# Patients With Focal Segmental Glomerulosclerosis (FSGS) Achieved Low Proteinuria Targets Earlier and More Often With Sparsentan (SPAR) vs Irbesartan (IRB) in DUPLEX

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- FSGS is associated with a substantial risk of kidney failure, with 40% to 60% of patients progressing to kidney failure or death within 10 to 20 years of diagnosis[1,2]
- There are no approved pharmacologic therapies for FSGS, highlighting an unmet need for safe and effective treatments[3]
- In large-scale analyses of observational data, proteinuria was identified as a biologically plausible and clinically meaningful endpoint, with lower proteinuria strongly associated with reduced kidney failure risk in patients with FSGS[4]
- SPAR is a non-immunosuppressive dual endothelin angiotensin receptor antagonist (DEARA)[5,6] that led to rapid and sustained proteinuria reductions in patients with FSGS in the phase 3 DUPLEX trial[7]

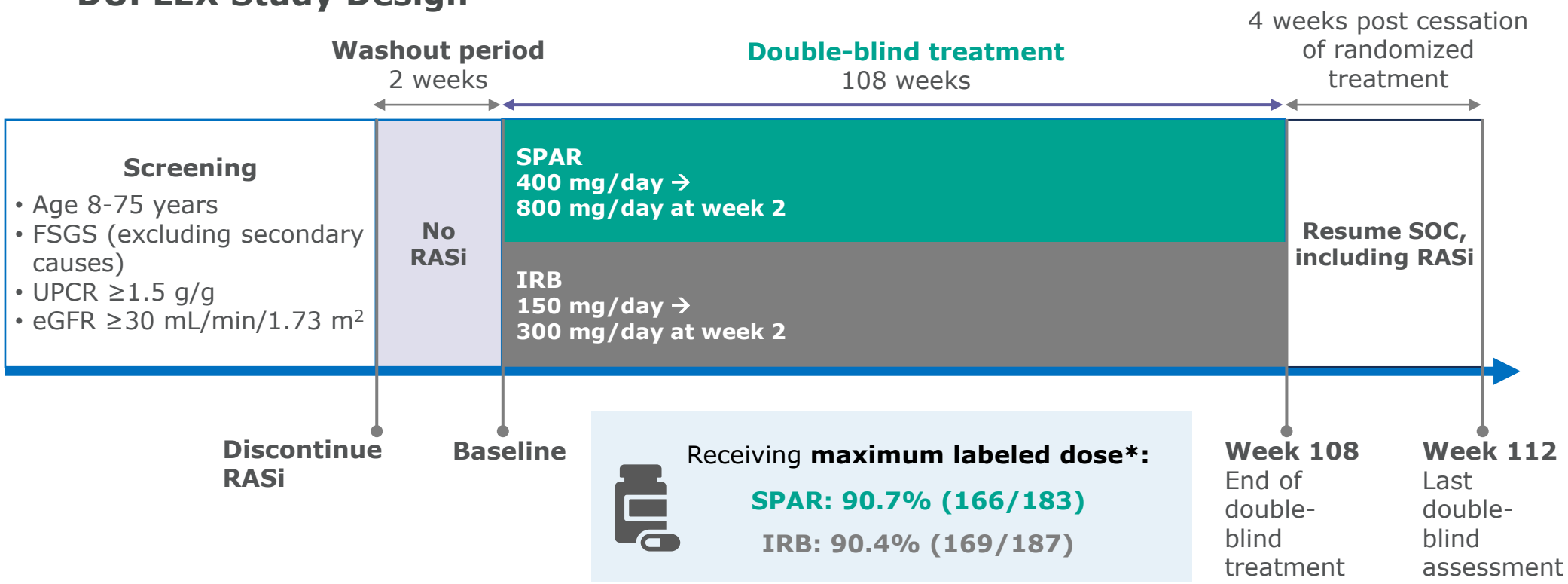
## Objective

- Expanding on earlier findings from this study, we investigated the comparative effects of SPAR vs IRB on low proteinuria targets and the effect of achieving complete remission (CR) of proteinuria or the FSGS partial remission endpoint and on progression to kidney failure in DUPLEX

CR, complete remission; DEARA, dual endothelin angiotensin receptor antagonist; FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; SPAR, sparsentan.

- DUPLEX (NCT03493685) is a phase 3, randomized, double-blind trial investigating the safety and efficacy of SPAR vs active control, maximum labeled dose IRB, in adult and pediatric patients (aged ≥8 years) with FSGS

## DUPLEX Study Design




eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; RASi, renin-angiotensin system inhibitor; SOC, standard of care; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
*Proportion of patients receiving the maximum target dose per treatment arm.

METHODS

- Study endpoints were defined as follows:
  1. CR of proteinuria: UPCR of <0.3 g/g
  2. FSGS partial remission endpoint: urine protein-to-creatinine ratio (UPCR) of ≤1.5 g/g and a >40% reduction from baseline[8]
  3. Kidney failure: eGFR of <15 mL/min/1.73 $m^2$ or kidney replacement therapy
- Analyses investigated the impact of SPAR vs IRB on the proportion of patients achieving CR of proteinuria, UPCR of <0.5 g/g, <1.0 g/g, or <1.5 g/g, and the FSGS partial remission endpoint at any time during the 108-week double-blind treatment period
- Post hoc analyses using pooled data from both treatment groups evaluated rates of progression to kidney failure among patients who achieved CR of proteinuria or the FSGS partial remission endpoint vs those who did not

