). Deaths due to COVID-19 were the most common reason. Based on the subject narratives, these deaths did not appear to be related to study drug.

Table 32. Adverse Events Leading to Death, Safety Population, DUPLEX Double-Blind Period

Preferred Term	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Any AE leading to death	4 (2.2)	3 (1.6)	0.6 (-2.2, 3.3)
Completed suicide	1 (0.5)	0	0.5 (-0.5, 1.6)
Neuroendocrine carcinoma	1 (0.5)	0	0.5 (-0.5, 1.6)
Subdural haematoma	1 (0.5)	0	0.5 (-0.5, 1.6)
COVID-19	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
COVID-19 pneumonia	0	1 (0.5)	-0.5 (-1.6, 0.5)
Respiratory distress	0	1 (0.5)	-0.5 (-1.6, 0.5)

Reviewer's analysis. Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of the study drug.
Duration is a median of 108 weeks.
Coded as MedDRA version 23.0 preferred terms.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event

During the OLE Period of DUPLEX, there were 4 additional deaths due to TEAEs: cardio-respiratory arrest/bradycardia (Subject (b) (6)), myocardial infarction (Subject (b) (6)), acute respiratory failure/multiple organ failure/septic shock (Subject (b) (6)), and pneumonia (Subject (b) (6)). Based on the subject narratives, these deaths did not appear to be related to study drug.

8.4.3. Serious Adverse Events

As noted above, the proportion of subjects who experienced an SAE was numerically higher in the irbesartan (44%) group compared to the sparsentan (37%) group. There was no SAE or grouped SAEs by narrow OCMQ or narrow SMQ that had a RD >1% for sparsentan compared to irbesartan. See Table 45 for a listing of all SAEs that occurred during the double-blind period of DUPLEX.

Regarding labeled adverse reactions, the incidence of SAEs was numerically lower in the sparsentan group compared to the irbesartan group for the following AEs: hypotension (0.5% versus 1.1%), hepatic injury (0% versus 0.5%), acute kidney injury (2.7% versus 4.3%), and peripheral edema (0% versus 3.2%). In the sparsentan group, two subjects (1.1%) reported SAEs related to anemia, while no such events were reported in the irbesartan group.

8.4.4. Adverse Events Leading to Treatment Discontinuations

As noted above, there were numerically more subjects who permanently discontinued treatment due to TEAEs in the sparsentan group. The PT with a RD >1% for sparsentan versus irbesartan was hypotension (2%). See Table 46 for listing of AEs leading to treatment discontinuation.

8.4.5. Treatment-Emergent Adverse Events

8.4.5.1. Common Treatment-Emergent Adverse Events

Table 33 provides an overview of the TEAEs reported for the safety population in the double-blind period of DUPLEX. The results of the MedDRA PT analysis and associated narrow OCMQs analyses were generally consistent with each other.

The most common TEAEs (RD) occurring with an incidence ≥10% in the sparsentan group and RD >3% were hypotension (22%), hyperkalemia (17%), anemia (16%), dizziness (16%) and lipid disorders (13%). Lipid disorders were identified using narrow OCMQs and are not listed as adverse reactions in the current FILSPARI PI. Lipid disorders are further discussed in section 8.4.5.5.

The incidence of fluid-retention-associated TEAEs was slightly lower in the sparsentan group compared with the irbesartan group in the double-blind period of DUPLEX. No heart failure adverse events were reported; however, subjects with a documented history of heart failure or unexplained heart failure symptoms were excluded.

Table 33. Treatment-Emergent Adverse Events Occurring with a Risk Difference >2%, DUPLEX Double-Blind Period

Related terms[1] or PT	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Hypotension (including orthostatic hypotension)[1]	40 (21.7)	25 (13.4)	8.4 (0.7, 16.1)
Anemia[1]	30 (16.3)	16 (8.6)	7.7 (1.1, 14.4)
Hyperkaliemia (PT)	31 (16.8)	20 (10.7)	6.2 (-0.8, 13.1)
Dyspnea[1]	14 (7.6)	5 (2.7)	4.9 (0.5, 9.4)
Lipid Disorder[1]	24 (13.0)	16 (8.6)	4.5 (-1.8, 10.8)
Dizziness[1]	29 (15.8)	23 (12.3)	3.5 (-3.6, 10.5)
Arthritis[1]	15 (8.2)	9 (4.8)	3.3 (-1.7, 8.3)

Reviewer's analysis. Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of the study drug.
Duration is a median of 108 weeks.
Risk difference (with 95% confidence interval) is shown between sparsentan and irbesartan.
Coded as MedDRA version 23.0 preferred terms.
[1]Grouped by narrow OCMQs.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; OCMQs, Office of New Drugs custom medical queries; PT, MedDRA preferred term

8.4.5.2. Drug-Induced Liver Injury

The approved FILSPARI PI includes a boxed warning for hepatotoxicity with elevated aminotransferases and FILSPARI is only available through a REMS because of the risk of hepatotoxicity. To evaluate the risk of hepatotoxicity, the review team conducted a grouped query of hepatic injury AEs. Based on narrow OCMQ, there was a numerical imbalance between the sparsentan (7%) and irbesartan (4%) groups, which was driven by increases in ALT and AST levels (Table 34). There were no hepatic disorder-related SAEs or severe AEs in the sparsentan group. There was one SAE of hepatic injury (OCMQ) in the irbesartan group. Two subjects in the sparsentan group and one subject in the irbesartan group permanently discontinued treatment due to elevations in liver enzymes. Narratives for the two subjects in the sparsentan group who discontinued treatment are provided below.

- **Subject** (b) (6) (a 41-year-old White male with FSGS since (b) (6)) permanently stopped sparsentan treatment on Day 105 after developing elevated ALT and AST levels on Day 83. On Day 106, lab results showed an increased ALT of 485 U/L (12 × ULN) and increased AST of 304 U/L (8 × ULN); GGT, ALP, albumin, total bilirubin, and total protein were within normal limits (WNL). On Day 113, ALT and AST had increased to 644 U/L (16 × ULN) and 359 U/L (10 × ULN), respectively. On Day 117, the subject remained asymptomatic and reported feeling well overall. He denied taking new medication or drinking alcohol. On Day 169, the subject's ALT and AST levels normalized to 37 U/L and 34 U/L, respectively, and the events were considered resolved. The events were considered mild and possibly related to study treatment although the subject was

concurrently receiving febuxostat, which has a labeled warning for transaminase elevations.

Dr. Hayashi previously reviewed this case and concluded that it is a case of probable DILI due to sparsentan (see Dr. Paul Hayashi's review in DARRTS, 09/20/2022).

- **Subject** (b) (6) (a 49-year-old White female with FSGS since (b) (6) and with a past medical history of cholelithiasis since (b) (6)) permanently discontinued sparsentan treatment after developing an elevated AST on Day 337. On Day 247, the ALT levels increased to 41 U/L (NR: ≤33 U/L), and AST to 69 U/L. On Day 333, the investigator evaluated her labs from Day 312 and reported that they were not clinically significant owing to a history of cholelithiasis. On the same day, labs showed LFTs increased further with ALT at 79 U/L, and AST at 136 U/L (4.38 × ULN). The subject had the last blinded sparsentan dose on Day 337 and permanently discontinued the study medication due to the increased AST. On Day 338, a retest showed that the AST levels remained elevated over 4.3 × ULN. On Day 351, the subject was admitted for cholelithiasis surgery. The next day, labs showed AST levels of 97 U/L, ALT of 51 U/L, amylase of 214 U/L and lipase 220 U/L. The subject underwent a cholecystectomy for cholelithiasis. From Day 402, the AST levels started to decline but remained elevated. On Day 431, the AST levels reached 64 U/L, and the event was considered resolved. The investigator assessed the increased AST as nonserious, moderate, and unlikely related to sparsentan. The investigator attributed the higher AST levels to cholelithiasis disease but could not rule out the possibility that the study medication also contributed to the increase in enzymes levels.

  This case was also previously reviewed by FDA as part of FDA's assessment of sparsentan's potential to cause DILI.

Table 34. Treatment-Emergent Adverse Events in Hepatic Injury Narrow OCMQ, Safety Population, DUPLEX Double-Blind Period

Adverse Event Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Any AE in group	12 (6.5)	8 (4.3)	2.2 (-2.4, 6.8)
Alanine aminotransferase increased	10 (5.4)	4 (2.1)	3.3 (-0.6, 7.2)
Aspartate aminotransferase increased	8 (4.3)	5 (2.7)	1.7 (-2.1, 5.4)
Cholestasis	1 (0.5)	0	0.5 (-0.5, 1.6)
Primary biliary cholangitis	1 (0.5)	0	0.5 (-0.5, 1.6)
Drug-induced liver injury	0	1 (0.5)	-0.5 (-1.6, 0.5)
Hepatic function abnormal	0	1 (0.5)	-0.5 (-1.6, 0.5)
Hepatocellular injury	0	1 (0.5)	-0.5 (-1.6, 0.5)
Steatohepatitis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Maximum severity			
Severe	0	0	0 (0, 0)
Moderate	2 (1.1)	6 (3.2)	-2.1 (-5.1, 0.8)
Mild	10 (5.4)	2 (1.1)	4.4 (0.8, 8.0)
Serious	0	1 (0.5)	-0.5 (-1.6, 0.5)
Deaths	0	0	0 (0, 0)

Adverse Event Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Resulting in discontinuation	2 (1.1)	1 (0.5)	0.6 (-1.3, 2.4)
Relatedness	3 (1.6)	3 (1.6)	0.0 (-2.5, 2.6)

Reviewer's analysis. Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of study medication, but within 30 days of the last dose.
Duration is median 108 weeks.
Serious AE preferred terms: Drug-induced liver injury
Relatedness as determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

The Division of Hepatology and Nutrition (DHN) was previously consulted to review the clinical and post-marketing data. Since approval of sparsentan for the treatment of IgAN through August 1, 2024, twenty-seven (27) subjects experienced transaminase elevations >3× ULN and/or serious liver-related events. These occurred in 20 subjects during OLE phases of the clinical trials (PROTECT n=6; DUPLEX n=10; DUET n=4) and in 7 subjects in the REMS population. Among 15 cases with transaminase elevations >5× ULN identified post-approval, DHN assessed 4 cases as probable DILI, 10 cases as possible/unlikely DILI and one case as indeterminate for DILI. There were no Hy's Law cases, but there was one case with hyperbilirubinemia and some imbalances in Temple's Corollary at >5xULN. (see Dr. Selena DeConti's review in DARRTS, 08/25/2025).

Liver Biochemistry Tests

Numerically more subjects had ALT, AST, or ALP level 2 and level 3 elevations (high) in the sparsentan group compared to the irbesartan group (Table 35). Three subjects in the sparsentan group had LFTs >8× ULN (1 subject with elevated AST; 1 subject with elevated ALT; and 1 subject with both elevated AST and ALT).

None of the subjects in either treatment group had elevations in AST or ALT accompanied by concurrently elevated total bilirubin. There were no subjects who reported jaundice (serum total bilirubin >2×ULN).

Table 35. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, DUPLEX Double-Blind Period

Parameter Level	Sparsentan N=184 n/Nw (%)	Irbesartan N=187 n/Nw (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	6/184 (3.3)	4/185 (2.2)	1.1 (-2.2, 4.4)
Level 2 (>2X ULN)	3/184 (1.6)	1/185 (0.5)	1.1 (-1.0, 3.2)
Level 3 (>3X ULN)	0/184 (0)	0/185 (0)	0 (0, 0)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	3/184 (1.6)	4/185 (2.2)	-0.5 (-3.3, 2.3)
Level 2 (>5X ULN)	2/184 (1.1)	1/185 (0.5)	0.5 (-1.3, 2.4)
Level 3 (>10X ULN)	1/184 (0.5)	0/185 (0)	0.5 (-0.5, 1.6)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	4/184 (2.2)	3/185 (1.6)	0.6 (-2.2, 3.3)

Parameter Level	Sparsentan N=184 n/Nw (%)	Irbesartan N=187 n/Nw (%)	Risk Difference % (95% CI)
Level 2 (>5X ULN)	3/184 (1.6)	1/185 (0.5)	1.1 (-1.0, 3.2)
Level 3 (>10X ULN)	0/184 (0)	0/185 (0)	0 (0, 0)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	1/184 (0.5)	1/185 (0.5)	0.0 (-1.5, 1.5)
Level 2 (>2X ULN)	0/184 (0)	0/185 (0)	0 (0, 0)
Level 3 (>3X ULN)	0/184 (0)	0/185 (0)	0 (0, 0)

Reviewer's analysis. Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is [treatment period or median and range].
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; ULN, upper limit of normal

8.4.5.3. Hypotension

The approved FILSPARI PI includes a Warning and Precaution for hypotension. In DUPLEX, there was an imbalance in observed hypotension-related AEs for sparsentan (22%) verses irbesartan (13%). Most of the events were mild or moderate in severity. However, in the sparsentan group, one subject reported severe hypotension and discontinued treatment (Subject (b) (6)), and one subject had a serious TEAE (Subject (b) (6)). Two subjects in the irbesartan group had serious TEAEs. Five subjects discontinued sparsentan treatment because of hypotension-related or dizziness AEs as compared to no subjects in the irbesartan group. The most common TEAEs (PT) were hypotension and orthostatic hypotension (Table 36). Although not included in the narrow OCMQ grouping of PTs, dizziness (including postural dizziness and vertigo) also occurred more frequently in the sparsentan group (15.8%) compared to the irbesartan group (12.3%). Dizziness is a labeled adverse reaction for sparsentan and is thought to be related to hypotension. Narratives for the two subjects in the sparsentan group with a severe or serious TEAE of hypotension are provided below.

- **Subject** (b) (6) (a 73-year-old White male with FSGS since (b) (6)) experienced an SAE of moderate hypotension on Day 89, presenting with dizziness and chest pressure. This episode was part of a pattern of hypotensive events, with previous incidents occurring on Day 1 and Day 67. On Day 91, the subject was weak and hypotensive at 83/45 mmHg, which improved to a BP reading of 107/71 mmHg on the same day. In response to the symptomatic hypotension, the dosage of sparsentan was reduced to 400 mg daily on Day 92. The investigator classified the event as serious and moderate, possibly related to sparsentan administration. Other potential contributing factors included pre-existing illness and concomitant use of carvedilol.
- **Subject** (b) (6) (a 27-year-old Asian female with FSGS since (b) (6) experienced a severe adverse event of hypotension on Day 16 and discontinued sparsentan treatment. On Day 8, the subject experienced dizziness and vomiting (both of moderate severity), which were treated with difenidol hydrochloride (orally; Day 15-Day 36). On Day 15, the subject's BP was 112/71 mmHg. On Day 16, the subject developed hypotension (BP readings were not provided). No treatment was given for the event. On Day 29, the subject's BP reading was 113/76 mmHg. The subject had the last blinded sparsentan dose on Day 29 and permanently discontinued study medication due to hypotension. On

Day 36 (end of treatment visit), the dizziness, vomiting, and hypotension were considered resolved. The investigator assessed the hypotension as nonserious, severe, and related to sparsentan.

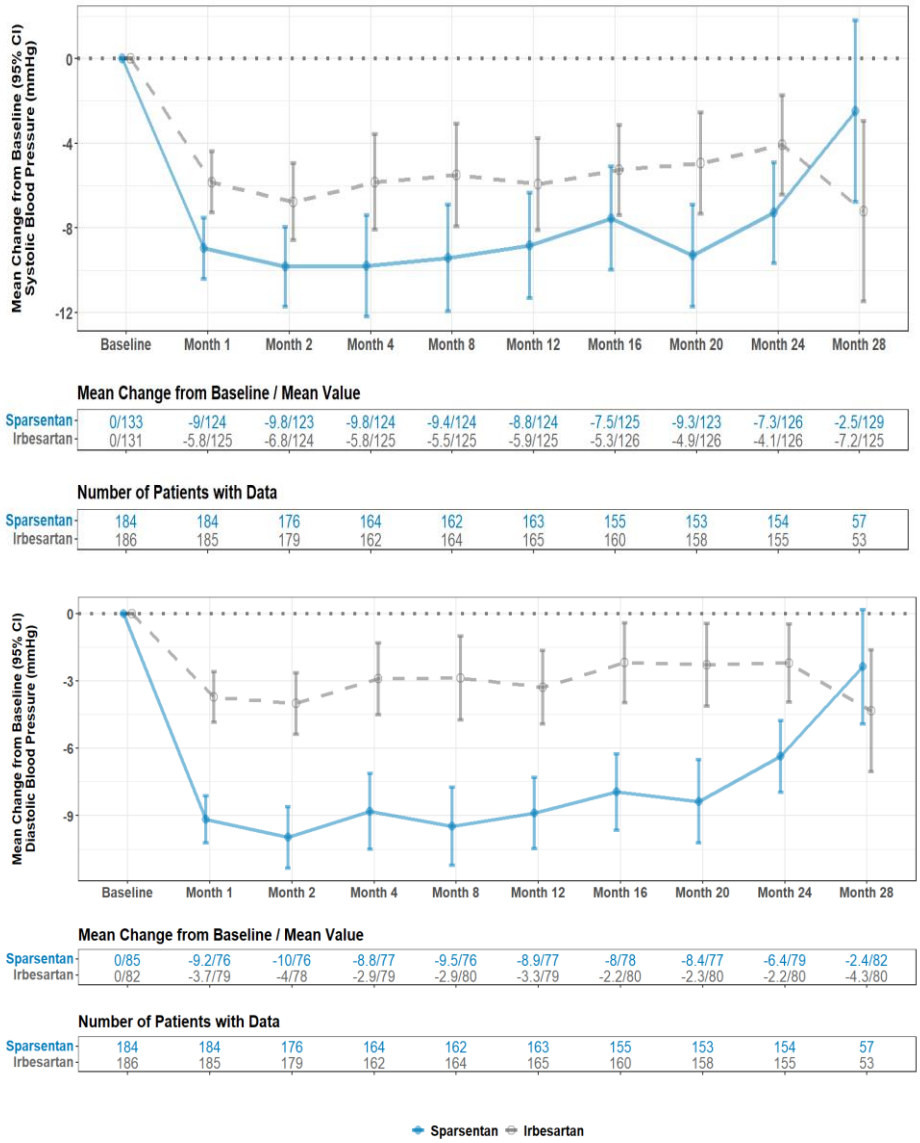
Table 36. Treatment-Emergent Adverse Events in Hypotension Narrow OCMQ, Safety Population, DUPLEX Double-Blind Period

Adverse Event Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Any AE in group	40 (21.7)	25 (13.4)	8.4 (0.7, 16.1)
Hypotension	33 (17.9)	21 (11.2)	6.7 (-0.5, 13.9)
Orthostatic hypotension	8 (4.3)	5 (2.7)	1.7 (-2.1, 5.4)
Blood pressure decreased	1 (0.5)	0	0.5 (-0.5, 1.6)
Blood pressure diastolic decreased	1 (0.5)	0	0.5 (-0.5, 1.6)
Maximum severity			
Severe	1 (0.5)	0	0.5 (-0.5, 1.6)
Moderate	12 (6.5)	9 (4.8)	1.7 (-3.0, 6.4)
Mild	27 (14.7)	16 (8.6)	6.1 (-0.4, 12.6)
Serious	1 (0.5)	2 (1.1)	-0.5 (-2.3, 1.3)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation[1]	4 (2.2)	0	2.2 (0.1, 4.3)
Relatedness	31 (16.8)	22 (11.8)	5.1 (-2.0, 12.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of study medication, but within 30 days of the last dose.
Duration is median of 108 weeks.
Serious AE preferred terms: Hypotension
[1]An additional subject in the sparsentan group discontinued treatment due to nonserious dizziness, which is not included in the OCMQ.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

The mean decrease in systolic and diastolic BP over time was greater in the sparsentan group over the 24-month double-blind period compared to the irbesartan group (Figure 14**)**. Compared to irbesartan, there were more subjects on sparsentan with a systolic BP <90 mmHg or a diastolic BP <60 mmHg (Table 37).

Figure 14. Mean and 95% Confidence Interval of Systolic (Top) and Diastolic (Bottom) Blood Pressure Change Over Time by Treatment Arm, Safety Population, Double-Blind Period



Reviewer's analysis. Source: advs.xpt; Software: R
Vertical bars show 95% confidence intervals.
Treatment with study medication was discontinued after 24 months.
Abbreviations: CI, confidence interval

Table 37. Percentage of Subjects Meeting Specified Hypotension Levels Postbaseline, Safety Population, Double-Blind Period

Blood Pressure	Sparsentan N=184 n/Nw (%)	Irbesartan N=187 n/Nw (%)	Risk Difference % (95% CI)
SBP <90 mmHg	14/184 (7.6)	3/186 (1.6)	6.0 (1.8, 10.2)
DBP <60 mmHg	54/184 (29.3)	27/186 (14.5)	14.8 (6.5, 23.1)

Source: advs.xpt; Software: R

Blood pressure threshold levels are based on the 2020 International Society of Hypertension Global Hypertension Practice Guidelines for office measurements.
Abbreviations: CI, confidence interval; DPB, diastolic blood pressure; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; SBP, systolic blood pressure.

