LB-07

Patients in DUPLEX Achieved Partial or Complete Remission of Proteinuria Earlier and More Often With Sparsentan vs Irbesartan: Implications for Slowing Progression to Kidney Failure in Focal Segmental Glomerulosclerosis (FSGS)

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Disclosures

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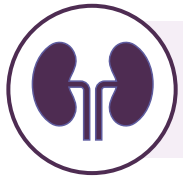
Learning Objectives

1. Explain how endothelin-1 and angiotensin II contribute to kidney injury in patients with FSGS, emphasizing their role in podocyte damage, proteinuria, and disease progression
2. Discuss the link between proteinuria reduction and kidney survival in patients with FSGS, highlighting the importance of achieving low proteinuria targets
3. Review the latest DUPLEX trial data on sparsentan's effectiveness in reducing proteinuria in patients with FSGS
4. Enhance awareness of sparsentan's efficacy and safety in patients with FSGS to guide nephrologists in managing proteinuric kidney disease

FSGS Is Associated With a Substantial Patient, Clinical, and Economic Burden

- **FSGS** is a rare, progressive, kidney condition defined by a histological pattern of **glomerular and podocyte injury**[1,2]
- FSGS is associated with substantial burden:



Substantial risk of progression to kidney failure, with 40% to 60% of patients reaching ESKD within 10 to 20 years of diagnosis[3,4]

High physical symptom burden, including severe edema, fatigue, body pain/pressure, and shortness of breath[5]

High patient burden, with patients experiencing anxiety, depression, and **impaired HRQOL**[6]

High financial burden and comorbid burden in ESKD[7]

ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; HRQOL, health-related quality of life.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int* 2021;100(4S):S1-S276; 2. Shabaka A, et al. *Nephron.* 2020;144(9):413-427; 3. Cravedi P, et al. *Am J Transplant* 2013;13:266-274; 4. Pitcher D, et al. ERA 2024. Oral presentation 901; 5. Mathias SD, et al. *Am J Kidney Dis*. 2017;70:532-540; 6. Szklarzewicz J et al. ERA 2024. Poster 366; 7. Bensink ME, et al. *Kidney Med*. 2024;6(2):100760.

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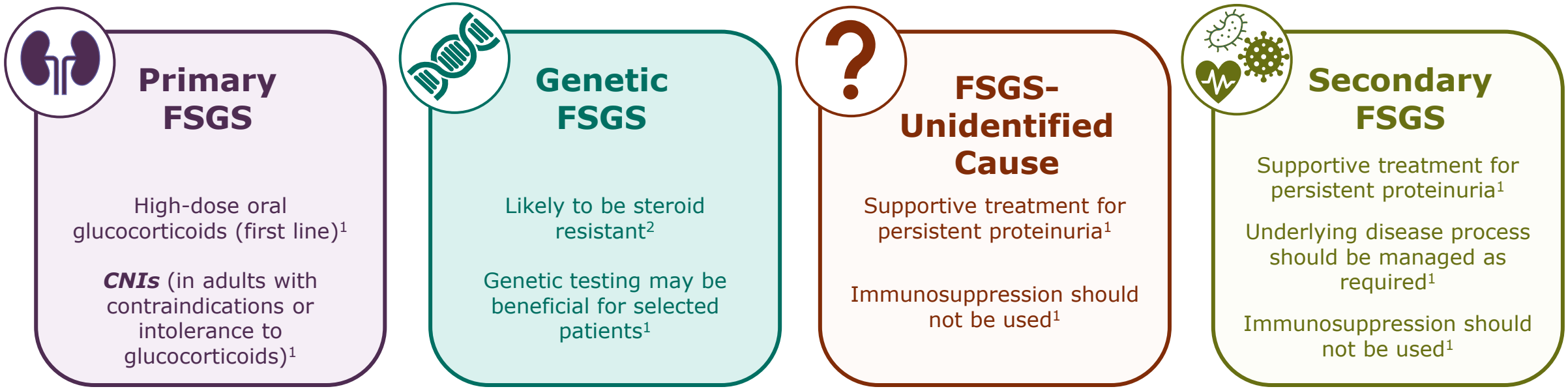
Effective Treatment Options for FSGS Are Limited