CR, complete remission; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

RESULTS

# Patient Demographics and Baseline Characteristics

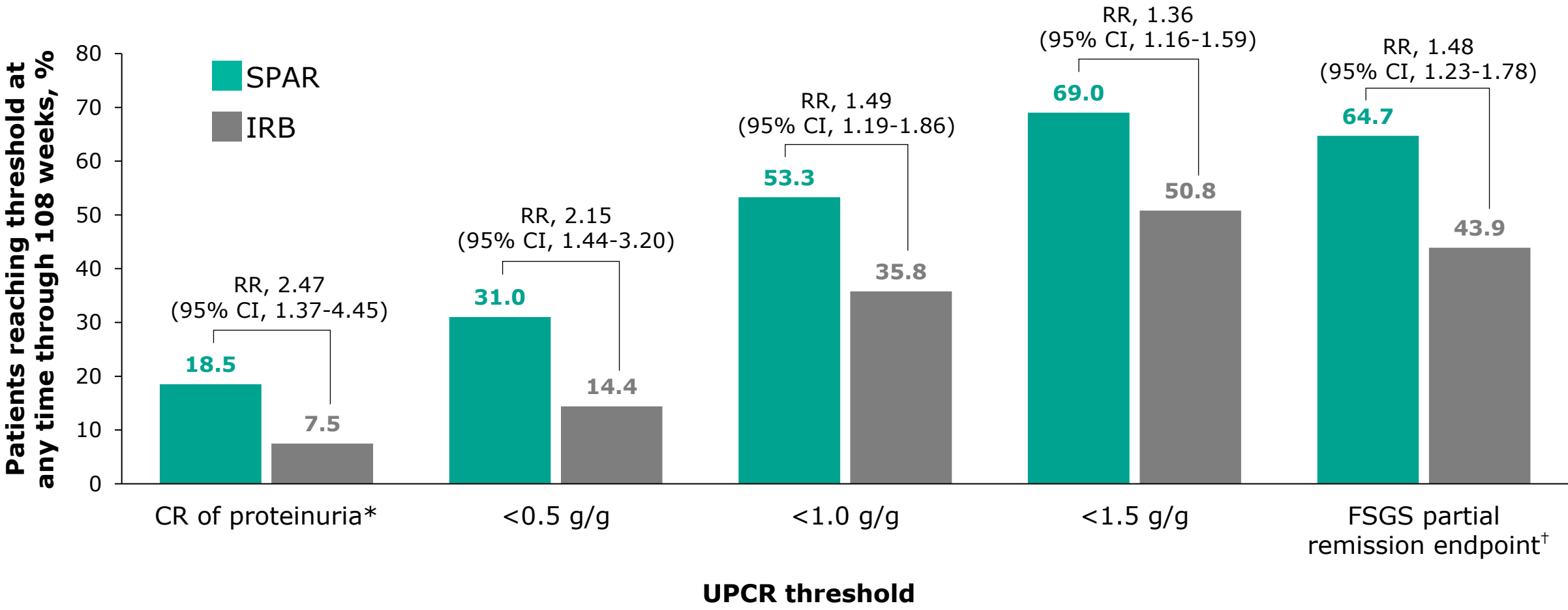
- A total of 371 patients were randomized to receive SPAR or IRB in DUPLEX

| | SPAR n=184 | IRB n=187 | All patients N=371 |
|---|---|---|---|
| **Age, mean (SD), years** | 41.7 (16.5) | 41.5 (17.3) | 41.6 (16.9) |
| <18 years, n (%) | 16 (8.7) | 19 (10.2) | 35 (9.4) |
| **Male sex, n (%)** | 101 (55) | 99 (53) | 200 (54) |
| **eGFR, mean (SD), mL/min/1.73 m²** | 63.3 (28.6) | 64.1 (31.7) | 63.7 (30.1) |
| **UPCR, g/g*** | | | |
| Median (IQR) | 3.1 (2.3-4.5) | 3.0 (2.1-4.7) | 3.0 (2.2-4.6) |
| **Blood pressure, mean (SD) systolic/diastolic, mm Hg** | 133.1 (14.8)/85.5 (10.6) | 130.9 (14.6)/82.4 (10.1) | – |
| **FSGS-associated genetic variants, n (%)** | | | |
| Variants in podocyte structure/function proteins | 13 (7) | 18 (10) | 31 (8) |
| *COL4A3-5* variants | 11 (6) | 14 (7) | 25 (7) |
| High-risk *APOL1* variants | 9 (5) | 5 (3) | 14 (4) |
| **Prior RASi use (stopped before washout), n (%)** | 152 (83) | 143 (76) | 295 (80) |
| **Baseline use of immunosuppressive agents, n (%)** | 50 (27) | 46 (25) | 96 (26) |
| **Baseline use of diuretics, n (%)** | 68 (37) | 73 (39) | 141 (38) |

*APOL1*, apolipoprotein L1; *COL4A3-5*, collagen type IV alpha 3-5 chain; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; RASi, renin-angiotensin system inhibitor; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
*UPCR was calculated as the geometric mean of 2-3 first morning void samples collected within 5 days before each visit.