8.4.5.4. Anemia

Anemia/decreased hemoglobin is a known risk of ERAs and is thought to be due in part to hemodilution. The approved FILSPARI PI includes anemia as an adverse reaction. The proportion of subjects with anemia-related AEs based on a grouped query was higher in the sparsentan group (16%) compared to the irbesartan group (9%) (Table 38). There were no anemia-related AEs leading to discontinuation of treatment; however, two subjects (Subjects (b) (6) and (b) (6); described below**)** had severe and serious AEs that did not appear to be related to sparsentan treatment. There were no serious AEs of anemia in the irbesartan group.

- **Subject** (b) (6) (a 74-year-old Black or African American female with FSGS since (b) (6)) experienced a nonserious adverse event of chronic anemia from Day 263 to 266, which was moderate in severity. On Day 364, the subject was hospitalized due to symptomatic anemia, presenting with a one-week history of melena, and worsening chronic dyspnea. Laboratory results showed decreased hemoglobin levels, leading to treatment with blood transfusions and intravenous iron sucrose. Despite these interventions, the subject continued to experience weakness. Further diagnostic procedures were performed, including a chest x-ray, which was clear, and a colonoscopy on Day 366. The colonoscopy revealed diverticulosis and two polyps. An esophagogastroduodenoscopy performed on the same day showed gastritis with old blood but no ulcers. The subject was discharged on Day 367, with the symptomatic anemia considered resolved. The investigator assessed the event as serious due to hospitalization, severe in nature, but unrelated to the study treatment. Pre-existing illness was noted as a possible cause. No action was taken regarding the study drug, sparsentan. The subject continued in the double-blind period of the study, receiving the last blinded dose on Day 763, and completing the remainder of the period on Day 785.

- **Subject** (b) (6) (a 69-year-old White female with FSGS since (b) (6). The subject had a history of CKD, chronic glomerulonephritis, hypertension, nephrotic syndrome, peripheral edema, proteinuria (all since (b) (6)), and anemia (since (b) (6)). Concomitant medications included cetirizine hydrochloride, calcium citrate, magnesium, cyanocobalamin, biotin, atorvastatin, lactobacillus acidophilus, bumetanide, fish oil, zinc (all orally), fluticasone propionate, salbutamol (both respiratory [inhalation]), ascorbic acid/beta-carotene/cupric oxide/tocopheryl acetate/zinc oxide (intraocular). Ferrous sulfate and mycophenolate mofetil appeared to have been initiated (timing unclear) and she was on those medications approximately 2 weeks before the onset of symptomatic anemia. The subject was randomized to sparsentan.

  During screening, the subject's hemoglobin was 9.3 g/dL and on Day 1 it was 10.1 g/dL. From Day 15 to 176, hemoglobin ranged from 7.6 g/dL (Day 92) to 9.7 g/dL (Day 176). The subject's last hemoglobin on Day 276 before presenting with the AE of anemia was 11.3 g/dL; however, this value seemed out of keeping with the previous values

(approximately 8-9 g/dL) and it is not clear whether additional interventions/medications were administered before Day 276.

On Day 309 the subject presented to the hospital and was admitted for management of symptomatic anemia with symptoms of increasing swelling of the extremities, generalized malaise, fatigue, and shortness of breath with activity. Hemoglobin on Day 309 was 6.5 g/dL, hematocrit 20.4%, and GFR (14, no units provided). On Day 1, eGFR was 48 mL/min/1.73 m^2 and ranged from approximately 40 to 50 mL/min/1.73 m^2 until Day 176. On Day 276, eGFR decreased to 17 mL/min/1.73 m^2. The subject received a blood transfusion and was treated with metolazone and bumetanide (both orally). No action was taken with sparsentan due to the event.

On Day 310, following the blood transfusion, the subject's hemoglobin level was 7.9 g/dL. On Day 311, the symptomatic anemia was considered resolved, and the subject was discharged from the hospital. The investigator assessed the symptomatic anemia as serious (hospitalization), severe, and unrelated to sparsentan. According to the narrative, while the investigator commented that the study drug was known to be associated with a greater than 5% chance of developing anemia, he reported that pre-existing illness was another possible cause of the event and discontinuation of therapy with epoetin alfa and ferrous sulfate could also have been a possible aggravating factor or alternate etiology for the event. The subject's subsequent hemoglobin levels were 9.2 g/dL (Day 344), 8.6 d/dL (Day 424), and 9.6 g/dL (Day 478).

Table 38. Treatment-Emergent Adverse Events in Anemia Narrow OCMQ, Safety Population, DUPLEX Double-Blind Period

Adverse Event Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Any AE in group	30 (16.3)	16 (8.6)	7.7 (1.1, 14.4)
Anaemia	24 (13.0)	10 (5.3)	7.7 (1.9, 13.5)
Nephrogenic anaemia	4 (2.2)	2 (1.1)	1.1 (-1.5, 3.7)
Deficiency anaemia	1 (0.5)	0	0.5 (-0.5, 1.6)
Haemoglobin decreased	1 (0.5)	0	0.5 (-0.5, 1.6)
Iron deficiency anaemia	2 (1.1)	2 (1.1)	0.0 (-2.1, 2.1)
Blood loss anaemia	0	1 (0.5)	-0.5 (-1.6, 0.5)
Haematocrit decreased	0	1 (0.5)	-0.5 (-1.6, 0.5)
Microcytic anaemia	0	1 (0.5)	-0.5 (-1.6, 0.5)
Normocytic anaemia	0	1 (0.5)	-0.5 (-1.6, 0.5)
Maximum severity			
Severe	2 (1.1)	1 (0.5)	0.6 (-1.3, 2.4)
Moderate	8 (4.3)	6 (3.2)	1.1 (-2.7, 5.0)
Mild	20 (10.9)	9 (4.8)	6.1 (0.6, 11.5)
Serious	2 (1.1)	0	1.1 (-0.4, 2.6)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)
Relatedness	0	2 (1.1)	-1.1 (-2.5, 0.4)

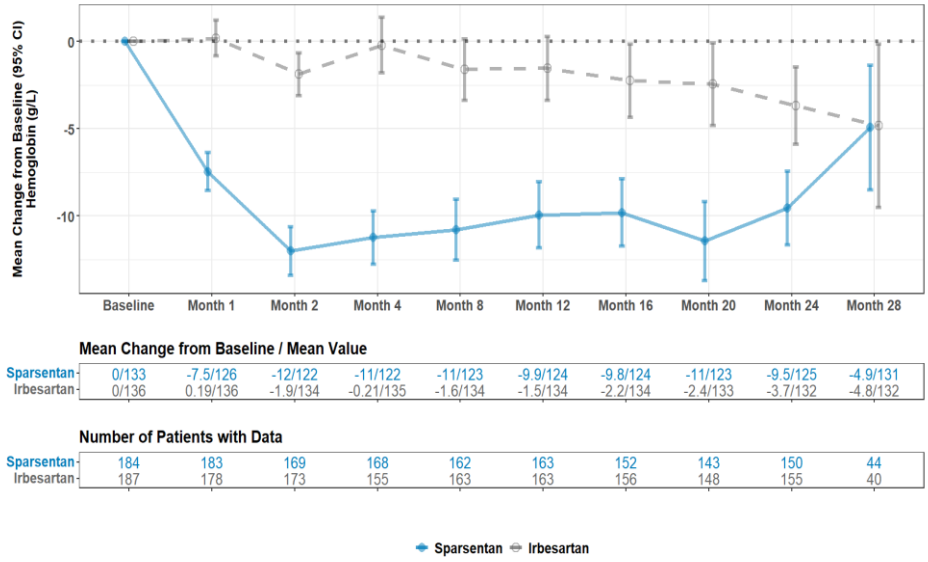
Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of study medication, but within 30 days of the last dose.
Duration is median 108 weeks.

Serious AE preferred terms: Anaemia
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

Hemoglobin Decreases

Subjects in the sparsentan group had a larger mean decrease in hemoglobin from baseline compared to those in the irbesartan group (Figure 15). More subjects in the sparsentan group also experienced a >2 g/dL decrease in hemoglobin compared to baseline during the trial (52% for sparsentan versus 23% for irbesartan).

Figure 15. Mean Hemoglobin Change from Baseline Over Time, Double-Blind Period



Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Treatment with study medication was discontinued after 24 months.
Abbreviations: CI, confidence interval

8.4.5.5. Hyperkalemia

The approved FILSPARI PI includes a Warning and Precaution for hyperkalemia. Hyperkalemia (PT) TEAEs were reported in 31 (17%) subjects in the sparsentan group and 20 (11%) subjects in the irbesartan group. One subject in the sparsentan group reported one hyperkalemia SAE that was severe. No subjects in the irbesartan group reported hyperkalemia SAEs. No subjects in either treatment group discontinued from treatment due to hyperkalemia TEAEs or increase in potassium levels.

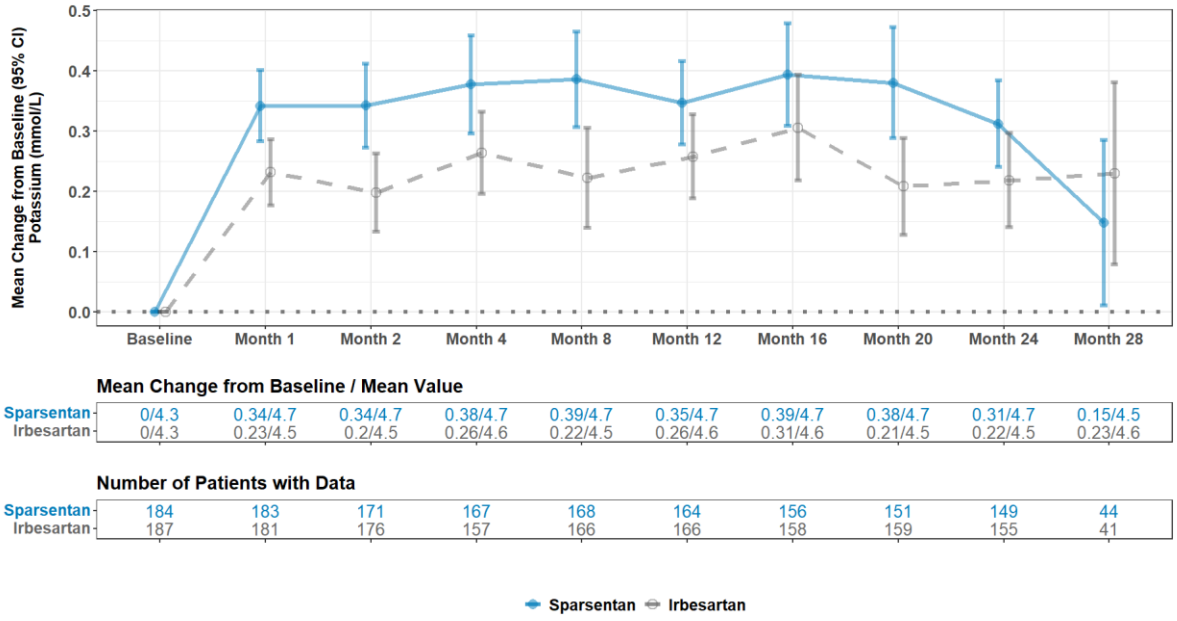
- **Subject** (b) (6) (a 69-year-old White female with FSGS since (b) (6)) was admitted to the hospital for CKD, hyperkalemia, and UTI on Day 445. She was also reported to have acute encephalopathy and anasarca. The subject was given unspecified treatment for the UTI. No treatment was given for hyperkaliemia. On Day 446, the subject underwent an operation for the placement of a fluoroscopic and ultrasound-guided non-tunneled dual-lumen central venous catheter due to the progression of CKD, which necessitated

chronic dialysis. No action was taken with sparsentan due to hyperkalemia and UTI. On Day 451, the CKD, hyperkalemia, and UTI were considered resolved, the subject was hemodynamically stable and was discharged from the hospital.

Potassium Increases

Subjects in the sparsentan group had a larger mean increase in potassium from baseline compared to those in the irbesartan group (Figure 16). Mean blood potassium increased by approximately 0.31 mmol/L at Week 2 in the sparsentan group and remained stable with a maximum mean increase from baseline of 0.39 mmol/L. Twenty subjects in each treatment group had elevations in potassium to ≥6 mmol/L.

Figure 16. Mean Hemoglobin Change from Baseline Over Time, Double-Blind Period



Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Treatment with study medication was discontinued after 24 months.
Abbreviations: CI, confidence interval

8.4.5.6. Lipid Disorders

Lipid disorders are not a known risk of ERAs. The percentage of subjects who experienced lipid disorder (narrow OCMQ) TEAEs was numerically higher in the sparsentan group (13%) than the irbesartan group (9%). The largest difference between arms occurred for the PT hyperlipidemia (Table 39). There were no SAEs, severe AEs, or AEs leading to treatment discontinuation.

There were no significant mean changes in total cholesterol, LDL cholesterol or triglycerides in either arm during the double-blind period. However, as shown in Table 40, more subjects in the sparsentan arm had high levels of total cholesterol (>225 mg/dL) compared to the irbesartan arm. Additional analyses were conducted in subjects with and without a history of nephrotic syndrome (a condition characterized by hypercholesterolemia). In subjects with a history of nephrotic syndrome at baseline, the proportion of subjects with severe hypercholesterolemia

(>225 mg/dL) was, in general, numerically higher in the sparsentan arm compared to the irbesartan arm (Table 41). In contrast, in subjects without a history of nephrotic syndrome at baseline, the proportion appeared to be similar in the two arms. What to make of this finding is unclear.

Table 39. Treatment-Emergent Adverse Events in Lipid Disorder Narrow OCMQ, Safety Population, DUPLEX Double-Blind Period

Adverse Event Category	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Any AE in group	24 (13.0)	16 (8.6)	4.5 (-1.8, 10.8)
Hyperlipidaemia	8 (4.3)	5 (2.7)	1.7 (-2.1, 5.4)
Dyslipidaemia	6 (3.3)	4 (2.1)	1.1 (-2.2, 4.4)
Blood triglycerides increased	2 (1.1)	0	1.1 (-0.4, 2.6)
Hypertriglyceridaemia	3 (1.6)	2 (1.1)	0.6 (-1.8, 2.9)
Lipids increased	1 (0.5)	0	0.5 (-0.5, 1.6)
Type V hyperlipidaemia	1 (0.5)	0	0.5 (-0.5, 1.6)
Blood cholesterol increased	2 (1.1)	2 (1.1)	0.0 (-2.1, 2.1)
Low density lipoprotein increased	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Hypercholesterolaemia	2 (1.1)	4 (2.1)	-1.1 (-3.6, 1.5)
Maximum severity			
Severe	0	1 (0.5)	-0.5 (-1.6, 0.5)
Moderate	7 (3.8)	3 (1.6)	2.2 (-1.1, 5.5)
Mild	17 (9.2)	12 (6.4)	2.8 (-2.6, 8.3)
Serious	0	0	0 (0, 0)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)
Relatedness	0	1 (0.5)	-0.5 (-1.6, 0.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that newly appears, increases in frequency, or worsens in severity following initiation of study medication, but within 30 days of the last dose.
Duration is median 108 weeks.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

Table 40. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, DUPLEX Double-Blind Period

Parameter Level	Sparsentan N=184 n/Nw (%)	Irbesartan N=187 n/Nw (%)	Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	158/184 (85.9)	153/185 (82.7)	3.2 (-4.3, 10.6)
Level 2 (>210)	151/184 (82.1)	139/185 (75.1)	6.9 (-1.4, 15.3)
Level 3 (>225)	139/184 (75.5)	121/185 (65.4)	10.1 (0.9, 19.4)
LDL, high (mg/dL)			
Level 1 (>130)	136/184 (73.9)	119/185 (64.3)	9.6 (0.2, 19.0)
Level 2 (>160)	95/184 (51.6)	77/185 (41.6)	10.0 (-0.1, 20.1)
Level 3 (>190)	66/184 (35.9)	56/185 (30.3)	5.6 (-4.0, 15.2)
Triglycerides, high (mg/dL)			
Level 1 (>150)	161/184 (87.5)	152/185 (82.2)	5.3 (-2.0, 12.6)
Level 2 (>300)	78/184 (42.4)	63/185 (34.1)	8.3 (-1.5, 18.2)
Level 3 (>500)	25/184 (13.6)	21/185 (11.4)	2.2 (-4.5, 9.0)

Reviewer's analysis. Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is [treatment period or median and range].
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data

Table 41. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels Stratified by History of Nephrotic Syndrome at Baseline, Safety Population, DUPLEX Double-Blind Period

	Documented Nephrotic Syndrome at-Baseline[1]			
	No n/Nw (%)		Yes n/Nw (%)	
	Sparsentan 129/184	Irbesartan 125/187	Sparsentan 55/184	Irbesartan 62/187
Cholesterol, total, high (mg/dL)				
Level 1 (>200)	107/129 (82.9)	102/125 (81.6)	51/55 (92.7)	51/60 (85.0)
Level 2 (>210)	100/129 (77.5)	92/125 (73.6)	51/55 (92.7)	47/60 (78.3)
Level 3 (>225)	90/129 (69.8)	80/125 (64.0)	49/55 (89.1)	41/60 (68.3)
LDL, high (mg/dL)				
Level 1 (>130)	85/129 (65.9)	78/125 (62.4)	51/55 (92.7)	41/60 (68.3)
Level 2 (>160)	57/129 (44.2)	45/125 (36.0)	38/55 (69.1)	32/60 (53.3)
Level 3 (>190)	33/129 (25.6)	28/125 (22.4)	33/55 (60.0)	28/60 (46.7)
Triglycerides, high (mg/dL)				
Level 1 (>150)	110/129 (85.3)	101/125 (80.8)	51/55 (92.7)	51/60 (85.0)
Level 2 (>300)	48/129 (37.2)	40/125 (32.0)	30/55 (54.5)	23/60 (38.3)
Level 3 (>500)	10/129 (7.8)	15/125 (12.0)	15/55 (27.3)	6/60 (10.0)

Reviewer's analysis. Source: adlb.xpt, adsl.xpt; Software: R
1Documented history of nephrotic syndrome is defined as follows: If the term "nephrotic syndrome" was present in medical history or if all of the following conditions were met at any of the visits prior to the first dose of randomized treatment: UP/C >3.5 g/g (adults) or UP/C >2 g/g (pediatrics), serum albumin <3.0 g/dL, and abnormal edema from physical examination.
Abbreviations: LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data

8.4.6. Laboratory Findings

Analysis of biochemistry and other hematology parameters did not reveal findings of concern that have not already been discussed.

8.4.7. Vital Signs

Beyond the blood pressure events previously described in section 8.4.5.3, analyses did not reveal any findings of interest or concern. There were no significant differences in mean heart rate or temperature.

8.4.8. Pregnancy

The approved FILSPARI PI includes a boxed warning for embryo-fetal toxicity. Based on data from animal reproduction studies, sparsentan may cause fetal harm and is contraindicated for use in pregnancy.

A total of 3 subjects (1 in the sparsentan group and 2 in the irbesartan group) reported pregnancy during the double-blind period. The pregnancies resulted in 1 spontaneous abortion in the sparsentan group and 1 normal labor and 1 premature baby in the irbesartan group.

In the entire sparsentan program, a total of 21 pregnancies have been reported as of August 1, 2024: 18 occurred in sparsentan clinical trials, 1 occurred through the compassionate use

program and 2 occurred in the post-marketing setting. Of the 21 pregnancies, 13 occurred in women receiving sparsentan at the time of conception which resulted in 2 elective abortions, 6 spontaneous abortions, 2 full term pregnancies with healthy babies, 1 ongoing pregnancy, and 2 pregnancies with unknown outcomes.

8.4.9. Key Safety Review Issues

No safety findings rose to the level of a key safety review issue.

8.4.10. Safety in Pediatric Subjects

In the DUPLEX double-blind period, 94% of pediatric subjects (n=16) in the sparsentan group and 100% (n=19) in the irbesartan group reported a TEAE (Table 47). Eight pediatric subjects (50%) in the sparsentan group reported SAEs compared to 12 (63%) in the irbesartan group. COVID-19 (n=4) and chronic kidney disease (n=2) were the only SAEs reported in the sparsentan group in more than 1 subject. Based on its mechanism of action, sparsentan is not likely to have played a causal role in predisposing to COVID-19, and chronic kidney disease is a manifestation of FSGS.

Review of the TEAEs by preferred term in the pediatric subgroup during the double-blind period (Table 47) showed no new adverse reactions compared to the labeled risks of sparsentan. There were no important differences in the overall incidence of TEAEs between pediatric and adult subjects treated with sparsentan; however, the sample size was small.

8.4.11. Integrated Assessment of Safety

Overall, the safety profile was consistent with the FILSPARSI product labeling.

9. Clinical Site and Other Good Clinical Practice Inspections

The review team requested clinical site inspections for DUPLEX study Sites 1021, 1048, and 1085. The reasons for inspections included a high proteinuria treatment effect for Site 1021 (n=9), a high proteinuria treatment response (b) (4) for Site 1048 (n=7), and a large amount of missing data and important protocol deviations for Site 1085 (n=8). Based on the clinical inspection findings, the trial was conducted in observance of Good Clinical Practice principles and in compliance with FDA regulations as described in the Office of Scientific Investigations review by Dr. John Lee (see review in DARRTS, 12/05/2026).

10. Advisory Committee Meeting and Other External Consultations

At a meeting with the Applicant on January 8, 2025, and in the filing communication to the Applicant dated May 14, 2025, the Division indicated that it was likely that the application would be discussed with an Advisory Committee. However, after further discussions with Center leadership, and after more detailed review of the application, including for the subset of patients with and without nephrotic syndrome, the review team and signatory determined that

there was a pathway to approval for patients without nephrotic syndrome without the need for external expertise.