- There remains an **unmet need for safe and effective treatments** that lower proteinuria and reduce the risk of kidney failure[3-5]
  - Current therapeutic strategies are limited and include ACEis, ARBs, calcineurin inhibitors, and steroids[1,6]
  - **47%** of children and **38%** of adults **do not respond** to currently available therapies[7]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int.* 2021;100(4S):S1-S276; 2. Harita Y. *Clin Exp Nephrol.* 2018;22:491-500; 3. Trachtman H. *Expert Opin Emerg Drugs*. 2020;25(3):367-375; 4. Gipson DS, et al. *JAMA Netw Open.* 2022;5(8):e2228701; 5. Hodson EM, et al. *Cochrane Database Syst Rev.* 2022;2(2):CD003233; 6. Korbet SM. *J Am Soc Nephrol.* 2012;23:1769-1776; 7. Gipson D. *Semin Nephrol.* 2016; 36:453-459.

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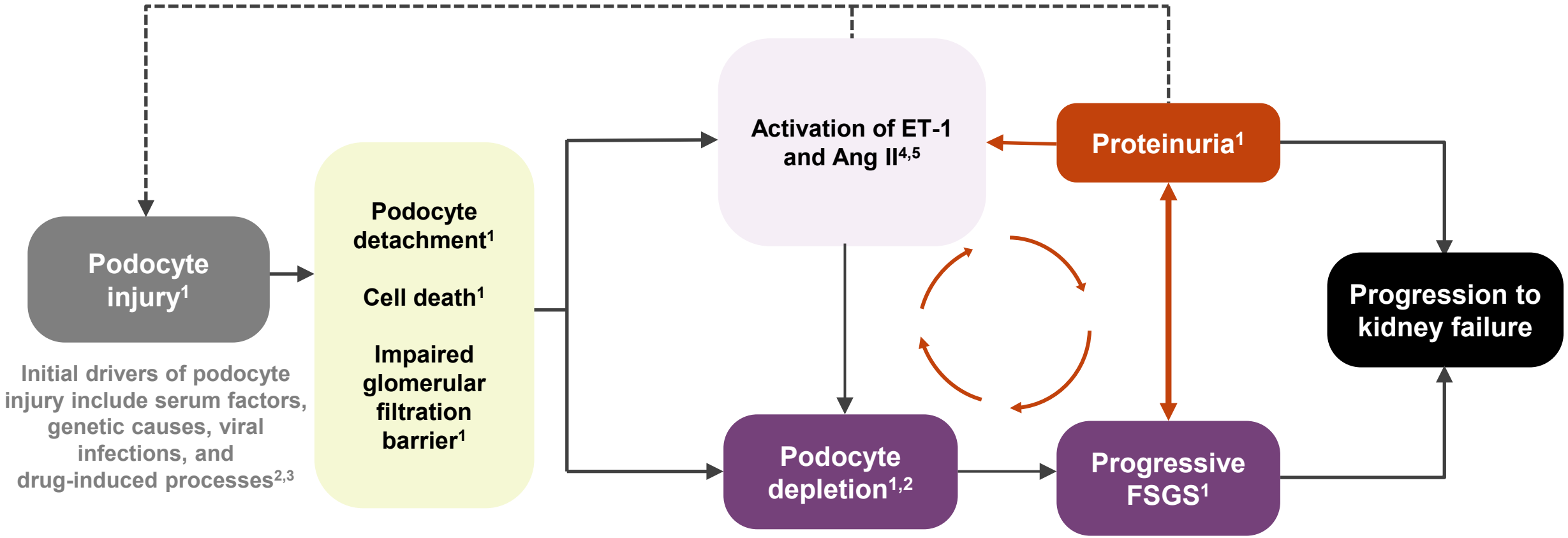
ET-1 and Ang II Are Key Mediators of Podocyte Damage in FSGS



Ang II, angiotensin II; ET-1, endothelin-1; FSGS, focal segmental glomerulosclerosis.

1. Jefferson JA, Shankland SJ. *Adv Chronic Kidney Dis.* 2014;21(5):408-416; 2. De Vriese AS, et al. *Nat Rev Nephrol.* 2021;17(9):619-630; 3. Rovin BH, et al. *Kidney Int.* 2021;100(4):753-779; 4. Ebefors K, et al. *Kidney Int*. 2019;96(4):957-970; 5. Kohan DE, Barton M. *Kidney Int*. 2014;86(5):896-904.