RESULTS

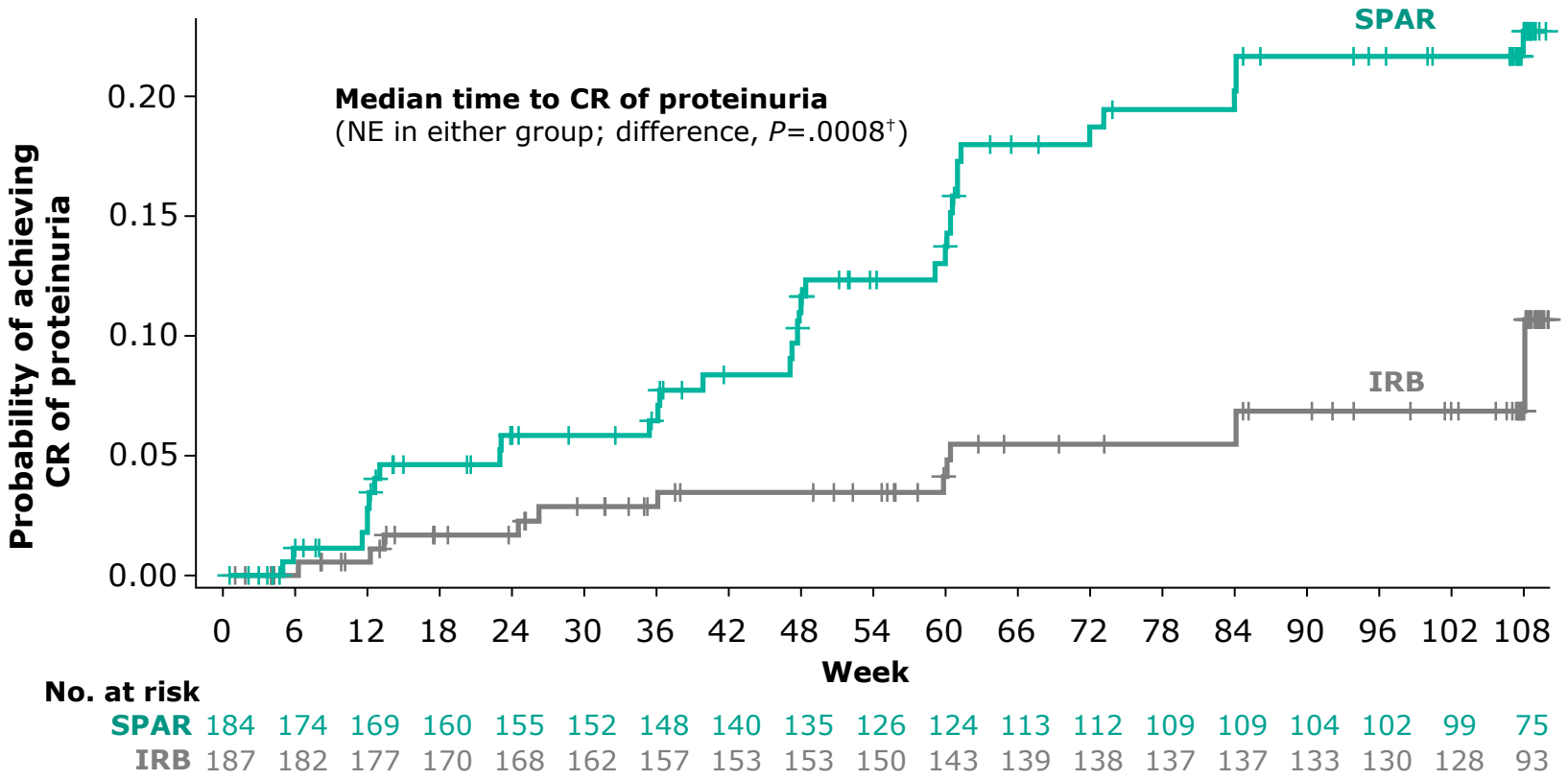
# SPAR Demonstrated Superior and Consistent Proteinuria Reduction Across Thresholds vs Maximum Labeled Dose IRB

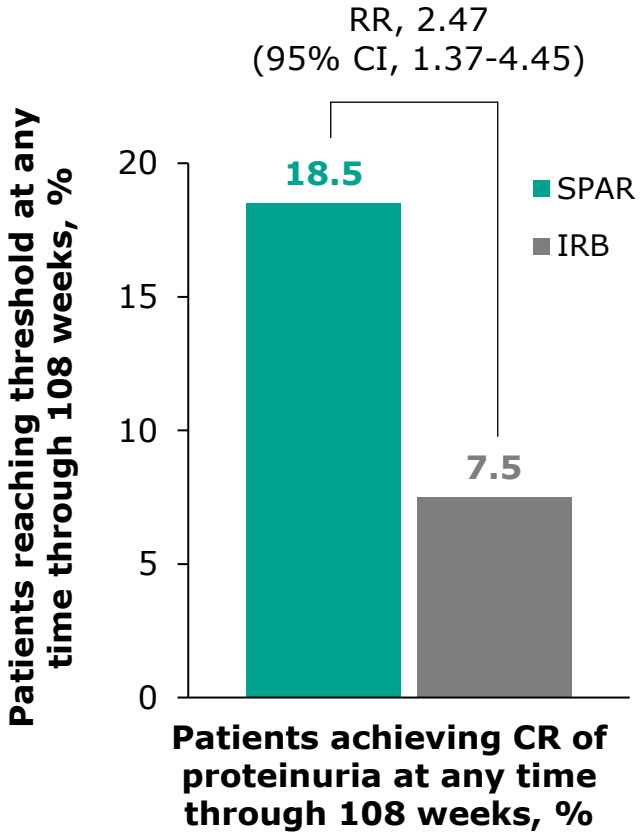



CR, complete remission; FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; RR, relative risk; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
*CR of proteinuria was defined as UPCR of <0.3 g/g. †The FSGS partial remission endpoint was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline.