The review team discussed the data supporting efficacy in the overall trial population with CDER's Medical Policy and Program Review Council (MPPRC) on February 25, 2026, and requested input from the MPPRC on the following questions: (1) Should the DUPLEX trial be viewed as an active control trial? (2) How should the use of irbesartan in DUPLEX (as an active control or standard of care) impact the interpretation of the efficacy findings, including sparsentan's effect on proteinuria and eGFR?

The Council was evenly divided on whether irbesartan constituted an active control in the DUPLEX trial. However, nearly all Council members who considered irbesartan as an active control did so with the caveat that the lack of available data on how irbesartan impacts clinical outcomes in patients with FSGS, undercuts the interpretability of the trial data. Additionally, all Council members agreed that neither the DUPLEX trial data in the overall population nor the Applicant's external evidence adequately demonstrated that sparsentan's effect on proteinuria would provide a clinically meaningful benefit to FSGS patients.

After the MPPRC meeting, the review team assessed the DUPLEX data in the subgroups with and without nephrotic syndrome and concluded that the data supported approval for patients without nephrotic syndrome (Sections 2 and 7.1.3.4).

11. Pediatrics

FDA granted orphan drug designation (Designation request #13-4101, dated January 05, 2015) for sparsentan for the treatment of FSGS. Therefore, the Applicant is exempt from the requirements of the Pediatric Research Equity Act for the proposed indication. The DUPLEX trial, however, did enroll pediatric subjects with FSGS down to 9 years of age. The trial was designed to include pediatric subjects down to 8 years of age. Even though the youngest enrolled subject was 9 years of age, given that the disease, drug pharmacology, weight-based dosing regimen, response to treatment, and safety is expected to be similar for an 8-year-old compared to a 9-year-old pediatric subject, the product will be labeled for use down to 8 years of age.

12. Labeling: Key Changes

This PI review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI. The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Boxed Warning, Dosage Forms and Strengths, Contraindications, Overdosage, Description, Nonclinical Toxicology and How Supplied/Storage and Handling:

No substantive revisions.

Indications and Usage:

This section has been revised to include a new indication for Focal Segmental Glomerulosclerosis, "FILSPARI is indicated to reduce proteinuria in adult and pediatric patients aged 8 years and older with focal segmental glomerulosclerosis (FSGS) without nephrotic syndrome."

Dosage and Administration:

This section has been revised to include dosage instructions for the new indication and to consolidate the recommended dosages for all indications in a table format.

Instructions have been added to prepare an extemporaneous suspension for administration to patients unable to swallow.

Warnings and Precautions:

The warning pertaining to Embryo-Fetal Toxicity was revised to add instructions to advise patients on this risk, as pertains to pre-pubertal females and use of effective contraception once they reach reproductive potential.

Adverse Reactions:

Adverse reactions data in the FSGS clinical studies have been added.

Drug Interactions:

The subsection pertaining to use with Antacids and Acid Reducing Agents has been removed.

The subsection pertaining to P-gp and BCRP substrates has been revised to strike BCRP substrates and revise the recommendation on use with P-gp substrates from 'avoid concomitant use with sensitive P-gp substrates' to 'monitor for adverse reactions and consider dosage reduction of P-gp substrates with narrow therapeutic indices when coadministered with FILSPARI."

Use in Specific Populations:

The Pediatric Use subsection has been revised to describe the use of FILSPARI in pediatric patients with FSGS.

Clinical Pharmacology:

The Mechanism of Action and Pharmacodynamics subsections were revised to describe the applicability of these sections to FSGS.

The Pharmacokinetics sections was revised include data supporting the preparation of an extemporaneous suspension for administration to patients who are unable to swallow. The apparent clearance of sparsentan following the initial 800 mg dose was described. Data regarding drug interactions was revised.

Clinical Studies:

A subsection describing the clinical studies supporting the new indication in FSGS was added.

13. Risk Evaluation and Mitigation Strategies (REMS)

Sparsentan is only available through a REMS program because of the risk of hepatotoxicity. The REMS will be modified to include adult and pediatric patients aged 8 years and older with FSGS without nephrotic syndrome. Liver function will be assessed prior to initiation of sparsentan and every 3 months during treatment. No changes are recommended to the existing elements to ensure safe use or liver analyte monitoring requirements.

14. Postmarketing Requirements and Commitment

No postmarketing requirements or commitments will be issued at the time of approval.

15. Appendices

15.1. References

Abugov R, Clark J, Higginbotham L, Li F, Nie L, Reasner D, Rothmann M, Yuan X, Sharretts J. Should responder analyses be conducted on continuous outcomes? Pharm Stat. 2023 Mar;22(2):312-327. doi: 10.1002/pst.2273. Epub 2022 Nov 23. PMID: 36418046.

D'Agati VD, Kaskel FJ, Falk RJ. Focal Segmental Glomerulosclerosis. *N Engl J Med*. 2011;365(25):2398-2411.

De Vriese AS, Sethi S, Nath KA, Glassock RJ, Fervenza FC. Differentiating Primary, Genetic, and Secondary FSGS in Adults: A Clinicopathologic Approach. *J Am Soc Nephrol*. 2018;29(3):759-774. doi:10.1681/ASN.2017090958Dupont WD, Plummer WD Jr. Power and sample size calculations for studies involving linear regression. Control Clin Trials. 1998 Dec;19(6):589-601. doi: 10.1016/s0197-2456(98)00037-3. PMID: 9875838.

De Vriese AS, Wetzels JF, Glassock RJ, Sethi S, Fervenza FC. Therapeutic trials in adult FSGS: lessons learned and the road forward. Nat Rev Nephrol. 2021 Sep;17(9):619-630. doi: 10.1038/s41581-021-00427-1. PMID: 34017116; PMCID: PMC8136112

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021 Oct;100(4S):S1-S276. doi: 10.1016/j.kint.2021.05.021

Ebefors K, Wiener RJ, Yu L, Azeloglu EU, Yi Z, Jia F, Zhang W, Baron MH, He JC, Haraldsson B, Daehn I. Endothelin receptor-A mediates degradation of the glomerular endothelial surface layer via pathologic crosstalk between activated podocytes and glomerular endothelial cells. Kidney Int. 2019 Oct;96(4):957-970. doi: 10.1016/j.kint.2019.05.007. Epub 2019 May 22. PMID: 31402170; PMCID: PMC7200072.

Fine RN. Recurrence of nephrotic syndrome/focal segmental glomerulosclerosis following renal transplantation in children. Pediatr Nephrol. 2007 Apr;22(4):496-502. doi: 10.1007/s00467-006-0361-6. Epub 2006 Dec 21. PMID: 17186280; PMCID: PMC1805045.

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021 Oct;100(4S):S1-S276. doi: 10.1016/j.kint.2021.05.021.

Li L, Bannick M, Sabanes Bove D, Xi D, Ye T, Yi Y (2025). RobinCar2: ROBust INference for Covariate Adjustment in Randomized Clinical Trials. R package version 0.2.1.9000, https://github.com/openpharma/RobinCar2/.

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011 Dec 10;30(28):3267-84. doi: 10.1002/sim.4102. Epub 2010 Nov 30. PMID: 22105690.

National Kidney Foundation, NephCure Kidney International. The Voice of the Patient Externally Led Patient-Focused Drug Development Meeting on: Primary Focal Segmental Glomerulosclerosis (FSGS). Published September 10, 2021.

Pitcher D, Braddon F, Hendry B, et al. Long-Term Outcomes in Nephrotic Syndrome by Kidney Biopsy Diagnosis and Proteinuria. J Am Soc Nephrol. 2025;36(7):1398-1413. doi:10.1681/ASN.0000000610

Rheault MN, Alpers CE, Barratt J, Bieler S, Canetta P, Chae DW, Coppock G, Diva U, Gesualdo L, Heerspink HJL, Inrig JK, Kirsztajn GM, Kohan D, Komers R, Kooienga LA, Lieberman K, Mercer A, Noronha IL, Perkovic V, Radhakrishnan J, Rote W, Rovin B, Tesar V, Trimarchi H, Tumlin J, Wong MG, Trachtman H; DUPRO Steering Committee and DUPLEX Investigators. Sparsentan versus Irbesartan in Focal Segmental Glomerulosclerosis. N Engl J Med. 2023 Dec 28;389(26):2436-2445. doi: 10.1056/NEJMoa2308550. Epub 2023 Nov 3. PMID: 37921461.

Sabanes Bove D, Li L, Dedic J, Kelkhoff D, Kunzmann K, Lang B, Stock C, Wang Y, James D, Sidi J, Leibovitz D, Sjoberg D, Krieger N (2025). mmrm: Mixed Models for Repeated Measures. R package version 0.3.15, https://openpharma.github.io/mmrm/.

Southworth MR, Psotka MA, Pomeroy JE, Stockbridge NL. Responder Analyses Can Be Misleading. J Am Coll Cardiol. 2025 Jan 21;85(2):196-198. doi: 10.1016/j.jacc.2024.11.017. PMID: 39814479.

Sun YBY, Qu X, Zhang X, Caruana G, Bertram JF, Li J (2013) Glomerular Endothelial Cell Injury and Damage Precedes That of Podocytes in Adriamycin-Induced Nephropathy. PLoS ONE 8(1): e55027.

Uffing A, Pérez-Sáez MJ, Mazzali M, Manfro RC, et al. Recurrence of FSGS after Kidney Transplantation in Adults. Clin J Am Soc Nephrol. 2020 Feb 7;15(2):247-256. PMID: 31974287; PMCID: PMC7015092.

United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2023.

van de Lest NA, Bakker AE, Dijkstra KL, Zandbergen M, Heemskerk SAC, Wolterbeek R, Bruijn JA, Scharpfenecker M. Endothelial Endothelin Receptor A Expression Is Associated With Podocyte Injury and Oxidative Stress in Patients With Focal Segmental Glomerulosclerosis. Kidney Int Rep. 2021 Apr 22;6(7):1939-1948. doi: 10.1016/j.ekir.2021.04.013. PMID: 34307988; PMCID: PMC8258598.

Wong K, Pitcher D, Braddon F, Downward L, Steenkamp R, Annear N, et al. Effects of rare kidney diseases on kidney failure: a longitudinal analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) cohort. Lancet. 2024;403(10433):1279-1289. doi:10.1016/S0140-6736(23)02843-X

15.2. Financial Disclosure

Seven investigators were deemed to have met the threshold of a potential financial interest in accordance with 21 CFR Part 54. The fees paid to these investigators were mainly for work in an advisory capacity as subject matter experts including for consulting in the design of the protocol, and advice on the future development of sparsentan. The fees were not paid for enrollment of subjects. The investigators also have no ownership (stock) interest in Travere Therapeutics, Inc. Study payments are made to the institution and not to the investigator directly. The investigator is paid their salary by the institution not the sponsor.

Covered Clinical Study (Name and/or Number): 021FSGS16010 /DUPLEX

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1307 principal and sub-investigators with FDA form 3454 and 7 with FDA Form 3455.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 7 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.3. Additional Efficacy Analyses

Multiple imputation Procedure

1. Data for proteinuria were log-transformed prior to conducting multiple imputation.
2. Data after occurrence of intercurrent event of initiation of renal replacement therapy were set as missing.

3. Data was made monotone missing using the PROC MI with the following SAS sample statement. Due to small samples within samples and missing data, imputation was not stratified by baseline stratification factors.

4. For each arm, subjects who completed randomized treatment were grouped together and imputed under a sequentially missing at random assumption. The option maximum was set at (b) (4) with minmaxiter set at (b) (4).
5. The copy reference approach was used to impute subjects who did not complete randomized treatment and were missing outcome at Week 108. Subjects on irbesartan arm and had available data at Week 108 was used to generate the multiple imputation model.
6. After all data were imputed, the "imputed data" for the missing data due to intercurrent event of initiation of renal replacement therapy were discarded. The worst 5% of the observed UPCR data prior to the multiple imputation procedure, i.e., large values, was obtained from the data. Then, the number of missing datapoints due to occurrence of intercurrent event of initiation of renal replacement therapy were sampled with replacement to impute the missing data. This was repeated according to the number of multiple imputation iterations.
7. The primary statistical regression model was used to analyze each of the completed multiply imputed datasets. After which, Rubin's rule was used to combine the results.

The above approach differs slightly from the Applicant's procedure. Differences between the Agency and Applicant's procedure are as follows

- During the review process, we asked for the imputation to be done according to the stratification factor (4 levels). However, there were convergence issues due to limited samples in some of the stratification groups. Thus, the Applicant redid the sampling according to eGFR categories for imputing missing eGFR data and UPCR categories for imputing missing UPCR data. Given the amount of missing data and multiple time points, the review team did not stratify the imputation procedure.
- In the Applicant's submission, the range of plausible UPCR values in their imputation procedure was set at 70. In our review, we used 30 or log(30).
- The Applicant followed the Agency's request and conducted an ANCOVA with heteroskedastic variance for the analysis. The Agency used the MMRM model specified in their SAP.

There were some differences in the conclusions of the multiple imputation procedure.

The Applicant obtained UPCR findings concluding no evidence of treatment effect when the approach of monotone regression model was applied. When the approach of predictive mean matching was used to impute missing data, the results were nominally statistically significant. The Applicant argued that they prefer the mean matching approach given there were less data which were above the maximum observed value of 30.

We had conclusions of treatment effect when we applied the monotone regression model and correctly specifying the maximum range to be 30. With this, none of our imputed UPCR values were above 30. The approach of PMM was evaluated without considering the worst 5% sampling and we obtain similar conclusions of treatment effect for UPCR.

Missing Data Rates Argument

The Applicant argued that the missing data rates in DUPLEX were consistent with other trials with long follow-up periods (b) (4) and PROTECT (based on UPCR at 2 years). However, the statistical team disagrees with the Applicant's assertion for the following reasons.

(b) (4)

- For PROTECT (conducted by the Applicant), the missing rates were lower for sparsentan arm compared to irbesartan. The observation differs from DUPLEX, where the missing rates were higher and similar between arms.

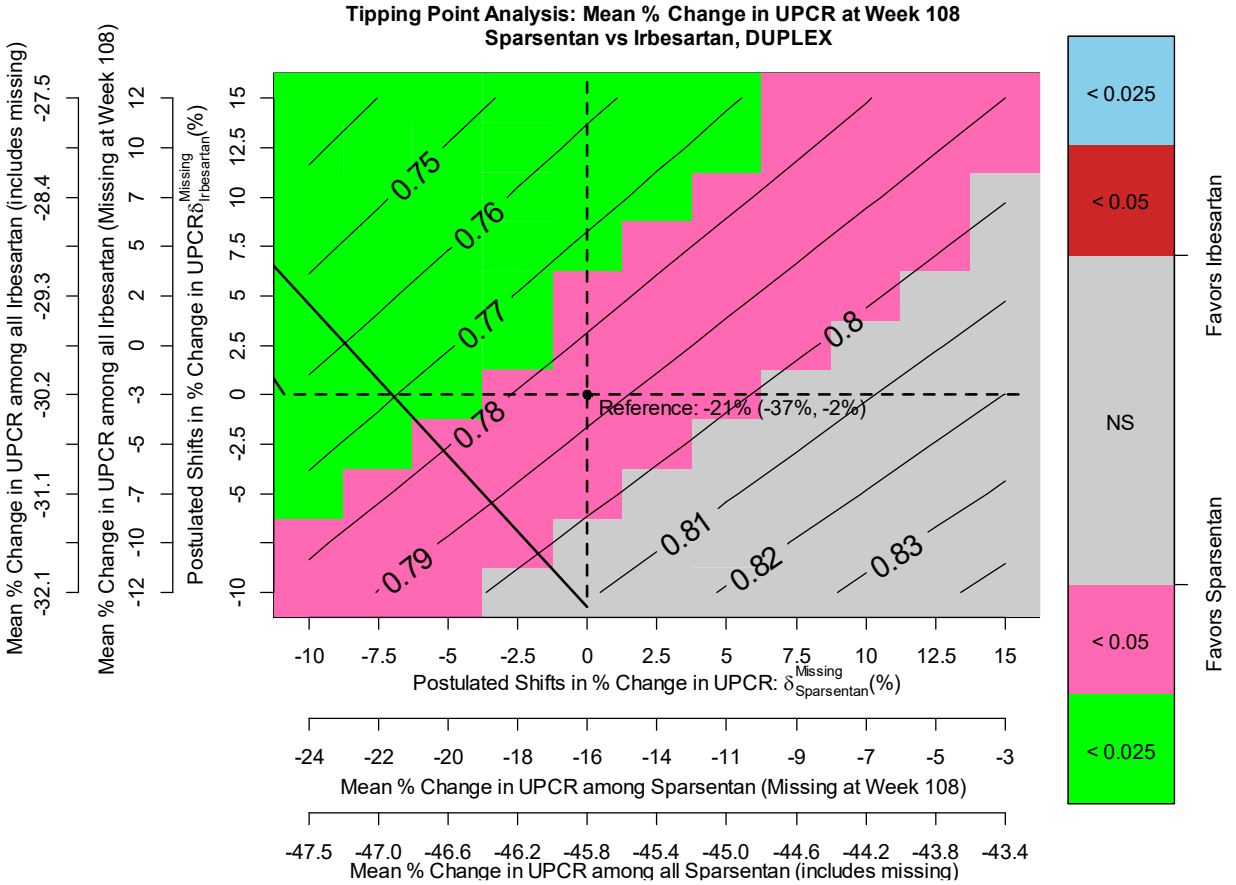
Tipping Point Sensitivity Analyses

Tipping point sensitivity analyses were conducted for UPCR findings at Week 108 for the overall population and subjects without documented history of nephrotic syndrome. Figure 17 and Figure 18 show the results for the overall population and subjects without documented history of nephrotic syndrome. In the overall population, the space of tipping points for the results to be nominally non-statistically significant are indicated by the gray color.

For example, using the horizonal dotted line as reference, subjects on irbesartan arm who are missing UPCR outcomes have a mean reduction of -3% or GMR of 0.97 and are not further shifted. For subjects on sparsentan arm and missing UPCR outcomes, their percent changes are shifted from -16% to -3% (i.e., GMR from .0.84 to 0.97), closer to no percent reduction. When shifting the percent changes from 0 to 15% (positive shifts indicate loss of efficacy) for sparsentan arm, at least 7.5% increase in percent change in UPCR (i.e., GMR of 0.84 for sparsentan and 0.91 on irbesartan arm) will change the results to be nominally non-significant. Given that subjects are off-treatment and were missing outcomes, it is not unreasonable for such shifts towards the null (of GMR of 1). For irbesartan arm, a GMR of 0.97 indicates almost

no reduction from baseline for those without outcomes and are off-treatment, the assumption of a GMR closer to 1 is not unreasonable. Across the space of tipping points, there are numerous other possibilities for the results to be tipped.