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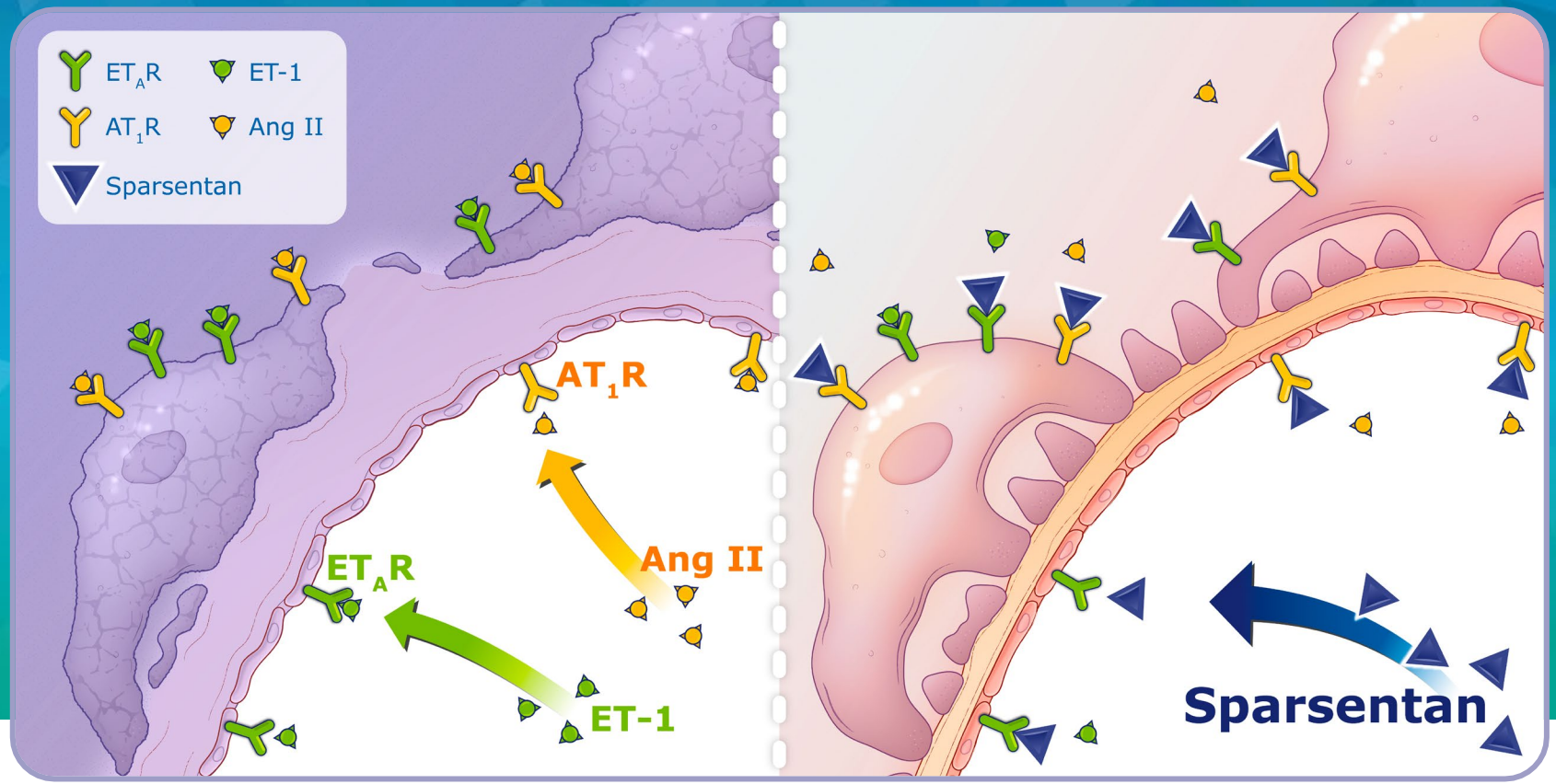
In FSGS, sparsentan protects the podocytes by simultaneously blocking ET-1 and Ang-II[1-3]

Sparsentan is a novel, non-immunosuppressive, Dual Endothelin Angiotensin Receptor Antagonist (DEARA)[1,4]



Sparsentan targets glomerular injury, reducing proteinuria and preserving kidney function[1-3,5-7]*

EFFECTS:

- **Podocyte-protective[2,3]***
- **Anti-proteinuric[5-7]**
- **Anti-fibrotic[2]***

*These effects are based on pre-clinical animal modeling data.