RESULTS

# Patients Achieved CR of Proteinuria* Earlier and More Often With SPAR vs Maximum Labeled Dose IRB

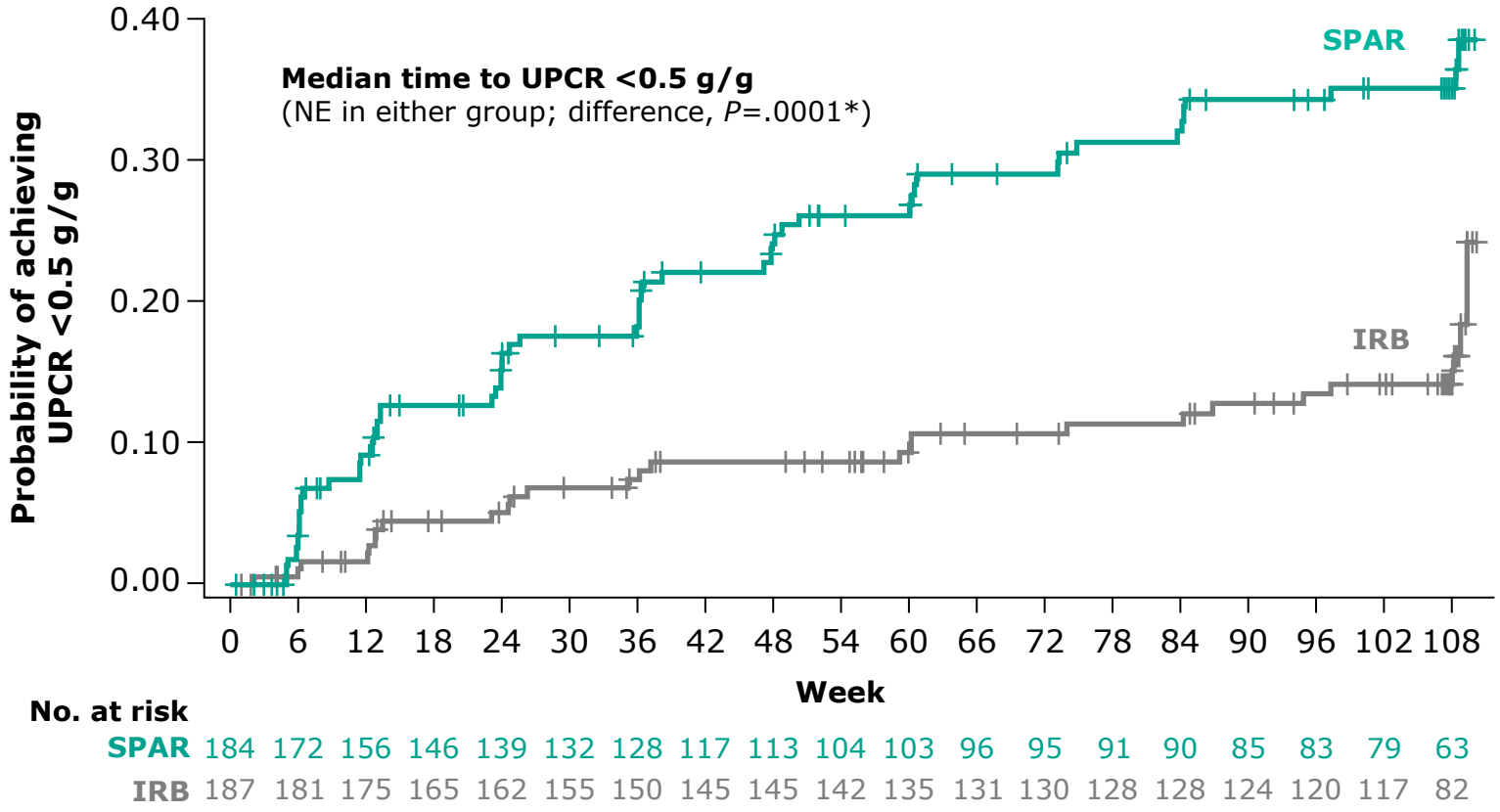


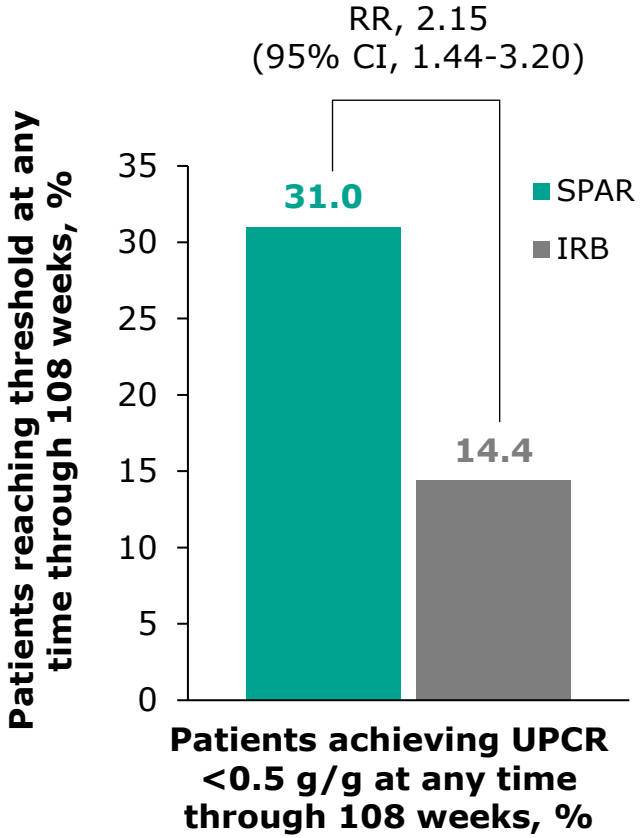




CR, complete remission; IRB, irbesartan; NE, not estimable; RR, relative risk; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
*CR of proteinuria was defined as UPCR of <0.3 g/g.
†*P* value generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