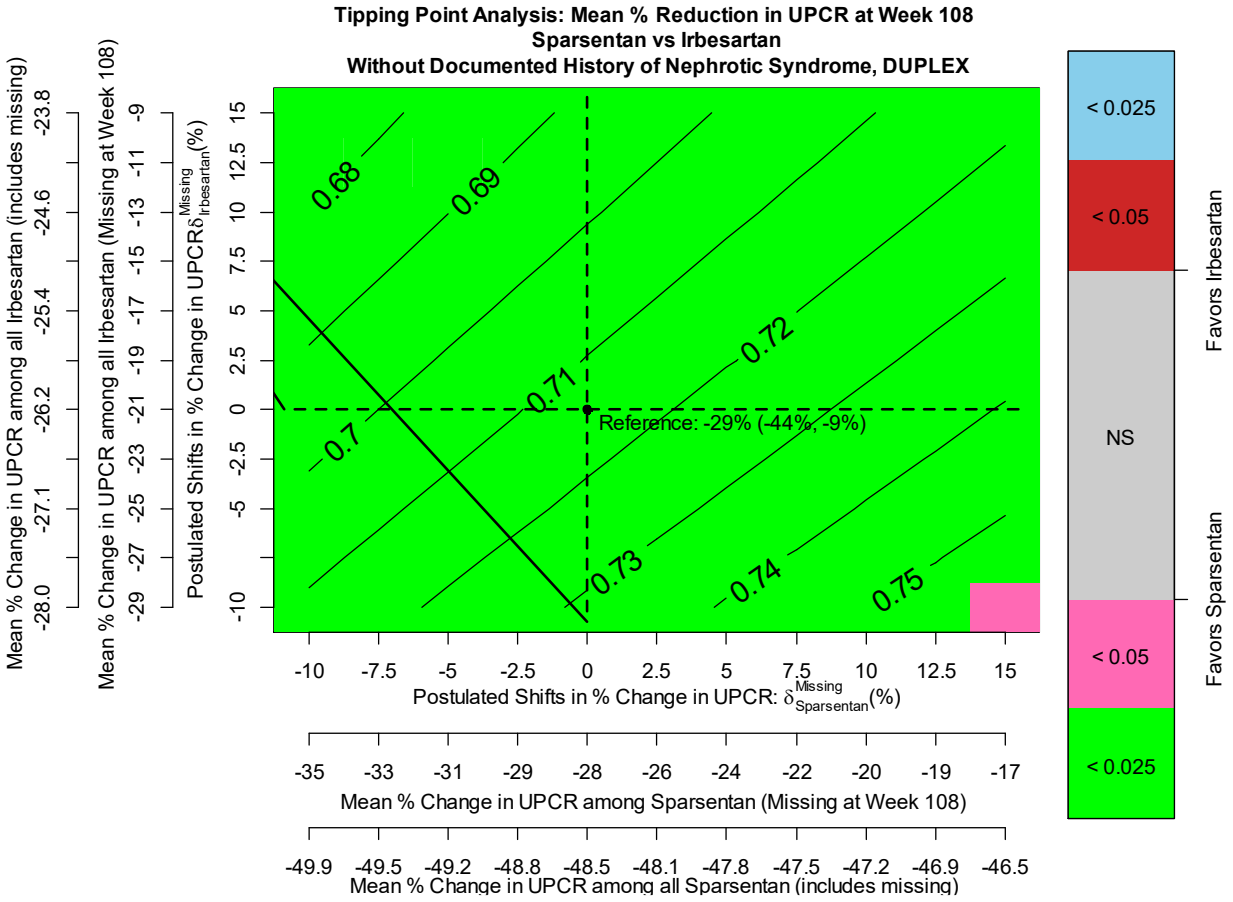
Figure 17 Tipping Point Analysis for UPCR at Week 108 for Overall Population, DUPLEX



Source: Statistical Reviewer
The contours correspond to the estimated ratio of geometric mean ratio between arms from the regression model based on Li et al 2023, ANHECOVA on the log UPCR with baseline log UPCR, treatment effect, stratification factors and accounting for block randomization using stratification factors. Heteroskedasticity is assumed using HC3 approach. Results after multiple imputation are combined using Rubin's rule.
Reference point is the relative percent change in UPCR at Week 108 with baseline comparing sparsentan with irbesartan based on Li et al 2023 at Week 108 (Est % Change: -21%, 95%CI: (-37, -2%)). There are no shifts in the % change in UPCR for the imputed data based on copy reference and worst 5% observed data for those with ICE due to initiation of kidney replacement therapy.
Postulated Shifts in % Change in UPCR (Inner axis) : Delta shifts to be added to the imputed missing data on the sparsentan arm (horizonal) or irbesartan arm (vertical)
Mean % change in UPCR among sparsentan (Missing at Week 108) (Middle axis): This axis is the mean % change in UPCR after adding the corresponding delta shift from the inner axis to the imputed data (middle) for the sparsentan arm. Similar description for irbesartan arm.
Mean % Change in UPCR among all Sparsentan (includes missing): The overall mean % reduction in UPCR for all subjects, including sparsentan subjects who were missing and had their data imputed according to multiple imputation plus the added delta according to the inner axis. Similar description for irbesartan arm.
Positive shifts in % change translates to a loss in treatment effect and negative shifts in % change translates to gains in treatment effect.
Abbreviations: UPCR, urine protein to creatinine ratio; %, percent; MMRM, mixed model repeated measures; CI, confidence interval; ANHECOVA, analysis of heterogeneous covariance, HC3, heteroskedasticity-consistent 3 robust estimator of the variance; Est, estimated.

In the subgroup of subjects without documented history of nephrotic syndrome, for the results to be non-statistically significant, subjects without outcome on the sparsentan arm have to have more than 15% shifts, not displayed in Figure 18. Because the shifts are more extreme and large, the findings for percent reduction in UPCR at Week 108 in the subgroup of subjects without documented history of nephrotic syndrome are more robust to deviation of assumptions of the missing outcome.

Figure 18 Tipping Point Analysis of UPCR at Week 108 for Subgroup Without Documented History of Nephrotic Syndrome, DUPLEX



Source: Statistical Reviewer
The contours correspond to the estimated ratio of geometric mean ratio between arms from the regression model based on Li et al 2023, ANHECOVA on the log UPCR with baseline log UPCR, treatment effect, stratification factors and accounting for block randomization using stratification factors. Heteroskedasticity is assumed using HC3 approach. Results after multiple imputation are combined using Rubin's rule.
Reference point is the relative estimated percent change in UPCR at Week 108 with baseline comparing sparsentan with irbesartan based on Li et al 2023 at Week 108 (Est % Change: -29%, 95%CI:(-44, -9%)) when there are no shifts in the % change in UPCR for the imputed data based on copy reference and worst 5% observed data for those with ICE due to initiation of kidney replacement therapy.
Postulated Shifts in % Change in UPCR (Inner axis) : Delta shifts to be added to the imputed missing data on the sparsentan arm (horizonal) or irbesartan arm (vertical)
Mean % change in UPCR among sparsentan (Missing at Week 108) (Middle axis): This is the mean % change in UPCR after adding the corresponding delta shift from the inner axis to the imputed data (middle) for the sparsentan arm.
Mean % Change in UPCR among all Sparsentan (includes missing): The overall mean % reduction in UPCR for all subjects, including sparsentan subjects who were missing and had their data imputed according to multiple imputation plus the added delta according to the inner axis. Similar description for irbesartan arm. Similar description for irbesartan arm.
Positive shifts in % change translates to a loss in treatment effect and negative shifts in % change translates to gains in treatment effect.

Abbreviations: UPCR, urine protein to creatinine ratio; %, percent; MMRM, mixed model repeated measures; CI, confidence interval; ANHECOVA, analysis of heterogeneous covariance, HC3, heteroskedasticity-consistent 3 robust estimator of the variance; Est, estimated

15.3.1. Additional Efficacy Tables

Table 42 Proportion of Subjects with eGFR Data According to their Treatment Status from Week 36 Onwards, FAS, DUPLEX

Visit Week	Description of Status	Sparsentan (N=184)	Irbesartan (N=187)	Total (N=371)
Week 48	**Available eGFR**	161 (88%)	163 (87%)	324 (87%)
Week 48	1: On Treatment	147 (80%)	151 (81%)	298 (80%)
Week 48	2: Discontinued Treatment	14 (8%)	12 (6%)	26 (7%)
Week 48	**Missing eGFR**	23 (12%)	24 (13%)	47 (13%)
Week 48	3: On Treatment	5 (3%)	8 (4%)	13 (4%)
Week 48	4: Discontinued Treatment	18 (10%)	16 (9%)	34 (9%)
Week 60	**Available eGFR**	157 (85%)	157 (84%)	314 (85%)
Week 60	1: On Treatment	140 (76%)	142 (76%)	282 (76%)
Week 60	2: Discontinued Treatment	17 (9%)	15 (8%)	32 (9%)
Week 60	**Missing eGFR**	27 (15%)	30 (16%)	57 (15%)
Week 60	3: On Treatment	4 (2%)	8 (4%)	12 (3%)
Week 60	4: Discontinued Treatment	23 (12%)	22 (12%)	45 (12%)
Week 72	**Available eGFR**	153 (83%)	156 (83%)	309 (83%)
Week 72	1: On Treatment	134 (73%)	142 (76%)	276 (74%)
Week 72	2: Discontinued Treatment	19 (10%)	14 (7%)	33 (9%)
Week 72	**Missing eGFR**	31 (17%)	31 (17%)	62 (17%)
Week 72	3: On Treatment	4 (2%)	5 (3%)	9 (2%)
Week 72	4: Discontinued Treatment	27 (15%)	26 (14%)	53 (14%)
Week 84	**Available eGFR**	151 (82%)	156 (83%)	307 (83%)
Week 84	1: On Treatment	134 (73%)	142 (76%)	276 (74%)
Week 84	2: Discontinued Treatment	17 (9%)	14 (7%)	31 (8%)
Week 84	**Missing eGFR**	33 (18%)	31 (17%)	64 (17%)
Week 84	3: On Treatment	2 (1%)	3 (2%)	5 (1%)
Week 84	4: Discontinued Treatment	31 (17%)	28 (15%)	59 (16%)
Week 96	**Available eGFR**	145 (79%)	153 (82%)	298 (80%)
Week 96	1: On Treatment	128 (70%)	137 (73%)	265 (71%)
Week 96	2: Discontinued Treatment	17 (9%)	16 (9%)	33 (9%)
Week 96	**Missing eGFR**	39 (21%)	34 (18%)	73 (20%)
Week 96	3: On Treatment	4 (2%)	4 (2%)	8 (2%)
Week 96	4: Discontinued Treatment	35 (19%)	30 (16%)	65 (18%)
Week 108	**Available eGFR**	134 (73%)	144 (77%)	278 (75%)
Week 108	1: On Treatment	119 (65%)	129 (69%)	248 (67%)
Week 108	2: Discontinued Treatment	15 (8%)	15 (8%)	30 (8%)
Week 108	**Missing eGFR**	50 (27%)	43 (23%)	93 (25%)
Week 108	3: On Treatment	10 (5%)	7 (4%)	17 (5%)
Week 108	4: Discontinued Treatment	40 (22%)	36 (19%)	76 (20%)

Source: Statistical Review Team
Subjects who died are handled as missing eGFR and discontinued randomized treatment. Subjects with intercurrent event of initiation of renal replacement therapy are handled according to on- or off-treatment status and whether data are available.
Abbreviation: eGFR, estimated glomerular filtration rate

Table 43. Proportion of Subjects with UPCR Data According to their Treatment Status from Week 36, FAS, DUPLEX

Visit Week	Description of Status	Sparsentan (N=184)	Irbesartan (N=187)	Total (N=371)
Week 48	**Available UPCR**	158 (86%)	159 (85%)	317 (85%)
Week 48	1: On Treatment	146 (79%)	150 (80%)	296 (80%)
Week 48	2: Discontinued Treatment	12 (7%)	9 (5%)	21 (6%)
Week 48	**Missing UPCR**	26 (14%)	28 (15%)	54 (15%)
Week 48	3: On Treatment	7 (4%)	9 (5%)	16 (4%)
Week 48	4: Discontinued Treatment	19 (10%)	19 (10%)	38 (10%)
Week 60	**Available UPCR**	154 (84%)	155 (83%)	309 (83%)
Week 60	1: On Treatment	138 (75%)	140 (75%)	278 (75%)
Week 60	2: Discontinued Treatment	16 (9%)	15 (8%)	31 (8%)
Week 60	**Missing UPCR**	30 (16%)	32 (17%)	62 (17%)
Week 60	3: On Treatment	6 (3%)	10 (5%)	16 (4%)
Week 60	4: Discontinued Treatment	24 (13%)	22 (12%)	46 (12%)
Week 72	**Available UPCR**	146 (79%)	151 (81%)	297 (80%)
Week 72	1: On Treatment	135 (73%)	138 (74%)	273 (74%)
Week 72	2: Discontinued Treatment	11 (6%)	13 (7%)	24 (6%)
Week 72	**Missing UPCR**	38 (21%)	36 (19%)	74 (20%)
Week 72	3: On Treatment	3 (2%)	9 (5%)	12 (3%)
Week 72	4: Discontinued Treatment	35 (19%)	27 (14%)	62 (17%)
Week 84	**Available UPCR**	150 (82%)	157 (84%)	307 (83%)
Week 84	1: On Treatment	135 (73%)	143 (76%)	278 (75%)
Week 84	2: Discontinued Treatment	15 (8%)	14 (7%)	29 (8%)
Week 84	**Missing UPCR**	34 (18%)	30 (16%)	64 (17%)
Week 84	3: On Treatment	1 (1%)	2 (1%)	3 (1%)
Week 84	4: Discontinued Treatment	33 (18%)	28 (15%)	61 (16%)
Week 96	**Available UPCR**	144 (78%)	144 (77%)	288 (78%)
Week 96	1: On Treatment	128 (70%)	132 (71%)	260 (70%)
Week 96	2: Discontinued Treatment	16 (9%)	12 (6%)	28 (8%)
Week 96	**Missing UPCR**	40 (22%)	43 (23%)	83 (22%)
Week 96	3: On Treatment	4 (2%)	9 (5%)	13 (4%)
Week 96	4: Discontinued Treatment	36 (20%)	34 (18%)	70 (19%)
Week 108	**Available UPCR**	128 (70%)	140 (75%)	268 (72%)
Week 108	1: On Treatment	119 (65%)	128 (68%)	247 (67%)
Week 108	2: Discontinued Treatment	9 (5%)	12 (6%)	21 (6%)
Week 108	**Missing UPCR**	56 (30%)	47 (25%)	103 (28%)
Week 108	3: On Treatment	10 (5%)	8 (4%)	18 (5%)
Week 108	4: Discontinued Treatment	46 (25%)	39 (21%)	85 (23%)

Source: Statistical Review Team
Subjects who died are handled as missing eGFR and discontinued randomized treatment. Subjects with intercurrent event of initiation of renal replacement therapy are handled according to on- or off-treatment status and whether data are available.
Abbreviation: UPCR, urine protein to creatinine.

Table 44. Summary of Total Slope for eGFR through Week 108 after Addressing Missing Data for Overall Population and Subgroup defined by Documented History of Nephrotic Syndrome, FAS, DUPLEX

	Overall Population		Without Nephrotic Syndrome		With Nephrotic Syndrome	
	Sparsentan	Irbesartan	Sparsentan	Irbesartan	Sparsentan	Irbesartan
N	184	187	129	125	55	62
FDA's Analysis						
Adjusted change in eGFR at Week 108 from baseline (SE)	-13.9 (1.4)	-12.8 (1.3)	-11.2 (1.3)	-12.2 (1.3)	-20.0 (3.2)	-14.1 (3.0)
Adj Diff (vs Irbesartan) [1] (95% CI)	-1.1 (-4.8, 2.7)		1.0 (-2.6, 4.7)		-6.0 (-14.6, 2.7)	
Total Slope (95% CI)	-6.0	-6.6	-5.1	-6.4	-8.2	-7.0
Diff in Total Slope [2] (95% CI)	0.6 (-1.4, 2.5)		1.4 (-0.5, 3.2)		-1.3 (-6.0, 3.4)	

Source: Statistical Review Team

[1,2] Positive values of adjusted difference (vs irbesartan) indicates numerical better for sparsentan; Negative values of adjusted difference (vs irbesartan) indicates numerically better for irbesartan.

Missing data were handled using copy reference multiple imputation and worst 5% percent of the data were used to impute outcome after intercurrent event due to renal replacement therapy, or death.

FDA Analysis for eGFR, different starting seeds were used from the Applicant and 500 multiple imputation were conducted.

The adjusted change in eGFR at Week 108 from baseline is based on the mixed model repeated measures fit to the change from baseline in eGFR post-baseline.

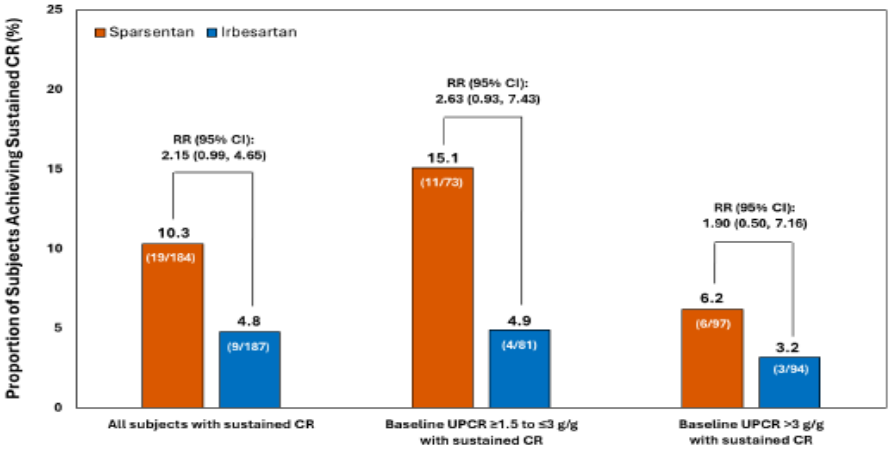
The total slope is estimated from a random coefficient model assuming a linear decline was used to estimate the rate of decline.

Abbreviations: UPCR, urine protein to creatinine ratio; eGFR, estimated glomerular filtration rate; CI, confidence intervals; Adj, adjusted; Diff, difference; %, percent; SE, standard error

15.3.2. Additional Efficacy Figures

Figure 19. Applicant's Figure Showing the Sustained Complete Remission Rates for DUPLEX "Through Week 108"

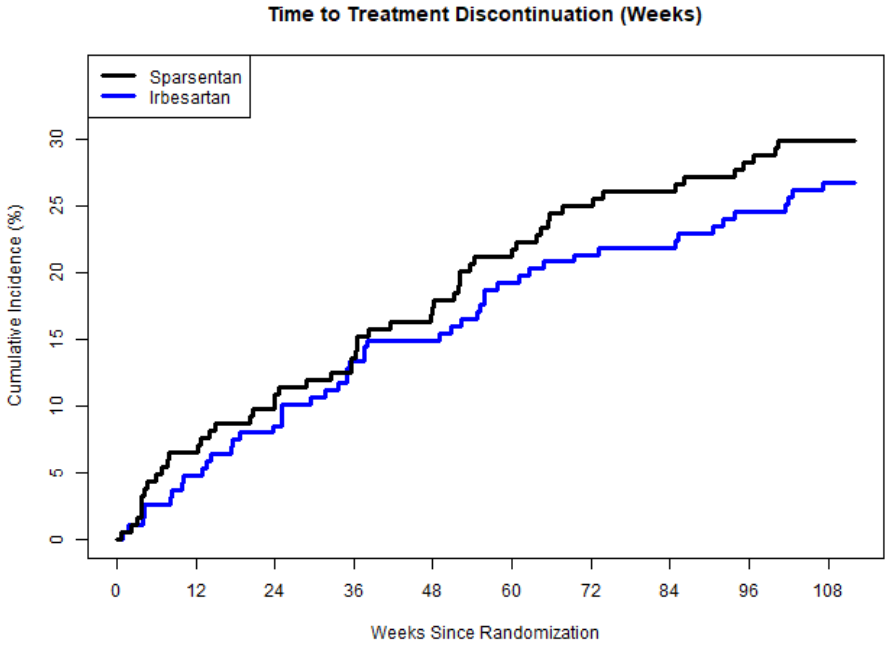
Figure 17: Percentage of Subjects Achieving Sustained Complete Remission (UPCR <0.3 g/g) by Repeated Consecutive Measures Through Week 108 (Full Analysis Set)



Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete remission (UPCR <0.3 g/g); CSR = clinical study report; DB = double-blind; RR = relative risk; SAP = statistical analysis plan; UPCR = urine protein to creatinine ratio.
Notes - Sustained CR is defined as repeated, consecutive UPCR<0.3 g/g.
- Percentages are based on all subjects in the Full Analysis Set within each group.
- Subjects with events are those who met the indicated criteria.
- Data presented are based on on-treatment results.
- 95% CIs for percentage with Events are generated from an Exact Binominal distribution. The difference in rates of events, relative risk, odds ratio, and their corresponding 95% CIs along with p-values are obtained from a CMH test controlling for randomization factors per Section 8.8.4 of the SAP (021FSGS16010 Full DB CSR SAP Version 4.0 [Appendix 16.1.9]).
Sources: TVTX-RE021-TR026 Table 14.2.4.1.65 (Program:T14.2.4.1.x-PropEffUPCCR.sas); Table 14.2.4.1.65.1 (Program: T14.2.4.1.x-PropEffUPCCRSubg.sas).

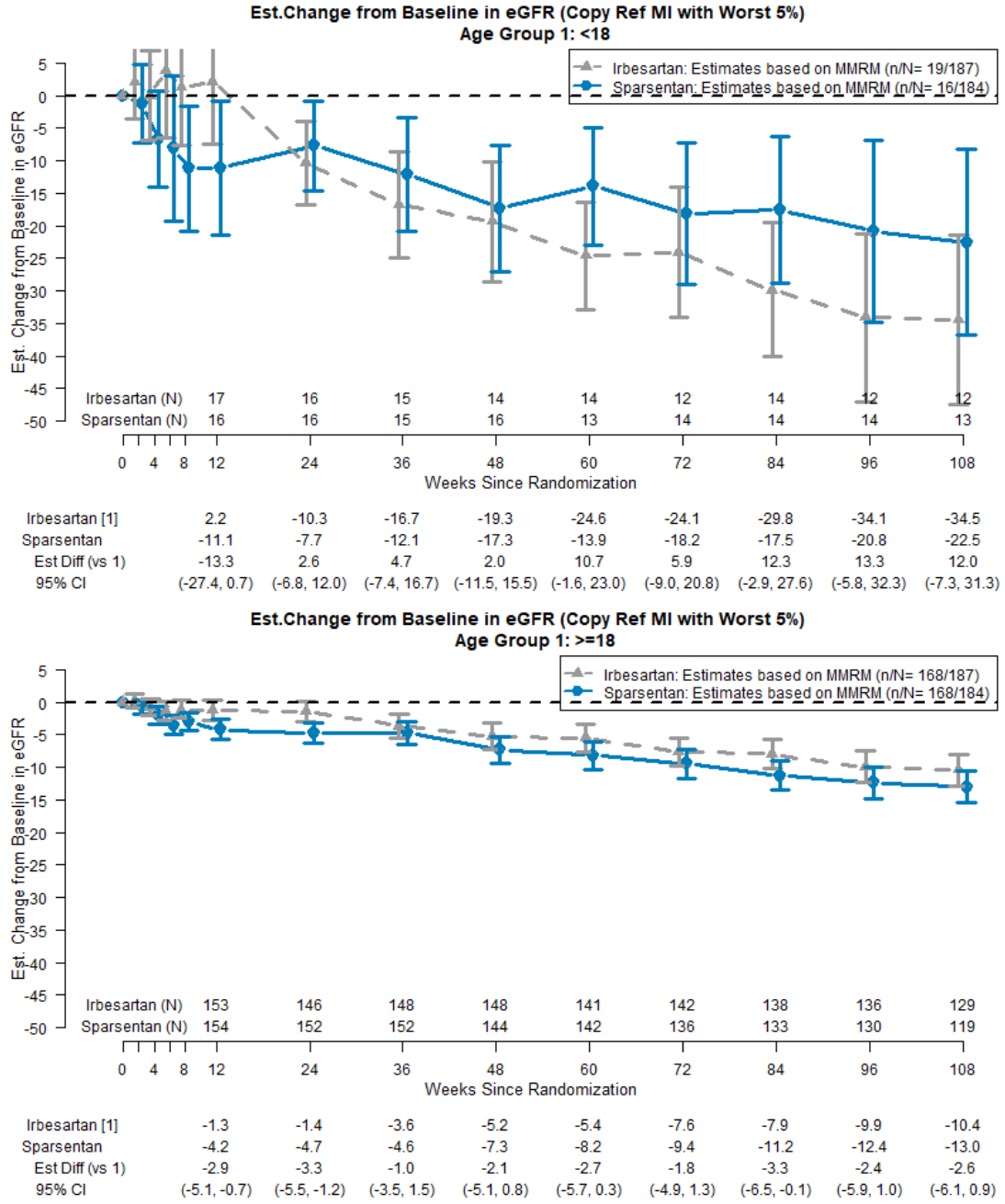
Source: Applicant Module 2.7.3, summary of clinical efficacy
Determination of sustained complete remission is only based on the next UPCR assessment.