AT$_1$R, angiotensin II subtype 1 receptor; DEARA, Dual Endothelin Angiotensin Receptor Antagonist; ET-1, endothelin 1; ET$_A$R, endothelin type A receptor; FSGS, focal segmental glomerulosclerosis.

1. Kohan DE et al. *Clin Sci*. 2024;138(11):645-662; 2. Gyarmati G et al. Presented at: 51st European Renal Association Congress 2021; June 5-8, 2021; Virtual and Berlin; 3. Gyarmati C et al. Presented at: American Society of Nephrology Kidney Week 2022; November 3-6, 2022; Orlando, Florida. FR OR56; 4. Trachtman H et al. *Expert Rev Clin Immunol*. 2024;20(6):571-576; 5. Trachtman H et al. *J Am Soc Nephrol*. 2018;29(11):2745-2754; 6. Hogan J et al. Presented at: American Society of Nephrology Kidney Week 2022; October 23-28, 2018; San Diego. FR OR087; 7. Rheault MN et al. *N Eng J Med*. 2023;389(26):2436-2445.

As of March 2025, sparsentan is an investigational therapeutic candidate for the treatment of FSGS. MA-SP-25-0017 | March 2025

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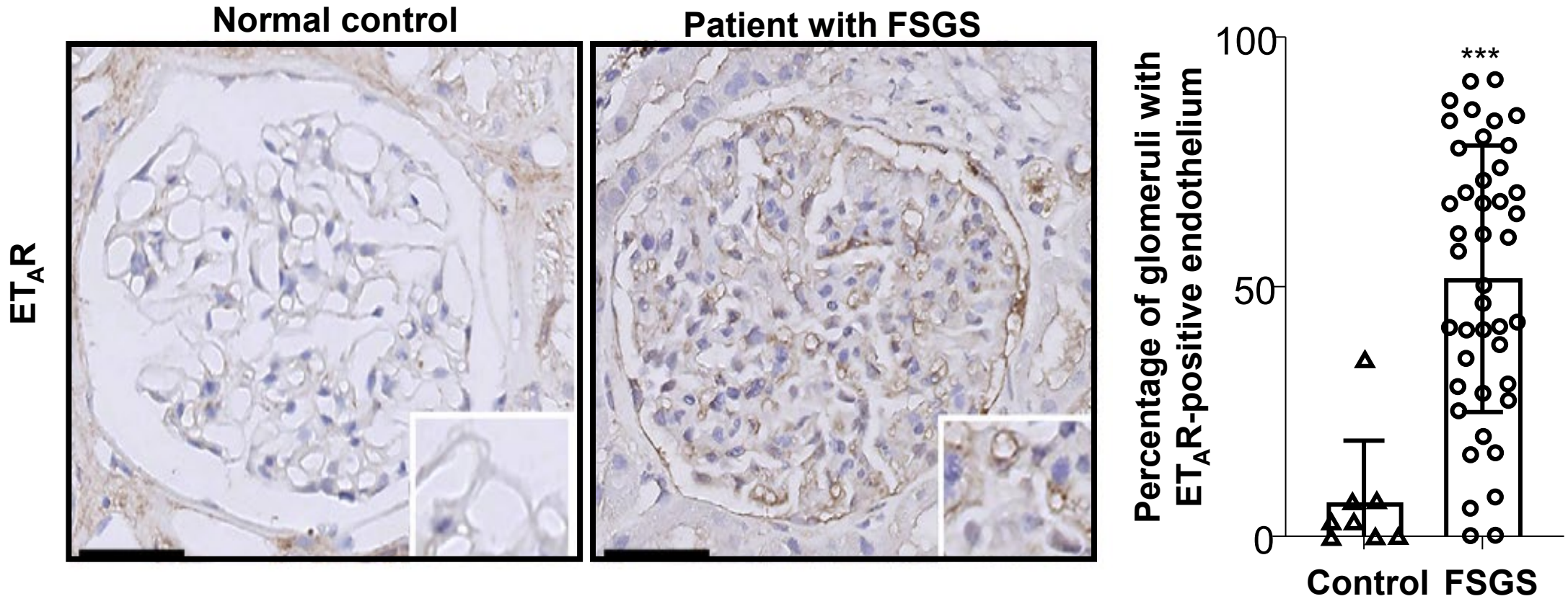
Glomerular ET_AR Expression Increased in Patients With FSGS