RESULTS

# Patients Achieved UPCR of <0.5 g/g Earlier and More Often With SPAR vs Maximum Labeled Dose IRB

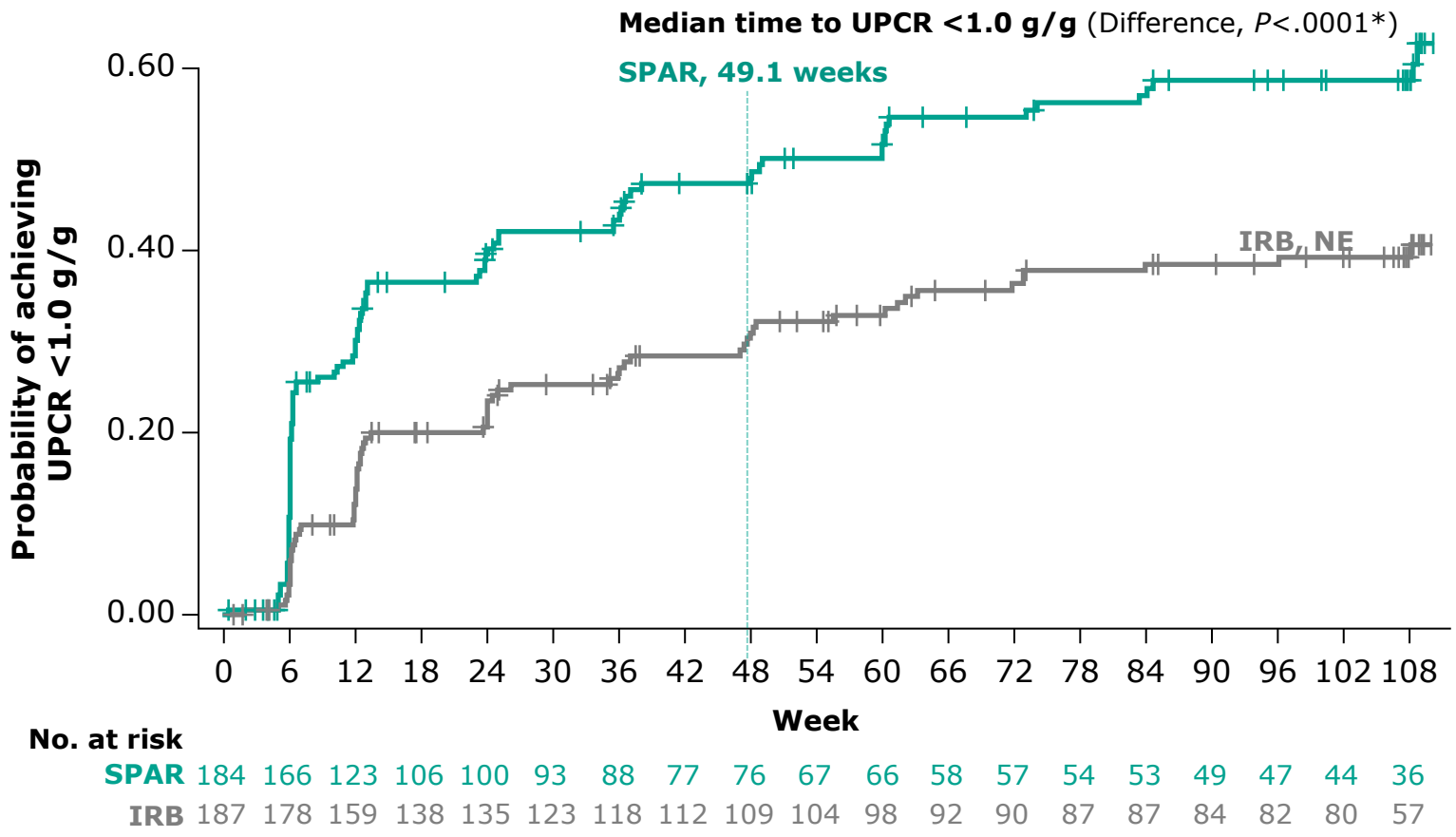


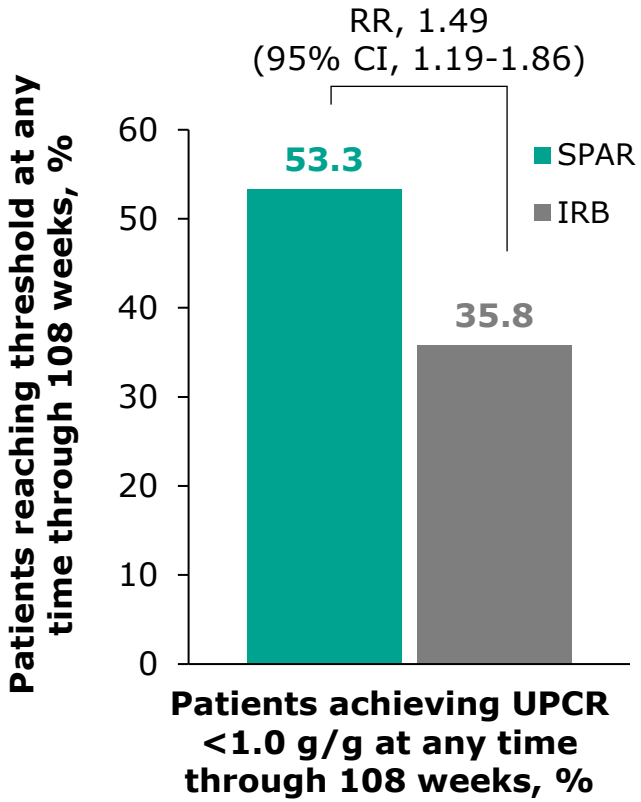




FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; NE, not estimable; RR, relative risk; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
**P* value generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