Figure 20. Time to Permanent Discontinuation of Randomized Treatment, DUPLEX



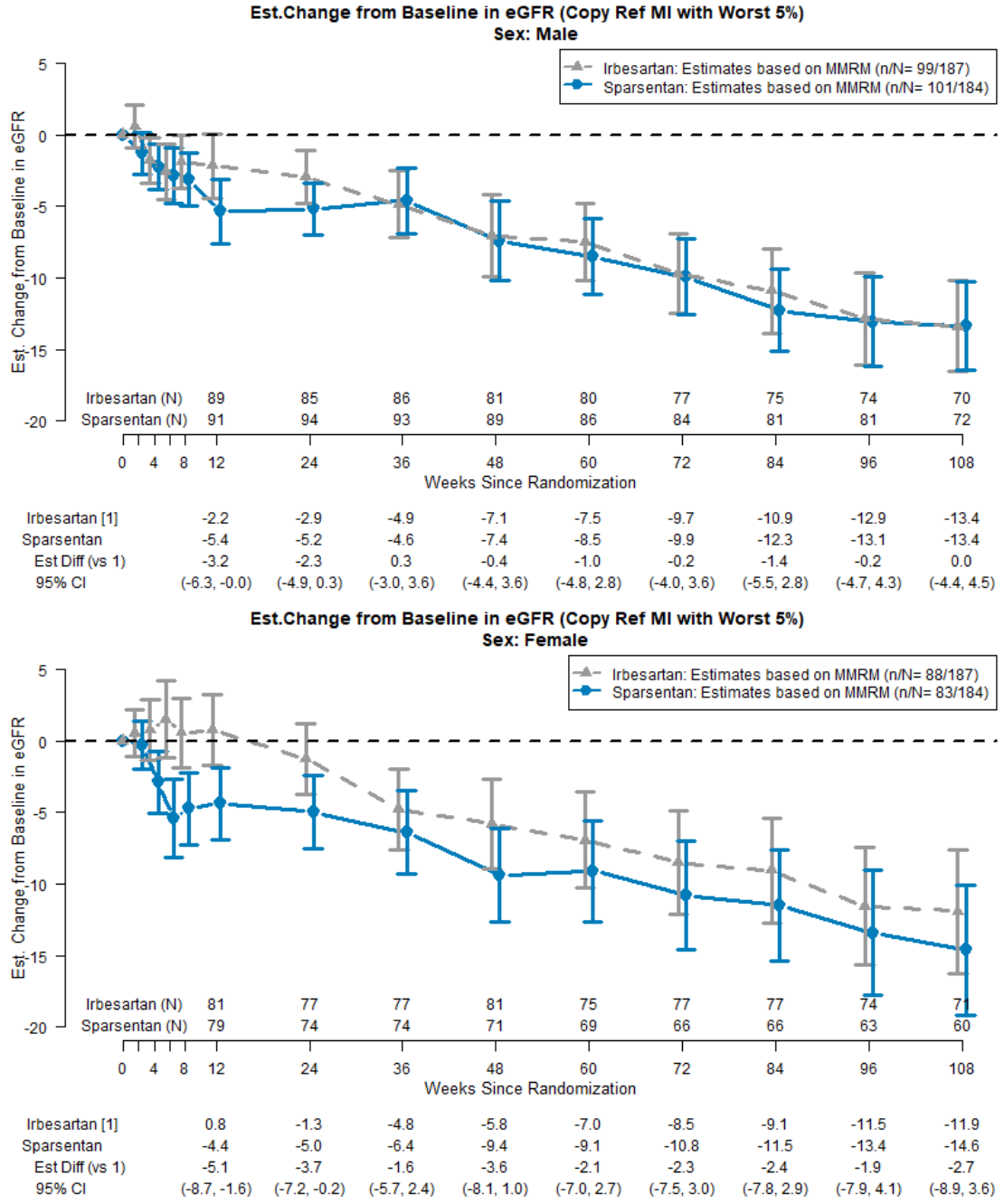
Source: Statistical Reviewer
The figure is generated using TRTEDT, the time of treatment end date, with end of treatment status as the event of interest.

Figure 21. Estimated Adjusted Change from Baseline in eGFR (95% CI) At Visit Weeks for Age Subgroup, FAS, DUPLEX



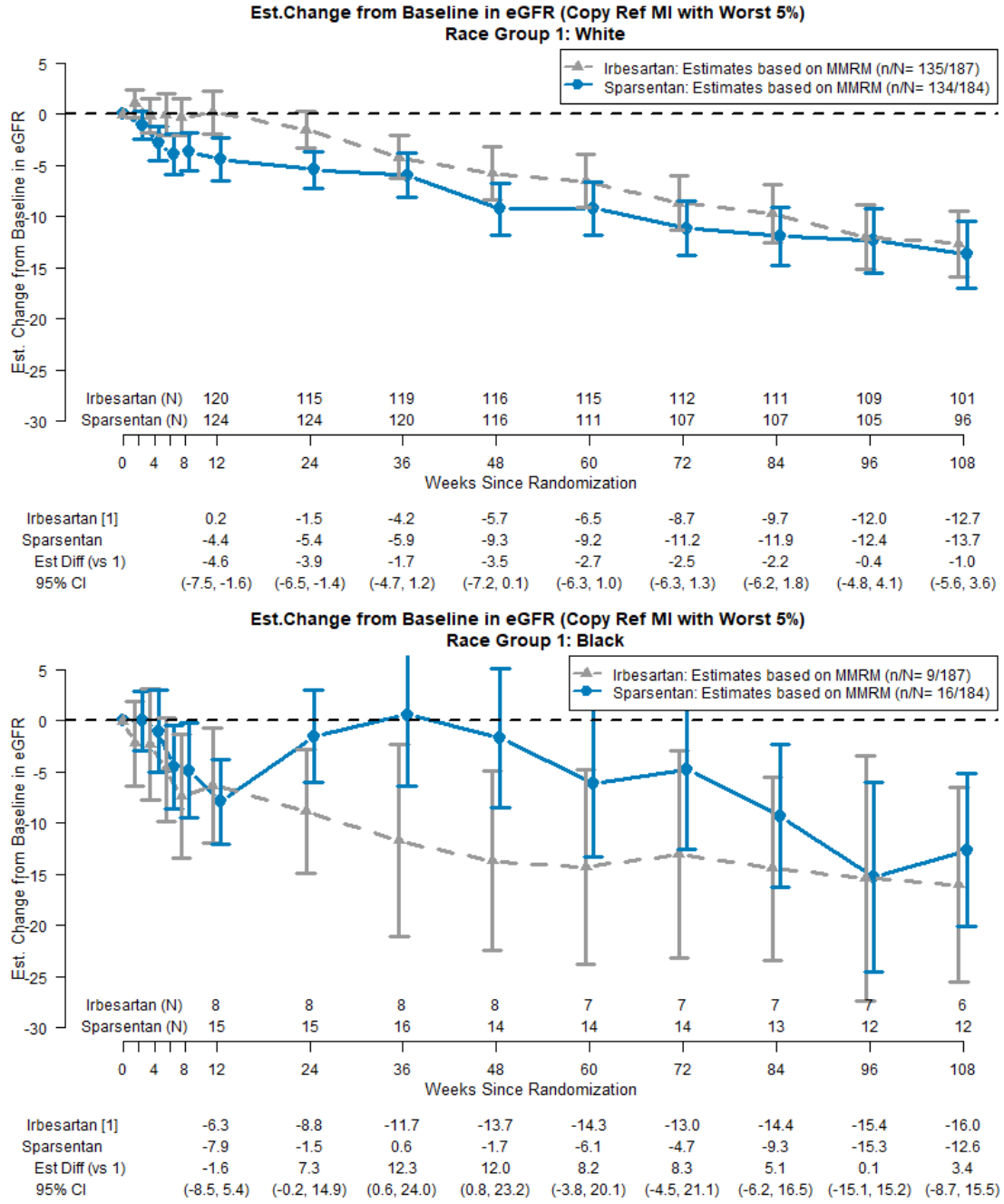
Source: Statistical Review Team
The MMRM was fit to all change from baseline in eGFR up to Week 108 adjusting for baseline eGFR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
Abbreviation: eGFR, estimated glomerular filtration rate; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; UPCR; urine protein to creatinine

Figure 22. Estimated Adjusted Change from Baseline in eGFR (95% CI) At Visit Weeks for Sex Subgroup, FAS, DUPLEX



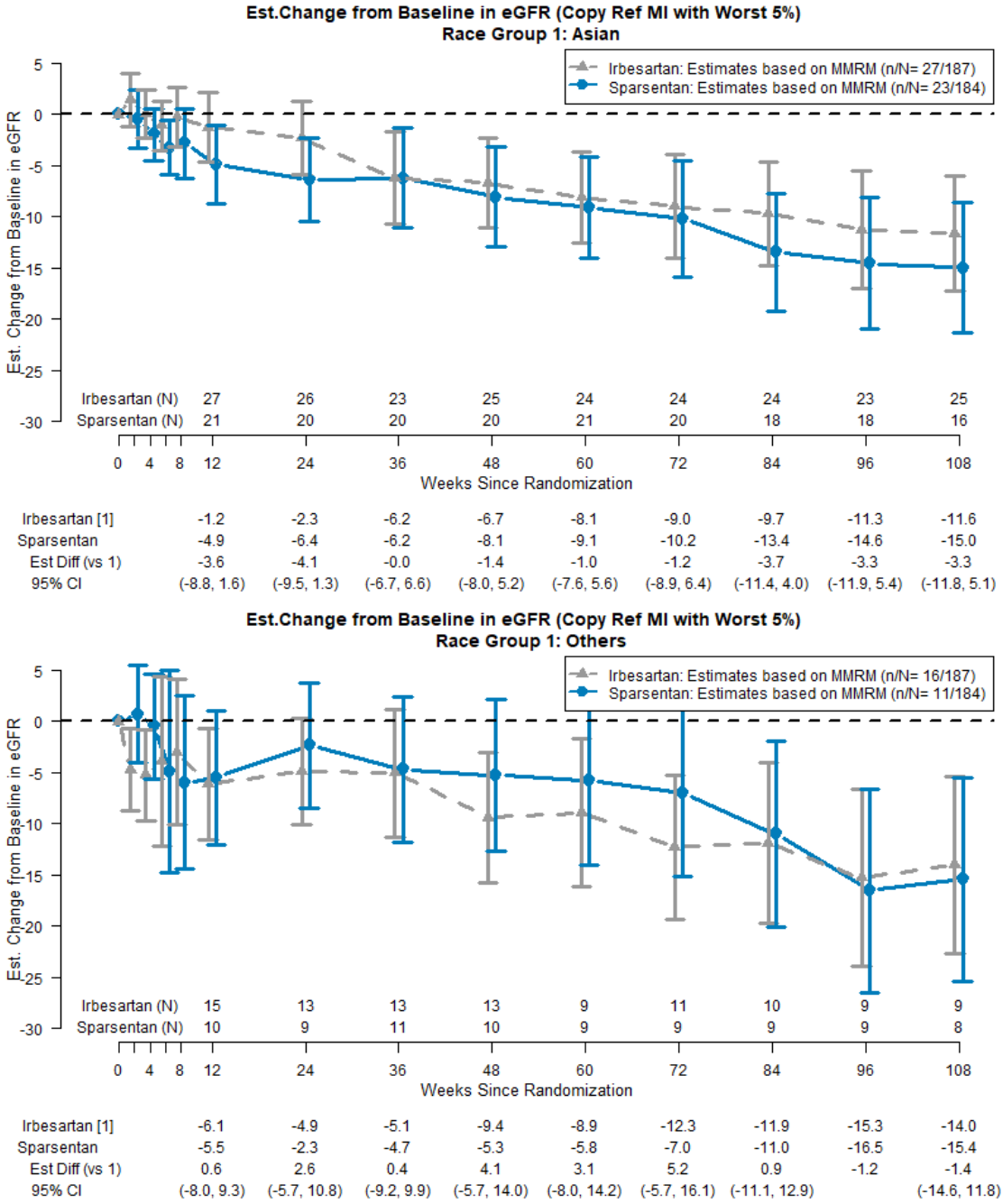
Source: Statistical Review Team
The MMRM was fit to all change from baseline in eGFR up to Week 108 adjusting for baseline eGFR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
Abbreviation: eGFR, estimated glomerular filtration rate; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; UPCR; urine protein to creatinine.

Figure 23. Estimated Adjusted Change from Baseline in eGFR (95% CI) At Visit Weeks for Race Subgroups (White and Black), FAS, DUPLEX



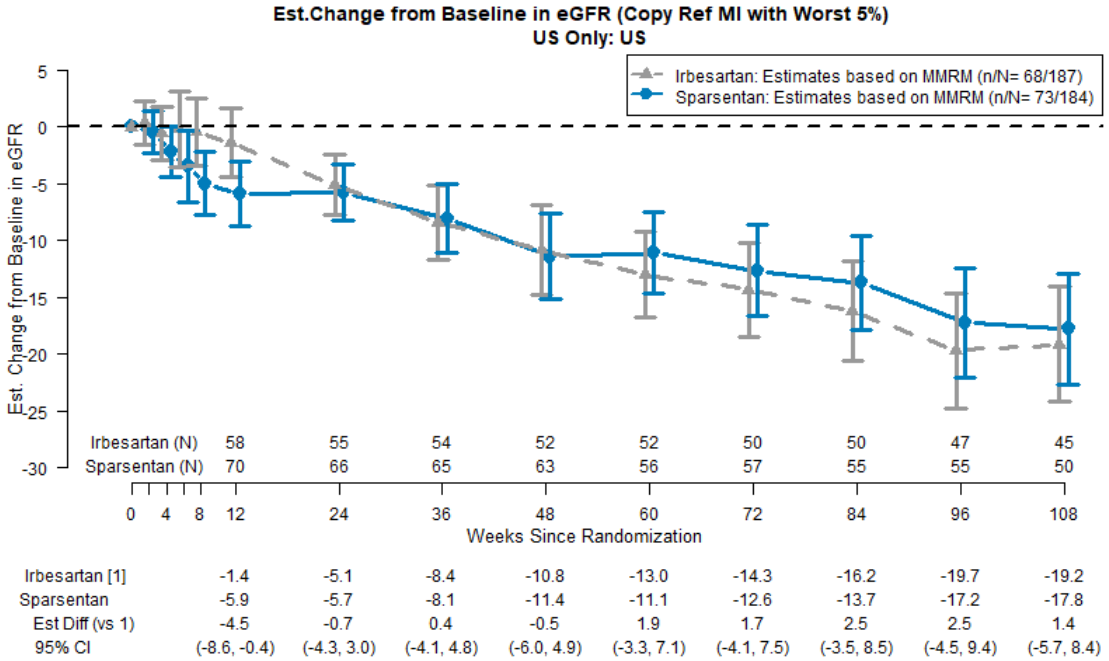
Source: Statistical Review Team
The MMRM was fit to all change from baseline in eGFR up to Week 108 adjusting for baseline eGFR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
Abbreviation: eGFR, estimated glomerular filtration rate; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; UPCR; urine protein to creatinine.

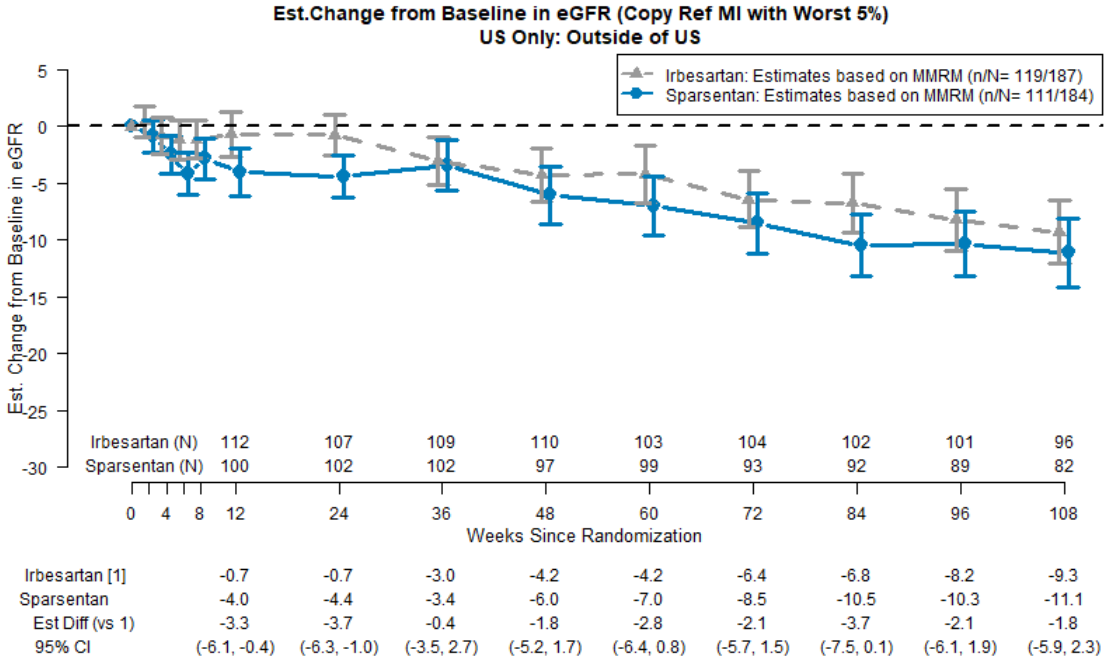
Figure 24. Estimated Adjusted Change from Baseline in eGFR (95% CI) At Visit Weeks for Race Subgroups (Asian and Others), FAS, DUPLEX



Source: Statistical Review Team
The MMRM was fit to all change from baseline in eGFR up to Week 108 adjusting for baseline eGFR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
Abbreviation: eGFR, estimated glomerular filtration rate; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; UPCR; urine protein to creatinine

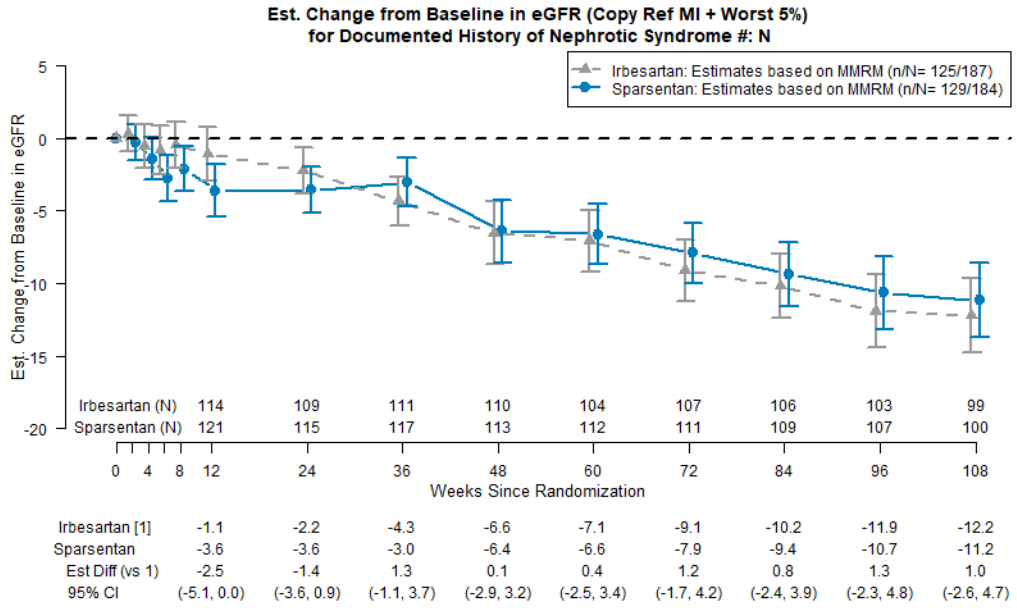
Figure 25. Estimated Adjusted Change from Baseline in eGFR (95% CI) At Visit Weeks for US and Outside of US Subgroup, FAS, DUPLEX

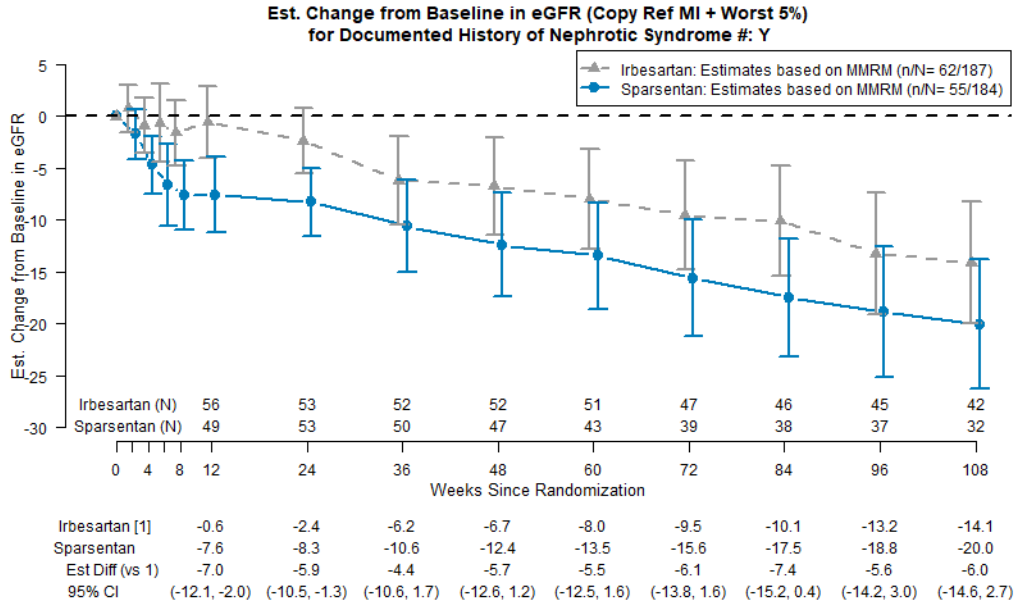




Source: Statistical Review Team
The MMRM was fit to all change from baseline in eGFR up to Week 108 adjusting for baseline eGFR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
Abbreviation: eGFR, estimated glomerular filtration rate; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; UPCR; urine protein to creatinine.