>5-Fold Increase in ET_AR Expression Glomerular Endothelium



***P<.001.
ET_AR, endothelin type A receptor; FSGS, focal segmental glomerulosclerosis.
van de Lest NA, et al. *Kidney Int Rep.* 2021;6:1939-1948.

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Proteinuria Reduction in FSGS: Target?

What endpoint predicts kidney function preservation and kidney health?

PARASOL: An International Initiative to Advance Understanding of Proteinuria and eGFR Endpoints in FSGS

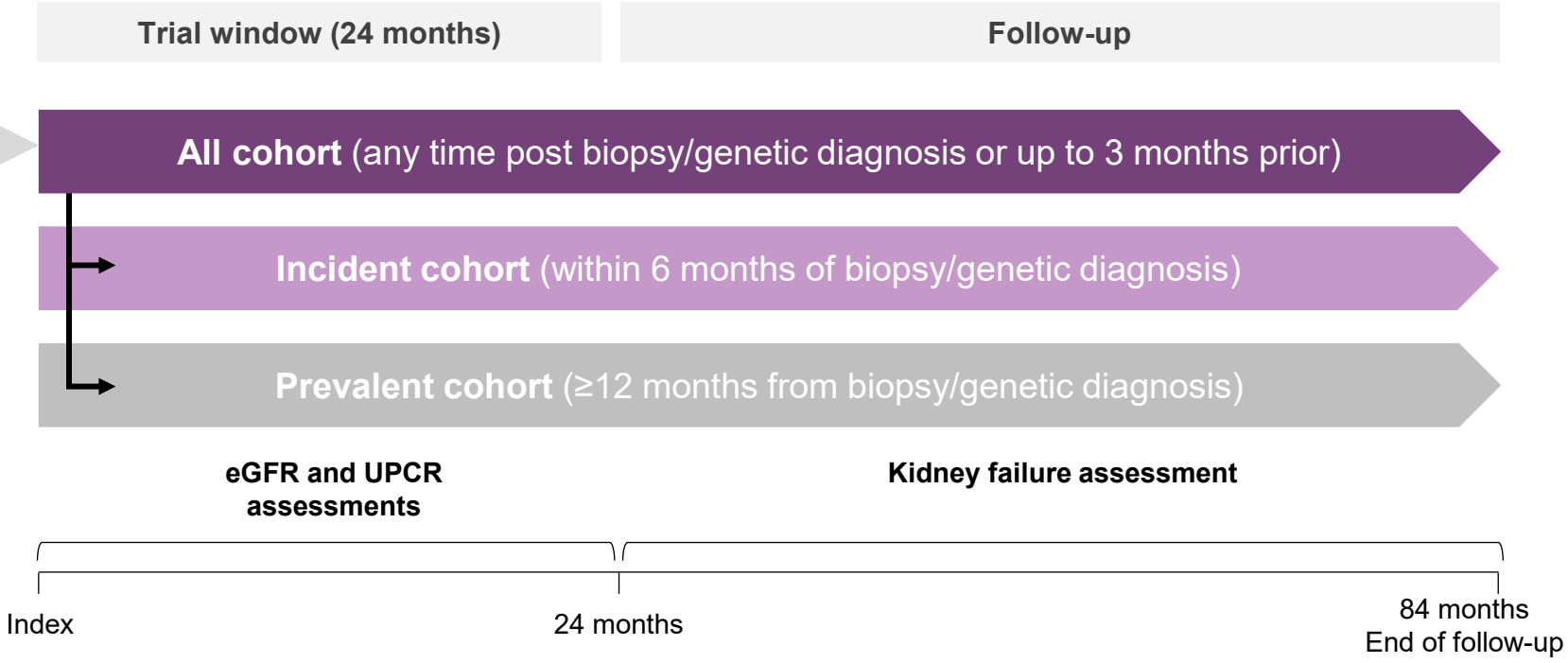
PARASOL: Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis

N=1626

- Biopsy-proven or genetic FSGS
- UPCR ≥1.5 g/g
- eGFR ≥30 mL/min/1.73 m^2

Global partnership with data from 9 registries*:

- NEPTUNE
- CureGN
- KRN
- UNC
- Gaslini
- Podonet
- Glosen
- Toronto GN Registry
- Indiana
- *RaDaR (validation)*



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eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; RaDaR, National Registry of Rare Kidney Diseases; UPCR, urine protein-to-creatinine ratio.
*Reported analyses are based on data from 9 registries. Analyses including data from additional registries are ongoing.
Smith AR, et al. ASN 2024. Translational session. Abstract INFO10-SA.

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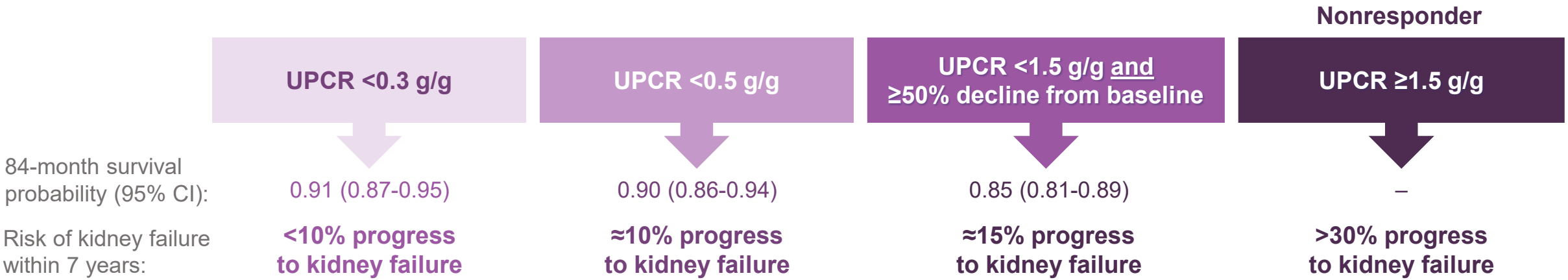
Proteinuria Endpoints in FSGS

PARASOL identified **proteinuria as a biologically plausible and clinically meaningful endpoint***

- Reduction in proteinuria at 2 years is strongly associated with lower kidney failure risk



- Proteinuria endpoints were consistent across subgroups and required feasible study sample sizes to detect treatment differences
- In contrast, eGFR demonstrated high variability, requiring long duration of follow-up and large study sample sizes that are difficult to achieve in this rare disease

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eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; UPCR, urine protein-to-creatinine ratio.
*Patients with biopsy-proven or genetic FSGS (secondary FSGS was not included in this study).
Smith AR, et al. ASN 2024. Translational session. Abstract INFO10-SA.