RESULTS

# Patients Achieved UPCR of <1.0 g/g Earlier and More Often With SPAR vs Maximum Labeled Dose IRB

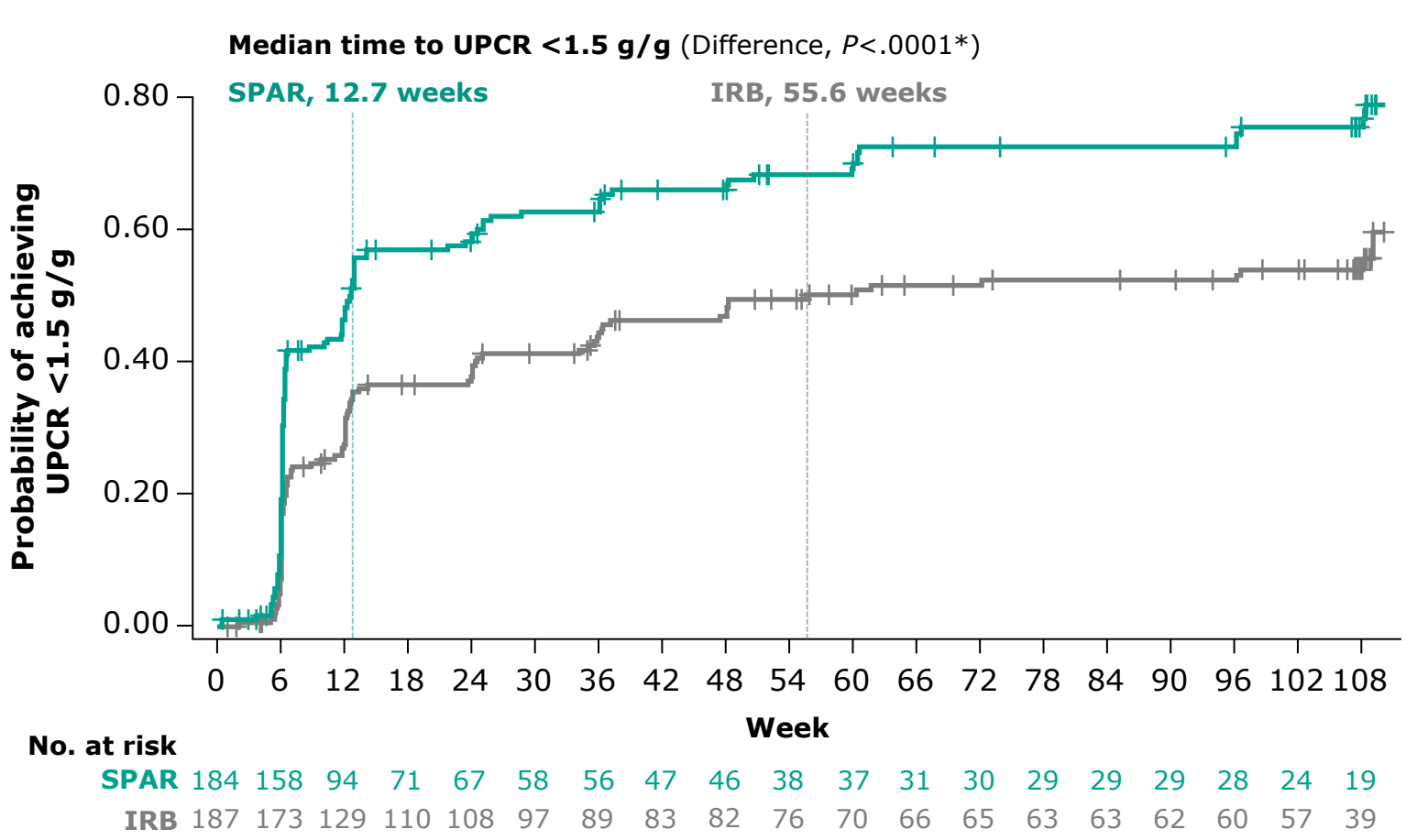


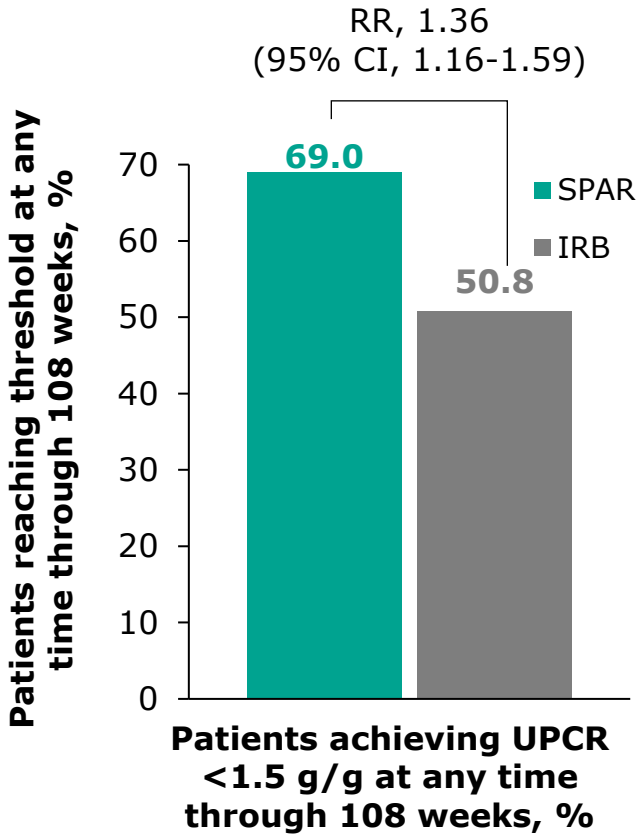




FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; NE, not estimable; RR, relative risk; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
**P* value generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