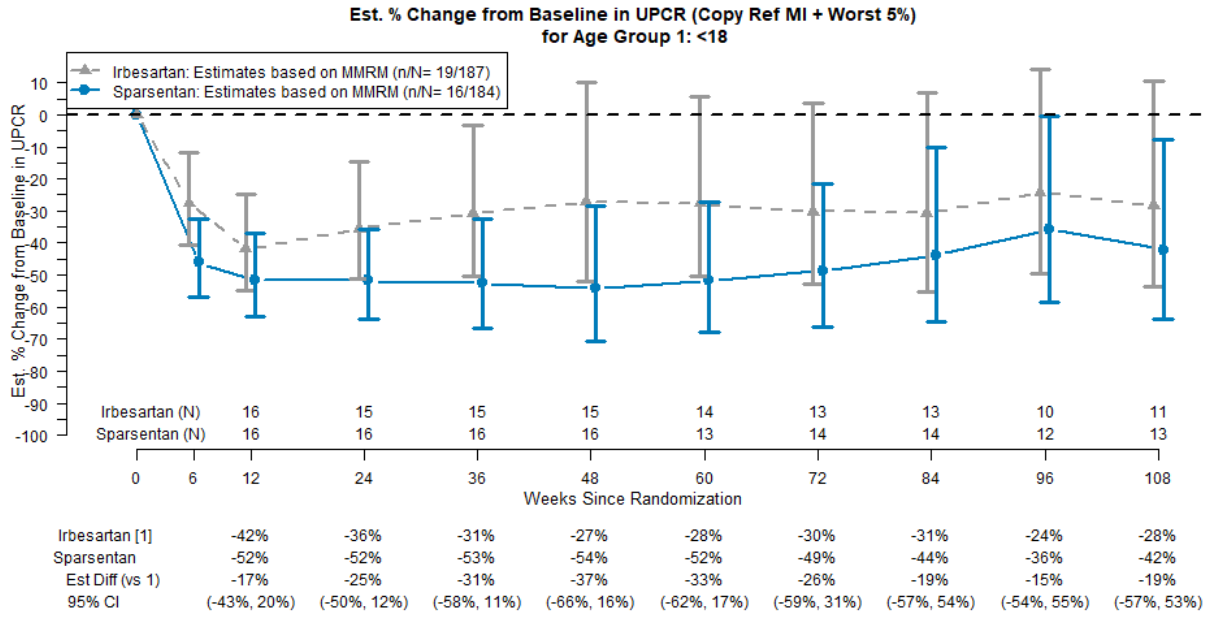
Figure 26. Estimated Adjusted Change from Baseline in eGFR (95% CI) At Visit Weeks for Documented History of Nephrotic Syndrome-Baseline (No vs Yes) Subgroup, FAS, DUPLEX

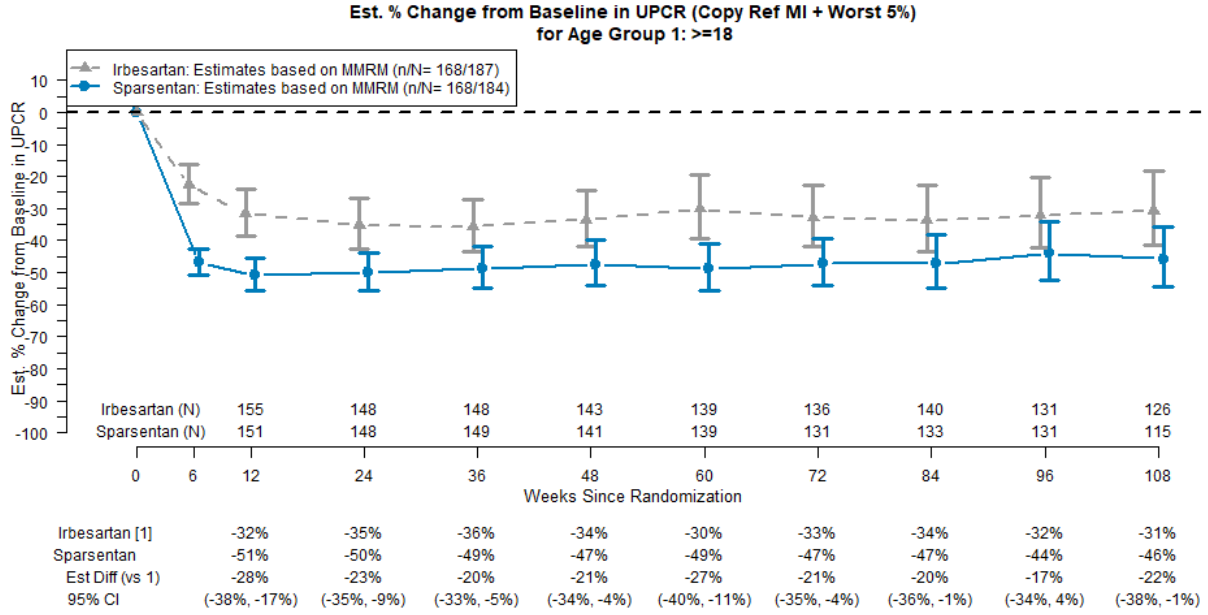




Source: Statistical Review Team
The MMRM was fit to all change from baseline in eGFR up to Week 108 adjusting for baseline eGFR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis, and any missing data (due to death or missing assessments) were imputed using the worst 5% of the observed data. Copy reference multiple imputation was used to impute missing off-treatment data while data missing while on treatment are imputed under missing at random according to the treatment arm.
Documented history of nephrotic syndrome is defined as follows: If the term “nephrotic syndrome” was present in medical history or if all of the following conditions were met at any of the visits prior to the first dose of randomized treatment: UP/C >3.5 g/g (adults) or UP/C >2 g/g (pediatrics), serum albumin <3.0 g/dL, and abnormal edema from physical examination
Abbreviation: eGFR, estimated glomerular filtration rate; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

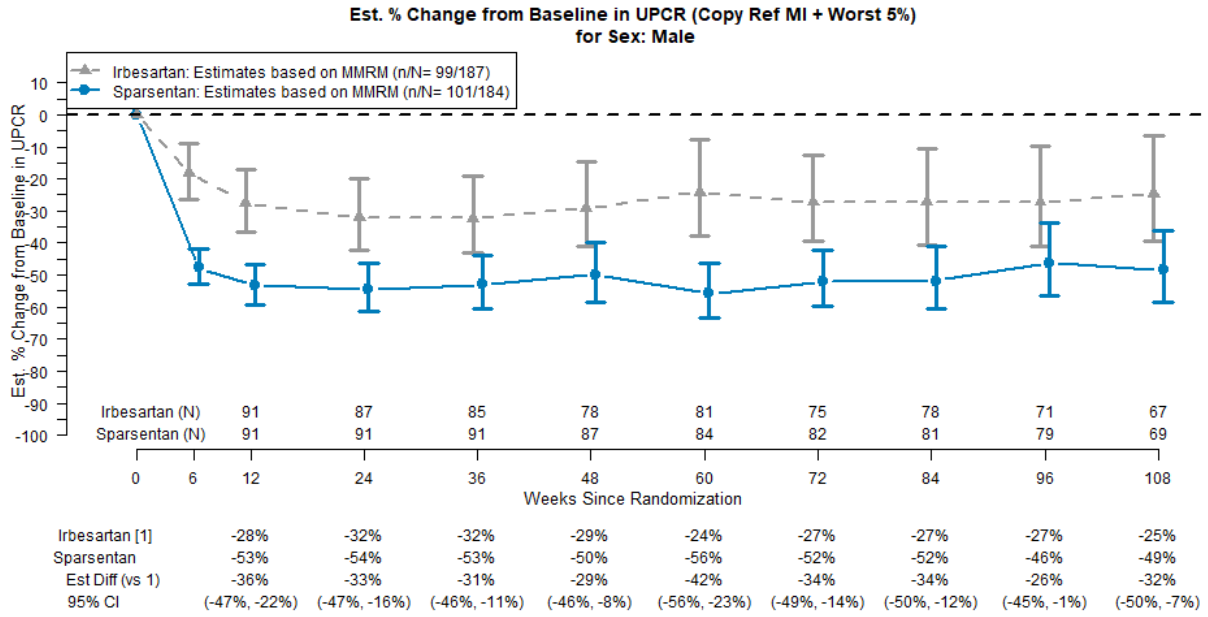
Figure 27. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Age (<18 vs ≥ 18) Subgroup, FAS, DUPLEX

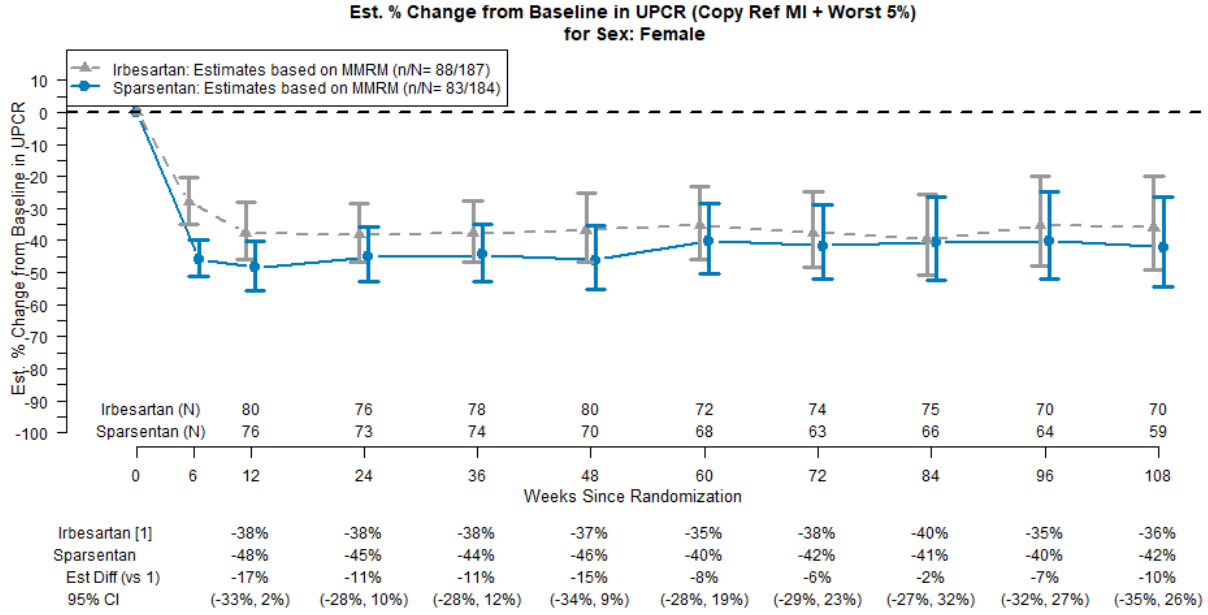




Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis, and any missing data (due to death or missing assessments) were imputed using the worst 5% of the observed data. Copy reference multiple imputation was used to impute missing off-treatment data while data missing while on treatment are imputed under missing at random according to the treatment arm.
Abbreviations: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

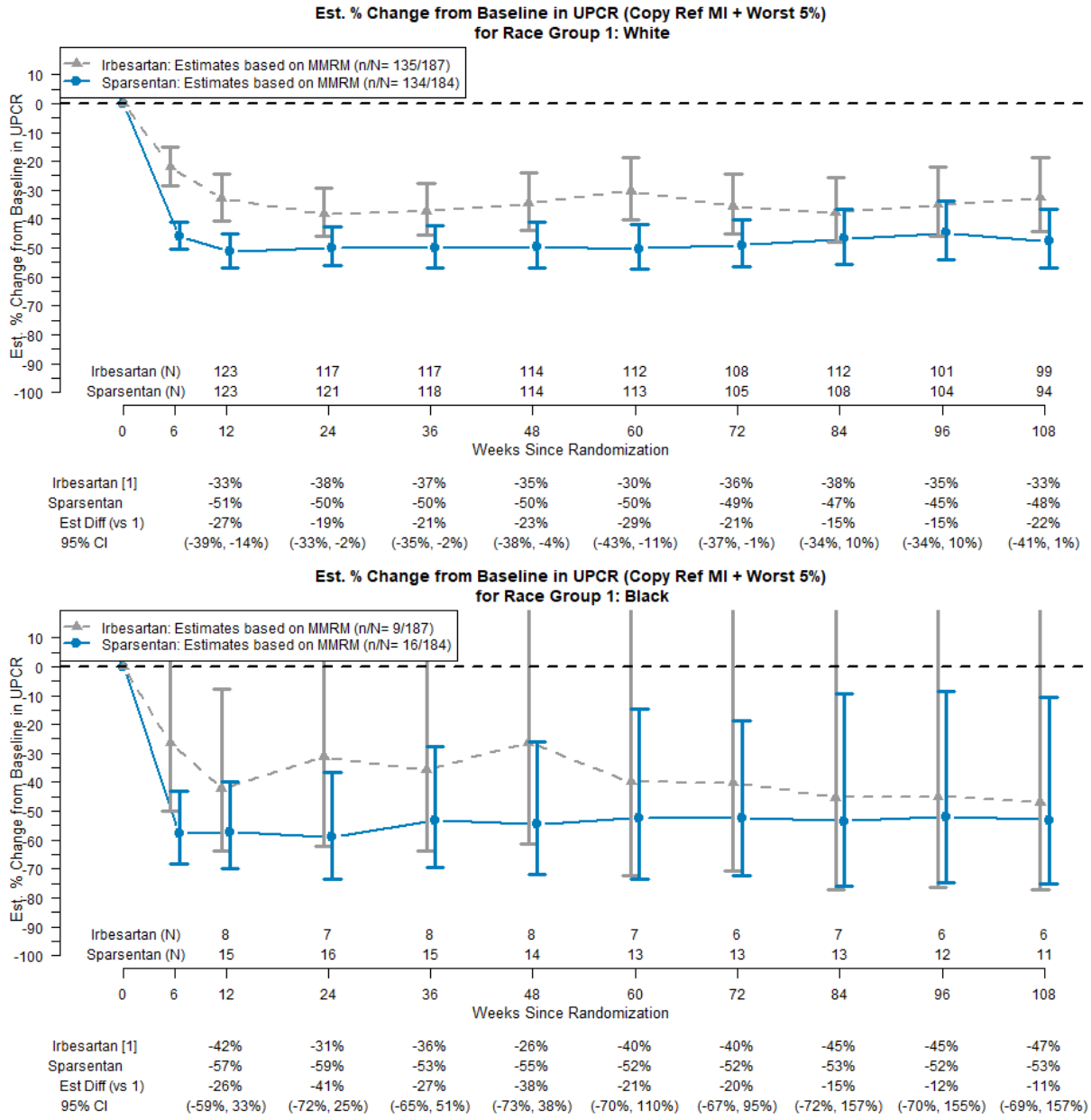
Figure 28. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Sex Subgroup, FAS, DUPLEX





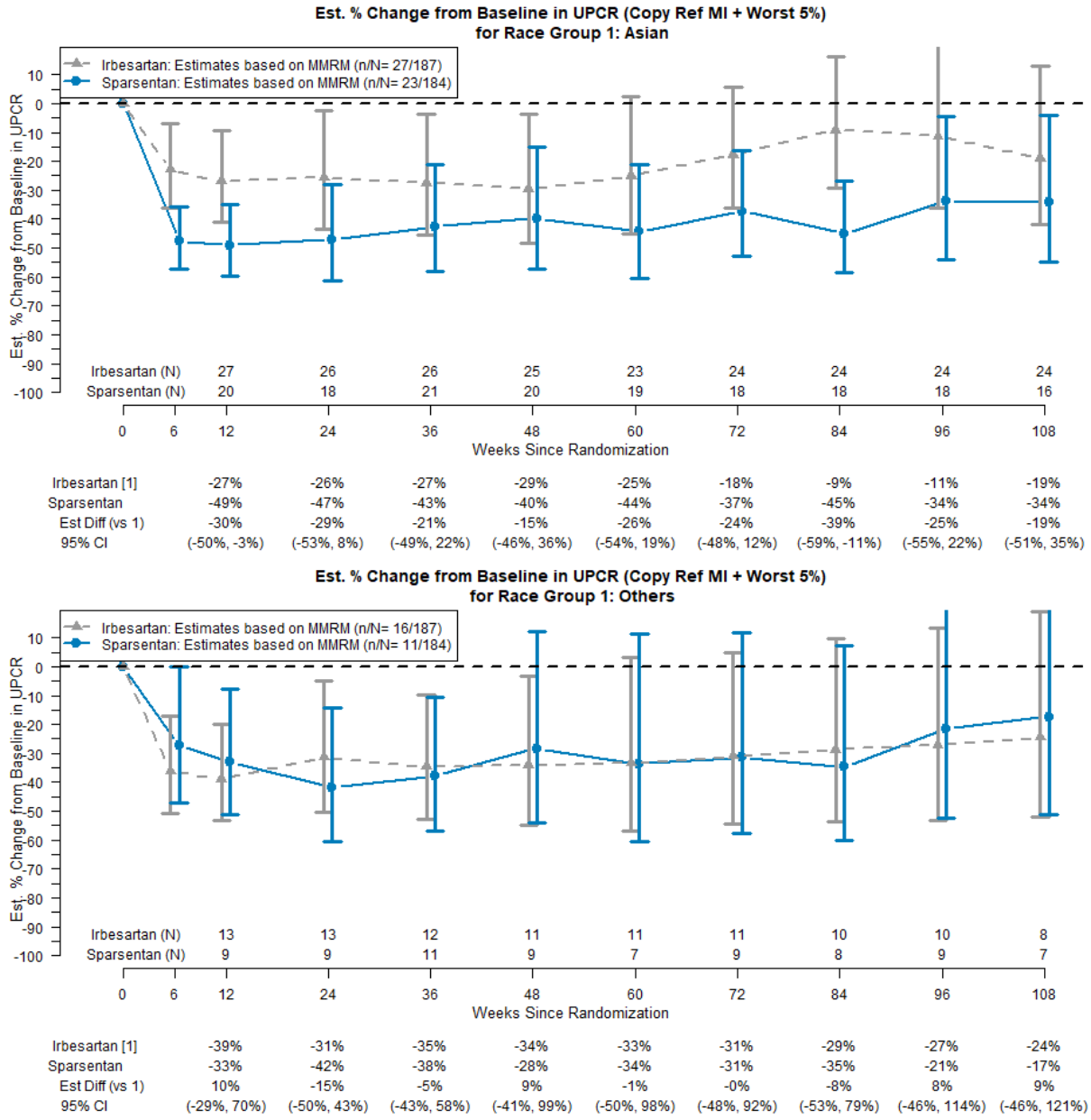
Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis, and any missing data (due to death or missing assessments) were imputed using the worst 5% of the observed data. Copy reference multiple imputation was used to impute missing off-treatment data while data missing while on treatment are imputed under missing at random according to the treatment arm.
Abbreviations: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

Figure 29. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Race (White, Black) Subgroup, FAS, DUPLEX