RESULTS

# Patients Achieved UPCR of <1.5 g/g Earlier and More Often With SPAR vs Maximum Labeled Dose IRB

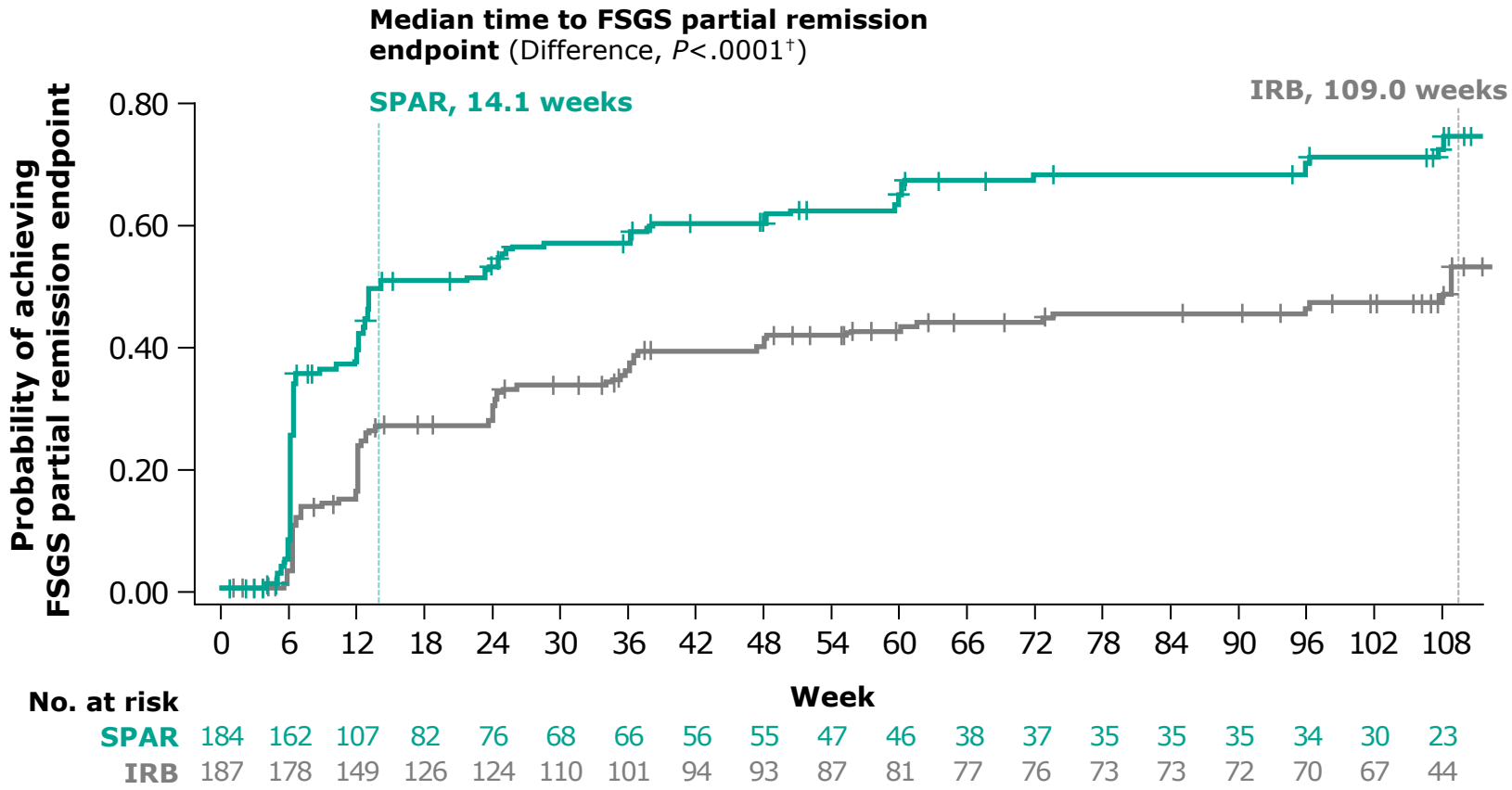


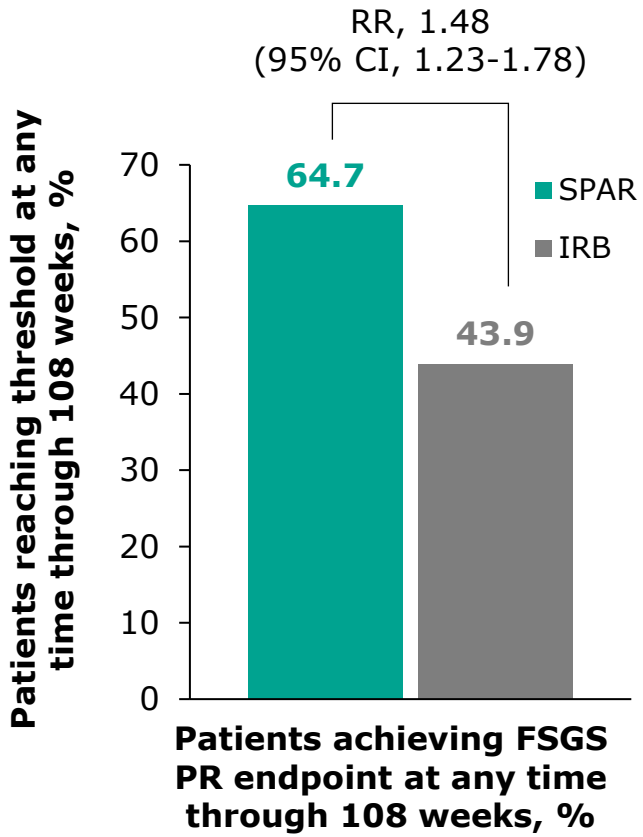




FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; NE, not estimable; RR, relative risk; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
**P* value generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

RESULTS

# Patients Achieved the FSGS Partial Remission Endpoint* Earlier and More Often With SPAR vs Maximum Labeled Dose IRB

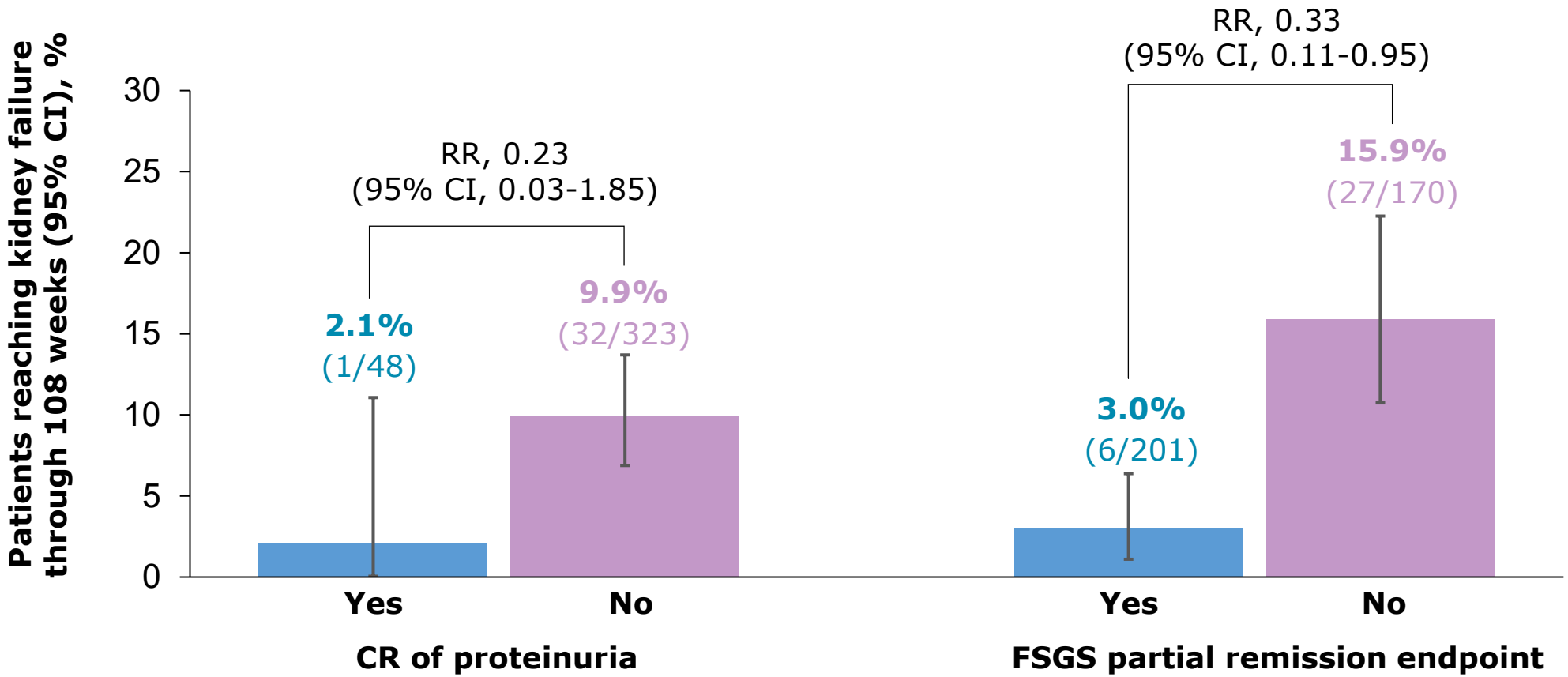



FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; PR, partial remission; RR, relative risk; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.
*The FSGS partial remission endpoint was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline.
†*P* value generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

RESULTS

# Irrespective of Treatment, Patients Who Achieved the FSGS Partial Remission Endpoint or CR of Proteinuria Were Less Likely To Develop Kidney Failure vs Those Who Did Not*




CR, complete remission; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; RR, relative risk.
*Results from post hoc analyses using pooled data irrespective of treatment arm. CR of proteinuria was defined as UPCR of <0.3 g/g. The FSGS partial remission endpoint was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline. Kidney failure was defined as confirmed eGFR of <15 mL/min/1.73 $m^2$ or kidney replacement therapy.