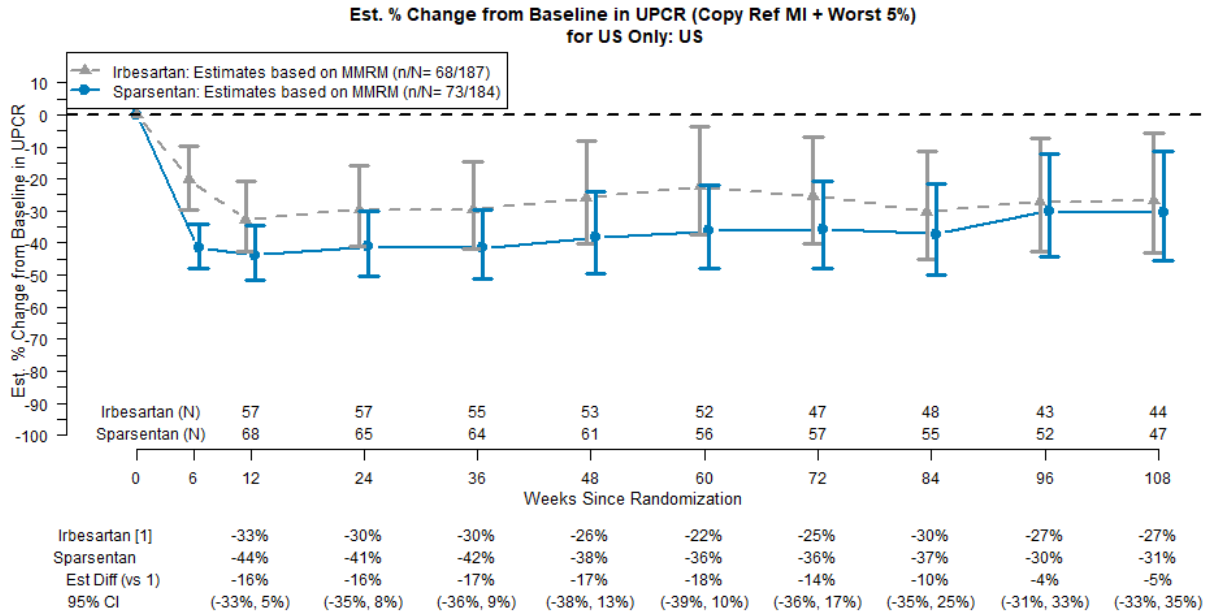
Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis, and any missing data (due to death or missing assessments) were imputed using the worst 5% of the observed data. Copy reference multiple imputation was used to impute missing off-treatment data while data missing while on treatment are imputed under missing at random according to the treatment arm.
Abbreviations: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

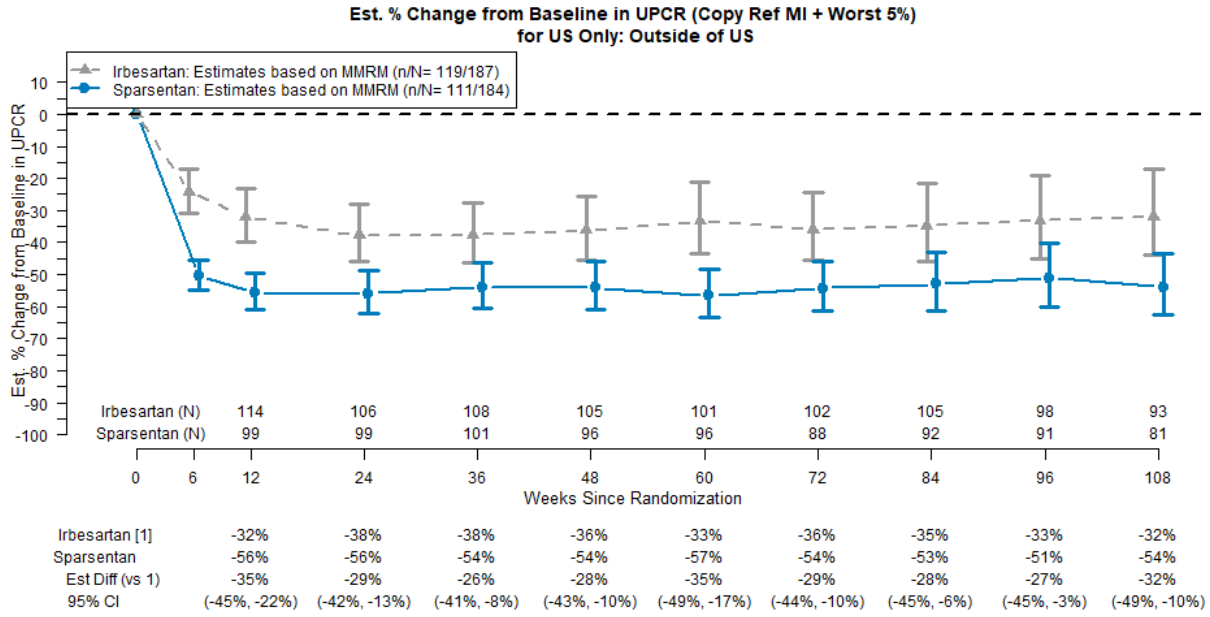
Figure 30. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Race (Asian, Others) Subgroup, FAS, DUPLEX



Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis, and any missing data (due to death or missing assessments) were imputed using the worst 5% of the observed data. Copy reference multiple imputation was used to impute missing off-treatment data while data missing while on treatment are imputed under missing at random according to the treatment arm.
Abbreviations: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

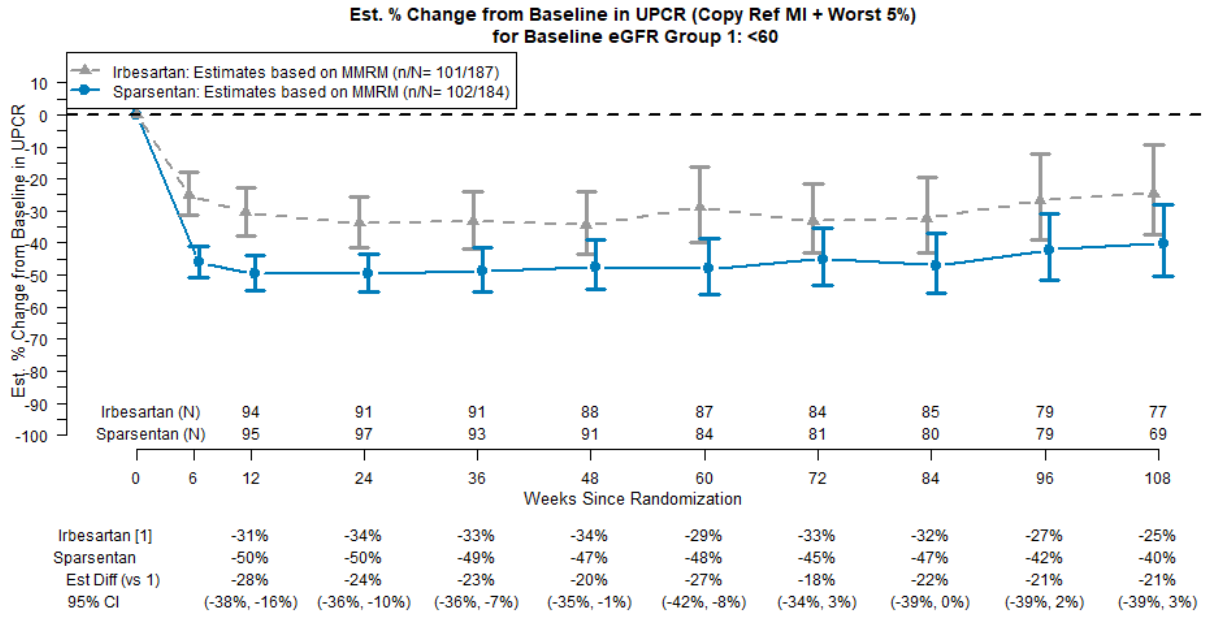
Figure 31. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for US vs Outside of US Subgroup, FAS, DUPLEX

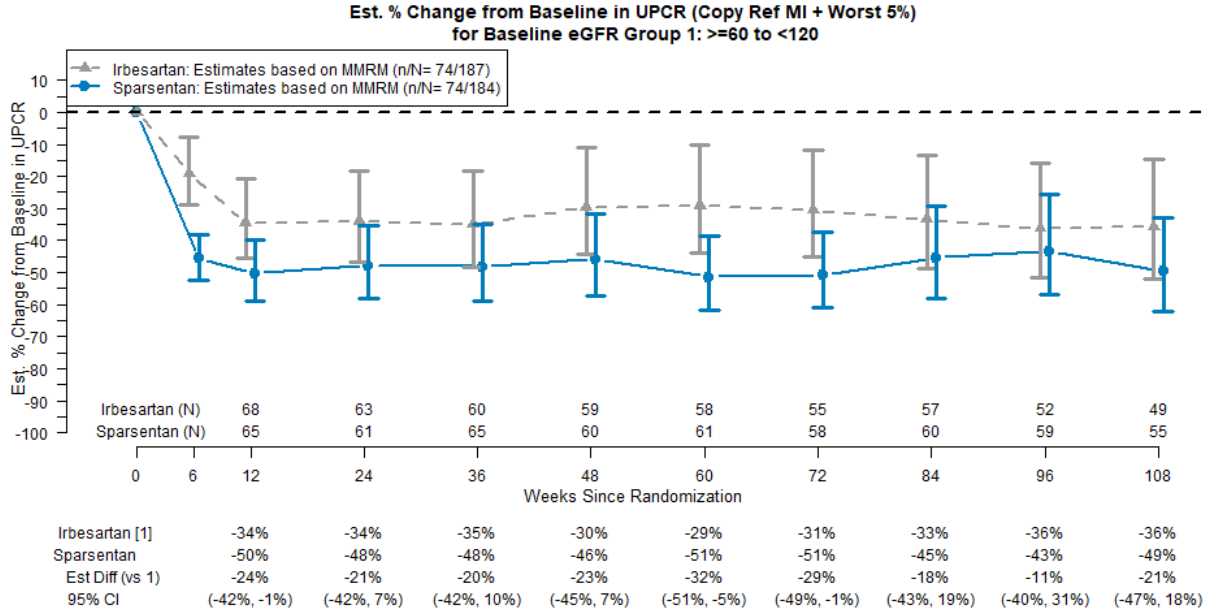




Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
Abbreviation: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

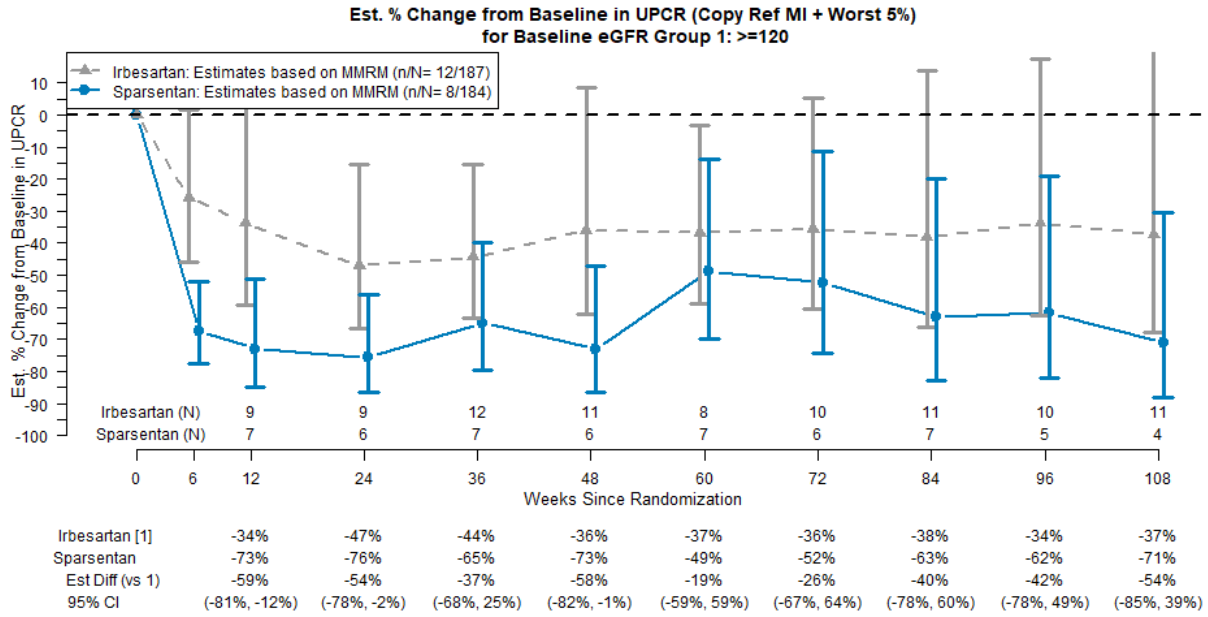
Figure 32. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Baseline eGFR (<60, 60 to <120 mL/min/1.73 m^2) Subgroup, FAS, DUPLEX





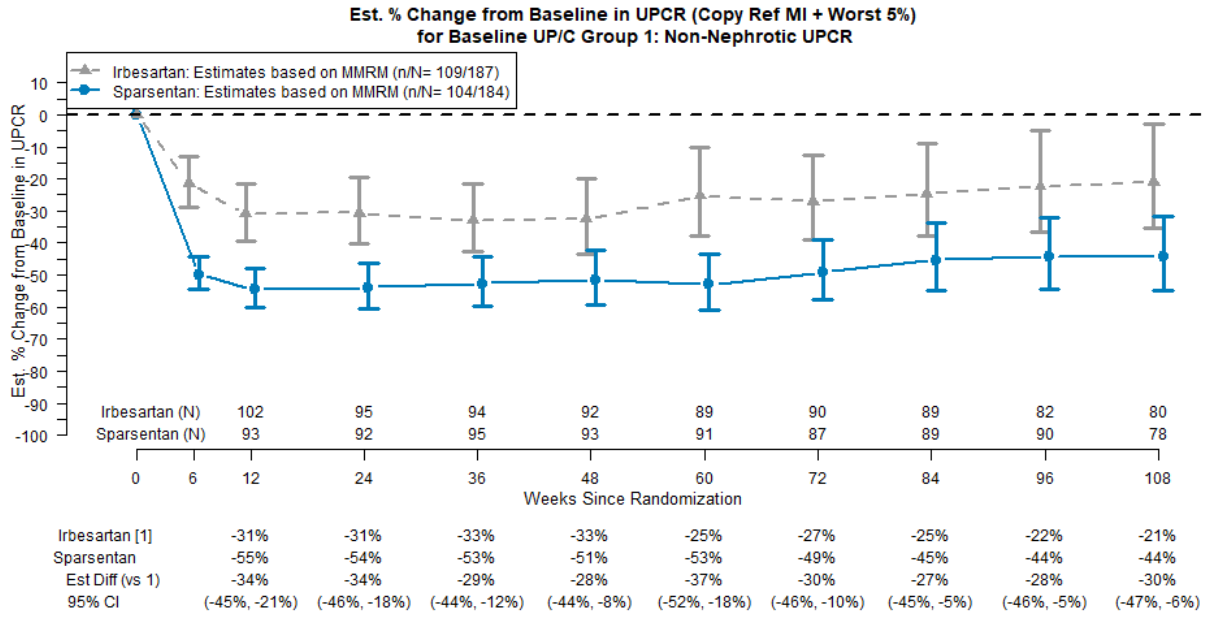
Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
The 95% CI are large given that there were few subjects in the eGFR subgroup ≥ 120 mL/min/1.73m^2.
Abbreviation: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated

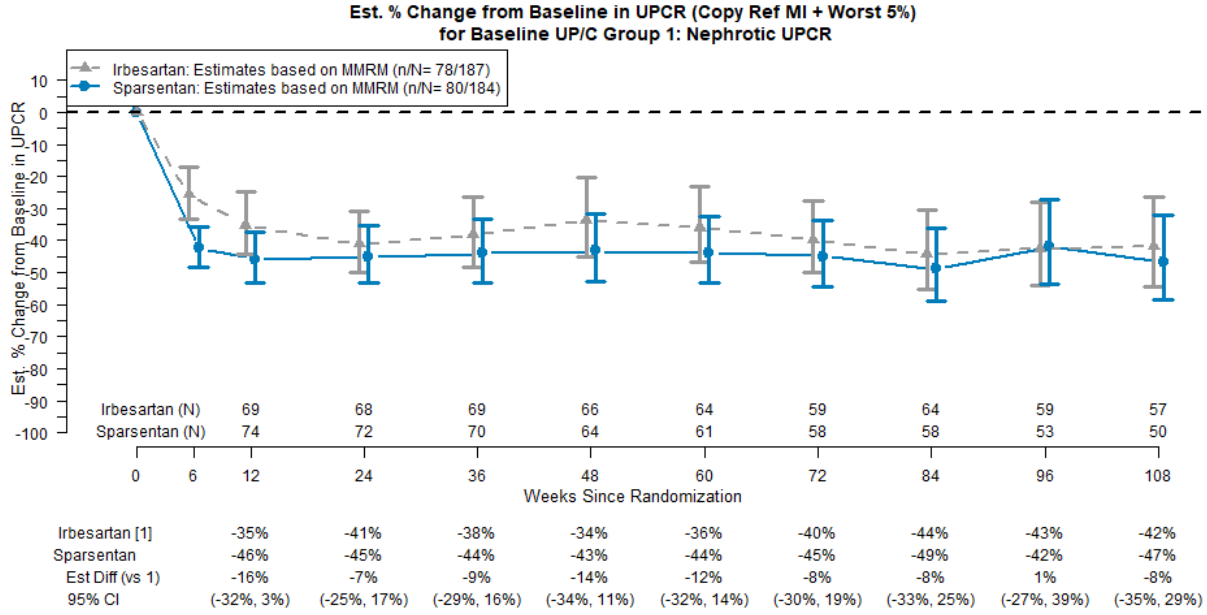
Figure 33. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Baseline eGFR ≥120 mL/min/1.73m2 Subgroup, FAS, DUPLEX



Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
The 95% CI are large given that there were few subjects in the eGFR subgroup ≥ 120 mL/min/1.73m^2.
Abbreviation: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

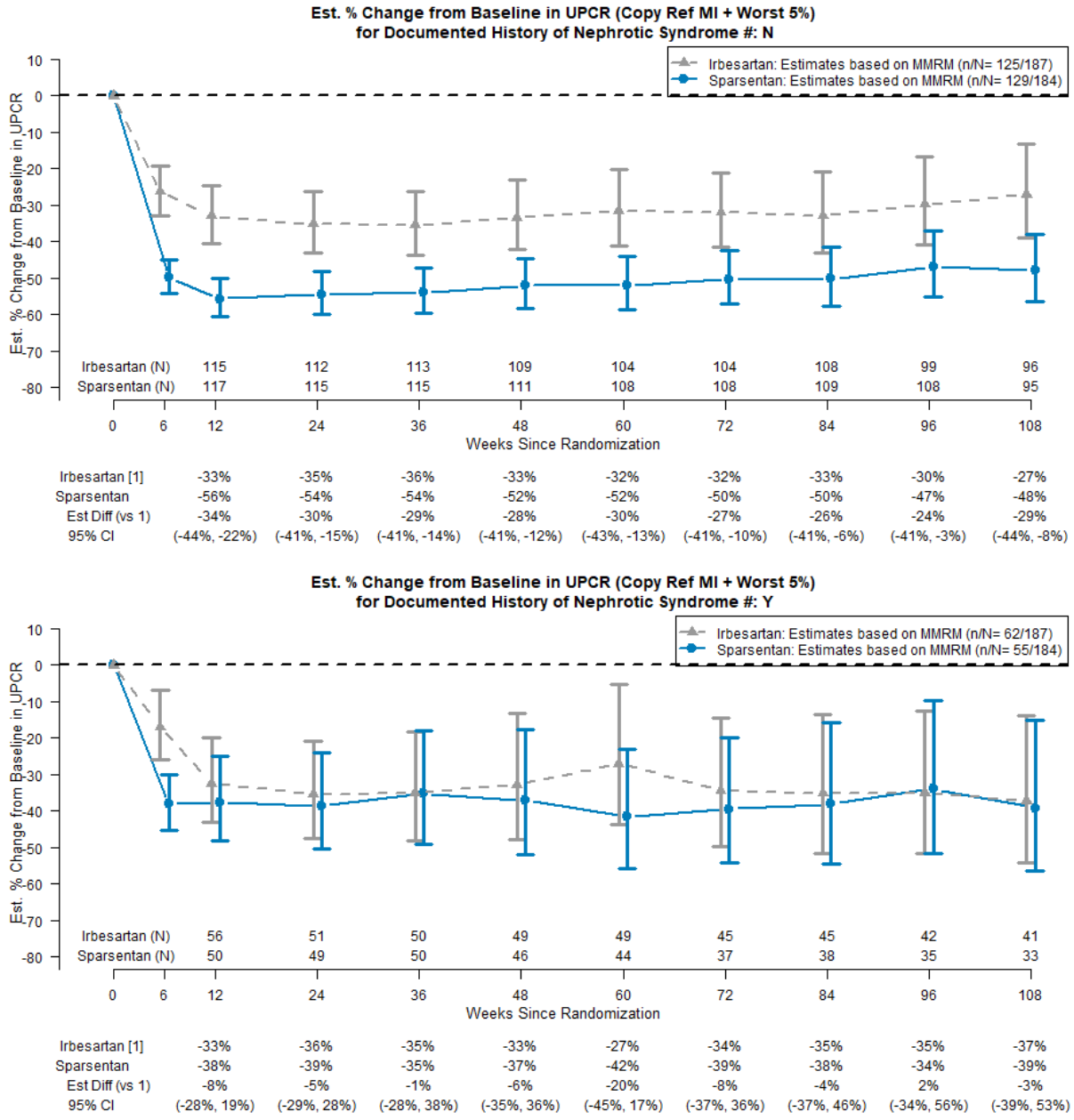
Figure 34. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Baseline UPCR Non-Nephrotic vs Nephrotic[1] Subgroup, FAS, DUPLEX





Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
[1] Non nephrotic is defined as UP/C ≤3.5 for subjects ≥18 years of age and ≤2 for subjects <18 years of age; Nephrotic is defined as UP/C >3.5 for subjects ≥18 years of age and >2 for subjects <18 years of age. Differs from documented history of nephrotic syndrome definition.
Abbreviation: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

Figure 35. Estimated Percentage Change in UPCR with Baseline (95% CI) At Each Visit Week for Documented History of Nephrotic Syndrome Subgroup, FAS, DUPLEX



Source: Statistical Review Team
The MMRM was fit to all change from baseline in log UPCR up to Week 108 adjusting for baseline log UPCR, treatment, visit week, stratification factors, interaction of treatment and visit week within each subgroup category. Data excluded after intercurrent events (ICE) of receipt of kidney transplantation, initiation of chronic dialysis were sampled from the worst 5% of the remaining observed data. Any remaining missing data were imputed using copy reference multiple imputation and missing at random assumption depending on whether they were on or off treatment by week 108.
Documented history of nephrotic syndrome is defined as follows: If the term “nephrotic syndrome” was present in medical history or if all of the following conditions were met at any of the visits prior to the first dose of randomized treatment: UP/C >3.5 g/g (adults) or UP/C >2 g/g (pediatrics), serum albumin <3.0 g/dL, and abnormal edema from physical examination
Abbreviation: UPCR, urine protein to creatinine ratio; ICE, intercurrent events; MMRM, mixed model repeated measures; Est, estimated; Diff; difference; CI, confidence interval; MI, multiple imputation; N, no; Y, yes; Est, estimated.