RESULTS

# SPAR Was Well Tolerated, With a Safety Profile Comparable To That of IRB

- The most common TEAEs (≥15% in either group) included COVID-19, hyperkalemia, peripheral edema, and hypotension

| Patients with TEAEs, n (%) | SPAR n=184 | IRB n=187 | All patients N=371 |
|---|---|---|---|
| **Any TEAEs** | 172 (93) | 174 (93) | 346 (93) |
| Serious TEAEs | 68 (37) | 82 (44) | 150 (40) |
| **TEAEs of interest** | | | |
| Fluid retention-associated TEAEs | 47 (26) | 56 (30) | 103 (28) |
| Hyperkalemia-associated TEAEs | 37 (20) | 21 (11) | 58 (16) |
| Hypotension | 33 (18) | 21 (11) | 54 (15) |
| Anemia | 24 (13) | 10 (5) | 34 (9) |
| Dizziness | 23 (13) | 21 (11) | 44 (12) |
| Acute kidney injury | 8 (4) | 13 (7) | 21 (6) |
| ALT or AST >3 × ULN | 5 (3) | 4 (2) | 9 (2) |
| Heart failure | 0 | 0 | 0 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRB, irbesartan; SPAR, sparsentan; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

# CONCLUSIONS

- Dual endothelin angiotensin receptor blockade with SPAR led to clinically meaningful low proteinuria thresholds, including CR of proteinuria or the FSGS partial remission endpoint, being achieved earlier and more often in patients with FSGS than did angiotensin receptor blockade alone with IRB
- Consistent with reported results from PARASOL,[4] patients who reached CR of proteinuria or the FSGS partial remission endpoint showed markedly reduced risk of progression to kidney failure
- SPAR was generally well tolerated over 108 weeks of treatment, with a safety profile comparable to that of IRB

## Key takeaway

- Patients with FSGS achieved proteinuria reductions, including CR of proteinuria or the FSGS partial remission endpoint, earlier and more often with SPAR vs IRB, and those who reached these targets had a lower risk of kidney failure, supporting the nephroprotective benefit of SPAR in FSGS

CR, complete remission; FSGS, focal segmental glomerulosclerosis; IRB, irbesartan; SPAR, sparsentan.

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8. Troost CJ, et al. *Clin J Am Soc Nephrol*. 2018;13(3):414-421.

# DISCLOSURES

- **VT** reports reports consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas Therapeutics, GSK, Eli Lilly, Novartis, Otsuka Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics; honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas Therapeutics, Eli Lilly, Novartis, Travere Therapeutics, Inc., and Vera Therapeutics; and membership of clinical trial steering committees for Calliditas Therapeutics, Novartis, Otsuka Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics.
- **HT** reports reports grants from AstraZeneca, Bayer, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, George Clinical, Novartis, Omeros, Otsuka Pharmaceuticals, and Vera Therapeutics; consulting fees from AstraZeneca, BioCryst Pharmaceuticals, Biogen Inc., Calliditas Therapeutics, Chinook Therapeutics, Dimerix, George Clinical, Novartis, Omeros, Takeda Pharmaceuticals, Timberlyne Therapeutics, Travere Therapeutics, Inc., and Vera Therapeutics; honoraria from AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, George Clinical, Novartis, and Travere Therapeutics, Inc.; travel support from BioCryst Pharmaceuticals, Calliditas Therapeutics, and Chinook Therapeutics; and membership of a data safety monitoring or advisory board for AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Novartis, and Travere Therapeutics, Inc.
- **JT** reports reports grants from Akebia Therapeutics, Alexion Pharmaceuticals, argenx, AstraZeneca, Aurinia Pharmaceuticals Inc., Dimerix Limited, Humacyte Global Inc., La Jolla Pharmaceutical Company, Mallinckrodt Pharmaceuticals, Medtronic Inc., Otsuka Pharmaceuticals, Palatin Technologies, Pfizer, Travere Therapeutics, Inc., Vera Therapeutics, and Vertex Pharmaceuticals; consulting fees from Akebia Therapeutics, Alexion Pharmaceuticals, argenx, AstraZeneca, Biogen Inc., La Jolla Pharmaceutical Company, Mallinckrodt Pharmaceuticals, Medtronic Inc., Palatin Technologies, Pfizer, Travere Therapeutics, Inc., Vera Therapeutics, and Vertex Pharmaceuticals; membership of advisory boards for Alexion Pharmaceuticals, Vera Therapeutics, and Vertex Pharmaceuticals; and serving as part of speakers bureaus for Otsuka Pharmaceuticals.
- **LK** is principal investigator for studies sponsored by Akebia Therapeutics, Alpine Therapeutics, AstraZeneca, Boehringer Ingelheim, Cara Therapeutics, Chinook Therapeutics, CSL Behring, Galderma, Mineralys Therapeutics, Inc., Novartis, Omeros, Otsuka Pharmaceuticals, Reata Pharmaceuticals, Travere Therapeutics, Inc., Vera Therapeutics, Visterra, and Walden Biosciences.
- **RK, JI,** and **EM** are employees and shareholders of Travere Therapeutics, Inc.
- **ER** reports nonfinancial support from GSK, Terumo, Otsuka, and Vifor; payments for scientific sessions from Terumo, GSK, and Otsuka; advisory board participation for Alexion and Otsuka; and basic research grants from Travere Therapeutics, Inc.


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