15.4. Additional Safety Analyses

Table 45. Subjects With Serious Adverse Events by System Organ Class, OND Custom Medical Query (Narrow), and Preferred Term, Safety Population, DUPLEX

System Organ Class OCMQ (Narrow) Preferred Term	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Respiratory, thoracic and mediastinal disorders (SOC)			
Bronchospasm (OCMQ)	2 (1.1)	0	1.1 (-0.4, 2.6)
Asthma	1 (0.5)	0	0.5 (-0.5, 1.6)
Bronchospasm	1 (0.5)	0	0.5 (-0.5, 1.6)
Dyspnea (OCMQ)	2 (1.1)	1 (0.5)	0.6 (-1.3, 2.4)
Dyspnoea	2 (1.1)	0	1.1 (-0.4, 2.6)
Respiratory distress	0	1 (0.5)	-0.5 (-1.6, 0.5)
Respiratory Failure (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Acute respiratory failure	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy (OCMQ)	3 (1.6)	1 (0.5)	1.1 (-1.0, 3.2)
Neuroendocrine carcinoma	1 (0.5)	0	0.5 (-0.5, 1.6)
Papillary renal cell carcinoma	1 (0.5)	0	0.5 (-0.5, 1.6)
Clear cell renal cell carcinoma	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Blood and lymphatic system disorders (SOC)			
Anemia (OCMQ)	2 (1.1)	0	1.1 (-0.4, 2.6)
Anaemia	2 (1.1)	0	1.1 (-0.4, 2.6)
Nervous system disorders (SOC)			
Seizure (OCMQ)	2 (1.1)	0	1.1 (-0.4, 2.6)
Generalised tonic-clonic seizure	1 (0.5)	0	0.5 (-0.5, 1.6)
Seizure	1 (0.5)	0	0.5 (-0.5, 1.6)
Syncope (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Syncope	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Stroke and TIA (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Amaurosis fugax	0	1 (0.5)	-0.5 (-1.6, 0.5)
Immune system disorders (SOC)			
Anaphylactic Reaction (OCMQ)	2 (1.1)	0	1.1 (-0.4, 2.6)
Anaphylactic reaction	1 (0.5)	0	0.5 (-0.5, 1.6)
Anaphylactic shock	1 (0.5)	0	0.5 (-0.5, 1.6)
Hypersensitivity (OCMQ)	2 (1.1)	1 (0.5)	0.6 (-1.3, 2.4)
Anaphylactic reaction	1 (0.5)	0	0.5 (-0.5, 1.6)
Anaphylactic shock	1 (0.5)	0	0.5 (-0.5, 1.6)
Drug hypersensitivity	0	1 (0.5)	-0.5 (-1.6, 0.5)
Psychiatric disorders (SOC)			
Self-Harm (OCMQ)	2 (1.1)	0	1.1 (-0.4, 2.6)
Completed suicide	1 (0.5)	0	0.5 (-0.5, 1.6)
Suicidal ideation	1 (0.5)	0	0.5 (-0.5, 1.6)
Anxiety (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Anxiety	0	1 (0.5)	-0.5 (-1.6, 0.5)
Eye disorders (SOC)			
Glaucoma (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)

System Organ Class OCMQ (Narrow) Preferred Term	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Open angle glaucoma	1 (0.5)	0	0.5 (-0.5, 1.6)
Reproductive system and breast disorders (SOC)			
Abnormal Uterine Bleeding (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Menorrhagia	1 (0.5)	0	0.5 (-0.5, 1.6)
Excessive Menstrual Bleeding (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Menorrhagia	1 (0.5)	0	0.5 (-0.5, 1.6)
Cardiac disorders (SOC)			
Arrhythmia (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Atrial fibrillation	1 (0.5)	0	0.5 (-0.5, 1.6)
Myocardial Ischemia (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Angina pectoris	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Systemic Hypertension (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Hypertension	1 (0.5)	0	0.5 (-0.5, 1.6)
Hypertensive emergency	0	1 (0.5)	-0.5 (-1.6, 0.5)
Heart Failure (OCMQ)	1 (0.5)	2 (1.1)	-0.5 (-2.3, 1.3)
Acute pulmonary oedema	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Pulmonary oedema	0	1 (0.5)	-0.5 (-1.6, 0.5)
Endocrine disorders (SOC)			
Hyperglycemia (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Diabetes mellitus	1 (0.5)	0	0.5 (-0.5, 1.6)
Hyperglycaemia	0	1 (0.5)	-0.5 (-1.6, 0.5)
Musculoskeletal and connective tissue disorders (SOC)			
Back Pain (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Back pain	1 (0.5)	0	0.5 (-0.5, 1.6)
Arthritis (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Osteoarthritis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Fracture (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Femur fracture	0	1 (0.5)	-0.5 (-1.6, 0.5)
Vascular disorders (SOC)			
Thrombosis (OCMQ)	2 (1.1)	2 (1.1)	0.0 (-2.1, 2.1)
Pulmonary embolism	2 (1.1)	2 (1.1)	0.0 (-2.1, 2.1)
Deep vein thrombosis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Thrombosis Venous (OCMQ)	2 (1.1)	2 (1.1)	0.0 (-2.1, 2.1)
Pulmonary embolism	2 (1.1)	2 (1.1)	0.0 (-2.1, 2.1)
Deep vein thrombosis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Hypotension (OCMQ)	1 (0.5)	2 (1.1)	-0.5 (-2.3, 1.3)
Hypotension	1 (0.5)	2 (1.1)	-0.5 (-2.3, 1.3)
Hemorrhage (OCMQ)	3 (1.6)	5 (2.7)	-1.0 (-4.0, 1.9)
Menorrhagia	1 (0.5)	0	0.5 (-0.5, 1.6)
Subdural haematoma	1 (0.5)	0	0.5 (-0.5, 1.6)
Epistaxis	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Haematoma	0	1 (0.5)	-0.5 (-1.6, 0.5)
Haematoma infection	0	1 (0.5)	-0.5 (-1.6, 0.5)
Haematuria	0	1 (0.5)	-0.5 (-1.6, 0.5)
Melaena	0	1 (0.5)	-0.5 (-1.6, 0.5)
Post procedural haemorrhage	0	1 (0.5)	-0.5 (-1.6, 0.5)
Renal haematoma	0	1 (0.5)	-0.5 (-1.6, 0.5)
Gastrointestinal disorders (SOC)			

System Organ Class OCMQ (Narrow) Preferred Term	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Abdominal Pain (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Abdominal pain	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Dyspepsia (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Dyspepsia	0	1 (0.5)	-0.5 (-1.6, 0.5)
Vomiting (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Vomiting	0	1 (0.5)	-0.5 (-1.6, 0.5)
Diarrhea (OCMQ)	0	2 (1.1)	-1.1 (-2.5, 0.4)
Diarrhoea	0	2 (1.1)	-1.1 (-2.5, 0.4)
Hepatobiliary disorders (SOC)			
Hepatic Injury (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Drug-induced liver injury	0	1 (0.5)	-0.5 (-1.6, 0.5)
Cholecystitis (OCMQ)	0	2 (1.1)	-1.1 (-2.5, 0.4)
Cholecystitis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Cholecystitis acute	0	1 (0.5)	-0.5 (-1.6, 0.5)
Renal and urinary disorders (SOC)			
Renal & Urinary Tract Infection (OCMQ)	2 (1.1)	4 (2.1)	-1.1 (-3.6, 1.5)
Escherichia urinary tract infection	1 (0.5)	0	0.5 (-0.5, 1.6)
Pyelonephritis	1 (0.5)	0	0.5 (-0.5, 1.6)
Urosepsis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Urinary tract infection	1 (0.5)	3 (1.6)	-1.1 (-3.2, 1.0)
Acute Kidney Injury (OCMQ)	5 (2.7)	8 (4.3)	-1.6 (-5.3, 2.2)
Tubulointerstitial nephritis	2 (1.1)	0	1.1 (-0.4, 2.6)
Acute kidney injury	3 (1.6)	8 (4.3)	-2.6 (-6.1, 0.8)
General disorders and administration site conditions (SOC)			
Pyrexia (OCMQ)	2 (1.1)	0	1.1 (-0.4, 2.6)
Pyrexia	2 (1.1)	0	1.1 (-0.4, 2.6)
Dizziness (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Dizziness	0	1 (0.5)	-0.5 (-1.6, 0.5)
Volume Depletion (OCMQ)	0	2 (1.1)	-1.1 (-2.5, 0.4)
Dehydration	0	1 (0.5)	-0.5 (-1.6, 0.5)
Hypovolaemia	0	1 (0.5)	-0.5 (-1.6, 0.5)
Peripheral Edema (OCMQ)	0	6 (3.2)	-3.2 (-5.7, -0.7)
Peripheral swelling	0	2 (1.1)	-1.1 (-2.5, 0.4)
Oedema peripheral	0	5 (2.7)	-2.7 (-5.0, -0.4)
Infections and infestations (SOC)			
Pneumonia (OCMQ)	4 (2.2)	2 (1.1)	1.1 (-1.5, 3.7)
Pneumonia	3 (1.6)	2 (1.1)	0.6 (-1.8, 2.9)
Pneumonia bacterial	1 (0.5)	0	0.5 (-0.5, 1.6)
Nasopharyngitis (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Upper respiratory tract infection	1 (0.5)	0	0.5 (-0.5, 1.6)
Bacterial Infection (OCMQ)	8 (4.3)	9 (4.8)	-0.5 (-4.7, 3.8)
Appendicitis	2 (1.1)	1 (0.5)	0.6 (-1.3, 2.4)
Cellulitis	1 (0.5)	0	0.5 (-0.5, 1.6)
Escherichia sepsis	1 (0.5)	0	0.5 (-0.5, 1.6)

System Organ Class OCMQ (Narrow) Preferred Term	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Escherichia urinary tract infection	1 (0.5)	0	0.5 (-0.5, 1.6)
Mycoplasma infection	1 (0.5)	0	0.5 (-0.5, 1.6)
Pneumonia bacterial	1 (0.5)	0	0.5 (-0.5, 1.6)
Pyelonephritis	1 (0.5)	0	0.5 (-0.5, 1.6)
Streptococcal bacteraemia	1 (0.5)	0	0.5 (-0.5, 1.6)
Bacteraemia	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Cholecystitis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Cholecystitis acute	0	1 (0.5)	-0.5 (-1.6, 0.5)
Device related infection	0	1 (0.5)	-0.5 (-1.6, 0.5)
Urosepsis	0	1 (0.5)	-0.5 (-1.6, 0.5)
Urinary tract infection	1 (0.5)	3 (1.6)	-1.1 (-3.2, 1.0)
Viral Infection (OCMQ)	24 (13.0)	44 (23.5)	-10.5 (-18.3, -2.7)
COVID-19 pneumonia	2 (1.1)	2 (1.1)	0.0 (-2.1, 2.1)
Rhinovirus infection	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Enterovirus infection	0	1 (0.5)	-0.5 (-1.6, 0.5)
Gastroenteritis norovirus	0	1 (0.5)	-0.5 (-1.6, 0.5)
Metapneumovirus infection	0	1 (0.5)	-0.5 (-1.6, 0.5)
Respiratory syncytial virus infection	0	1 (0.5)	-0.5 (-1.6, 0.5)
Viral infection	0	1 (0.5)	-0.5 (-1.6, 0.5)
COVID-19	22 (12.0)	39 (20.9)	-8.9 (-16.4, -1.4)

Source: adae.xpt; Software: R
Serious adverse events defined as any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Abbreviations: CI, confidence interval; OCMQ, OND custom medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Table 46. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, OND Custom Medical Query (Narrow), and Preferred Term, Safety Population, DUPLEX

System Organ Class OCMQ (Narrow) Preferred Term	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Vascular disorders (SOC)			
Hypotension (OCMQ)	4 (2.2)	0	2.2 (0.1, 4.3)
Hypotension	4 (2.2)	0	2.2 (0.1, 4.3)
Hemorrhage (OCMQ)	2 (1.1)	0	1.1 (-0.4, 2.6)
Contusion	1 (0.5)	0	0.5 (-0.5, 1.6)
Subdural haematoma	1 (0.5)	0	0.5 (-0.5, 1.6)
Thrombosis (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Pulmonary embolism	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Thrombosis Venous (OCMQ)	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Pulmonary embolism	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
General disorders and administration site conditions (SOC)			
Peripheral Edema (OCMQ)	3 (1.6)	1 (0.5)	1.1 (-1.0, 3.2)
Oedema peripheral	3 (1.6)	1 (0.5)	1.1 (-1.0, 3.2)
Dizziness (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Dizziness	1 (0.5)	0	0.5 (-0.5, 1.6)
Infections and infestations (SOC)			
Bacterial Infection (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Cellulitis	1 (0.5)	0	0.5 (-0.5, 1.6)
Pneumonia (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Pneumonia	1 (0.5)	0	0.5 (-0.5, 1.6)
Viral Infection (OCMQ)	1 (0.5)	2 (1.1)	-0.5 (-2.3, 1.3)
COVID-19	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Influenza	0	1 (0.5)	-0.5 (-1.6, 0.5)
Hepatobiliary disorders (SOC)			
Hepatic Injury (OCMQ)	2 (1.1)	1 (0.5)	0.6 (-1.3, 2.4)
Aspartate aminotransferase increased	2 (1.1)	0	1.1 (-0.4, 2.6)
Alanine aminotransferase increased	1 (0.5)	1 (0.5)	0.0 (-1.5, 1.5)
Gastrointestinal disorders (SOC)			
Vomiting (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Vomiting	1 (0.5)	0	0.5 (-0.5, 1.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Neuroendocrine carcinoma	1 (0.5)	0	0.5 (-0.5, 1.6)
Respiratory, thoracic and mediastinal disorders (SOC)			
Dyspnea (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Dyspnoea	1 (0.5)	0	0.5 (-0.5, 1.6)
Skin and subcutaneous tissue disorders (SOC)			
Rash (OCMQ)	1 (0.5)	0	0.5 (-0.5, 1.6)
Rash	1 (0.5)	0	0.5 (-0.5, 1.6)
Cardiac disorders (SOC)			
Heart Failure (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)

System Organ Class OCMQ (Narrow) Preferred Term	Sparsentan N=184 n (%)	Irbesartan N=187 n (%)	Risk Difference % (95% CI)
Pulmonary oedema	0	1 (0.5)	-0.5 (-1.6, 0.5)
Reproductive system and breast disorders (SOC)			
Sexual Dysfunction (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Libido decreased	0	1 (0.5)	-0.5 (-1.6, 0.5)
Renal and urinary disorders (SOC)			
Acute Kidney Injury (OCMQ)	1 (0.5)	2 (1.1)	-0.5 (-2.3, 1.3)
Tubulointerstitial nephritis	1 (0.5)	0	0.5 (-0.5, 1.6)
Acute kidney injury	0	2 (1.1)	-1.1 (-2.5, 0.4)
Urinary Retention (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Urinary hesitation	0	1 (0.5)	-0.5 (-1.6, 0.5)
Nervous system disorders (SOC)			
Confusional State (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Confusional state	0	1 (0.5)	-0.5 (-1.6, 0.5)
Headache (OCMQ)	0	1 (0.5)	-0.5 (-1.6, 0.5)
Migraine	0	1 (0.5)	-0.5 (-1.6, 0.5)

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Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OND custom medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class.

Table 47. Treatment-Emergent Adverse Events in ≥1 Subject in Sparsentan Group, Pediatric Population, DUPLEX Double-Blind Period

Preferred Term	Sparsentan N=16 n (%)	Irbesartan N=19 n (%)
Any AE	15 (93.8)	19 (100)
COVID-19	6 (37.5)	5 (26.3)
Dizziness	5 (31.2)	3 (15.8)
Blood creatinine increased	4 (25.0)	0
Pyrexia	4 (25.0)	1 (5.3)
Anaemia	4 (25.0)	3 (15.8)
Diarrhoea	4 (25.0)	3 (15.8)
Nasal congestion	3 (18.8)	0
Blood creatine phosphokinase increased	3 (18.8)	1 (5.3)
Cough	3 (18.8)	1 (5.3)
Depression	3 (18.8)	1 (5.3)
Glomerular filtration rate decreased	3 (18.8)	1 (5.3)
Hypotension	3 (18.8)	1 (5.3)
Oedema peripheral	3 (18.8)	1 (5.3)
Upper respiratory tract infection	3 (18.8)	2 (10.5)
Alanine aminotransferase increased	2 (12.5)	0
Blood potassium increased	2 (12.5)	0
Hypertension	2 (12.5)	0
Hypothyroidism	2 (12.5)	0
Metabolic acidosis	2 (12.5)	0
Pain in extremity	2 (12.5)	0
Back pain	2 (12.5)	1 (5.3)
Weight decreased	2 (12.5)	1 (5.3)
Abdominal distension	1 (6.2)	0
Abdominal pain lower	1 (6.2)	0
Allergy to animal	1 (6.2)	0
Aspartate aminotransferase increased	1 (6.2)	0
Blood chloride decreased	1 (6.2)	0
Blood cholesterol increased	1 (6.2)	0
Blood phosphorus increased	1 (6.2)	0
Blood sodium decreased	1 (6.2)	0
Blood triglycerides increased	1 (6.2)	0
Blood uric acid increased	1 (6.2)	0
Bronchitis	1 (6.2)	0
Bronchospasm	1 (6.2)	0
Chills	1 (6.2)	0
Clostridium test positive	1 (6.2)	0
Colitis	1 (6.2)	0
Cystatin C increased	1 (6.2)	0

Preferred Term	Sparsentan N=16 n (%)	Irbesartan N=19 n (%)
Decreased appetite	1 (6.2)	0
Fibrin D dimer increased	1 (6.2)	0
Gamma-glutamyltransferase increased	1 (6.2)	0
Hip fracture	1 (6.2)	0
Hypercholesterolaemia	1 (6.2)	0
Hyperlipidaemia	1 (6.2)	0
Hyperphosphataemia	1 (6.2)	0
Hyperuricaemia	1 (6.2)	0
Hypoaesthesia	1 (6.2)	0
Inflammation	1 (6.2)	0
Inflammatory marker increased	1 (6.2)	0
Intentional self-injury	1 (6.2)	0
Intraocular pressure increased	1 (6.2)	0
Lacrimation increased	1 (6.2)	0
Leukopenia	1 (6.2)	0
Lip exfoliation	1 (6.2)	0
Low density lipoprotein increased	1 (6.2)	0
Menorrhagia	1 (6.2)	0
Mycoplasma infection	1 (6.2)	0
Nephrotic syndrome	1 (6.2)	0
Night sweats	1 (6.2)	0
Nocturia	1 (6.2)	0
Non-cardiac chest pain	1 (6.2)	0
Orthostatic hypotension	1 (6.2)	0
Otitis media	1 (6.2)	0
Pneumonia	1 (6.2)	0
Pubic pain	1 (6.2)	0
Rash	1 (6.2)	0
Rhinorrhoea	1 (6.2)	0
Sinusitis	1 (6.2)	0
Skin laceration	1 (6.2)	0
Skin papilloma	1 (6.2)	0
Suicidal ideation	1 (6.2)	0
Swelling	1 (6.2)	0
Swelling face	1 (6.2)	0
Syncope	1 (6.2)	0
Tonsillitis streptococcal	1 (6.2)	0
Tooth fracture	1 (6.2)	0
Toothache	1 (6.2)	0
Troponin increased	1 (6.2)	0

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