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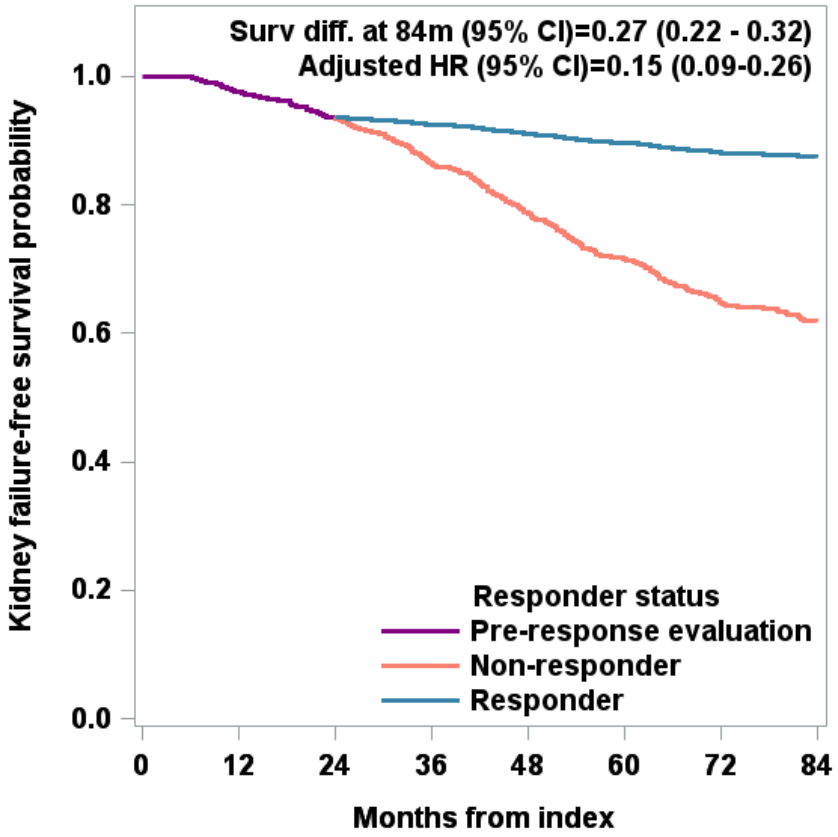
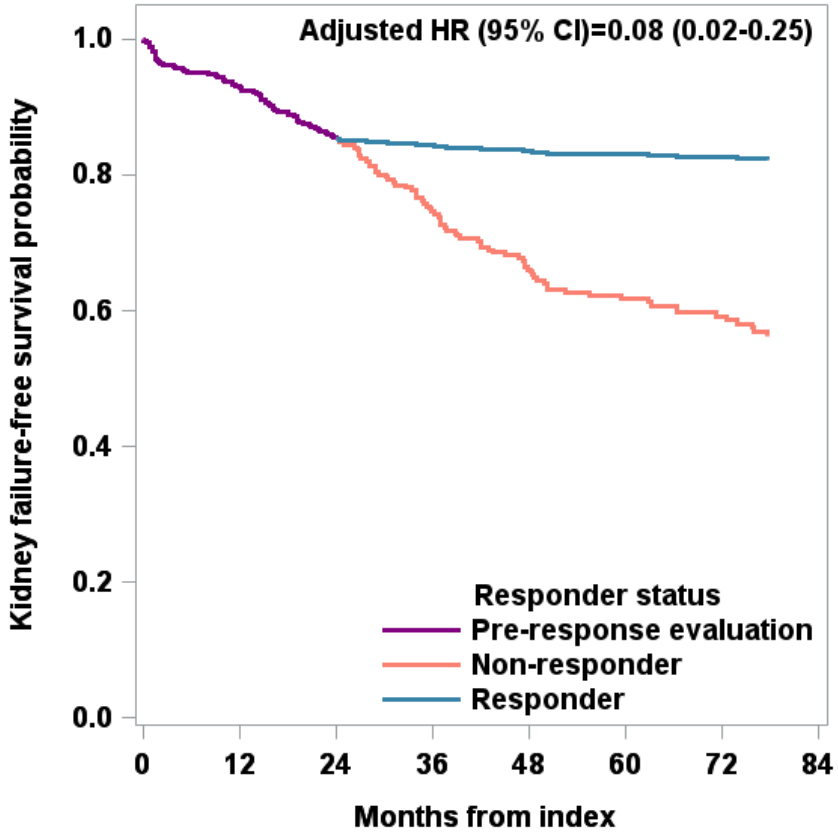
PARASOL: Achieving Proteinuria <0.7 g/g Is Associated With Meaningful Reduction in Kidney Failure Risk

PARASOL
Responder survival differences post index for UPCR <0.7 g/g (all)



RaDaR-FSGS
Independent validation of responder survival difference post index for UPCR <0.7 g/g (all)



Data were independently **validated in the UK FSGS RaDaR cohort** (<0.7 g/g), where the results from the PARASOL dataset were consistent with results from the RaDaR dataset

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CI, confidence interval; HR, hazard ratio; RaDaR, National Registry of Rare Kidney Diseases; UPCR, urine protein-to-creatinine ratio.
Smith AR, et al. ASN 2024. Translational session. Abstract INFO10-SA.

Sparsentan: DUET and DUPLEX Trials in FSGS

What is the efficacy of a dual endothelin angiotensin receptor antagonist (DEARA) in the treatment of FSGS?

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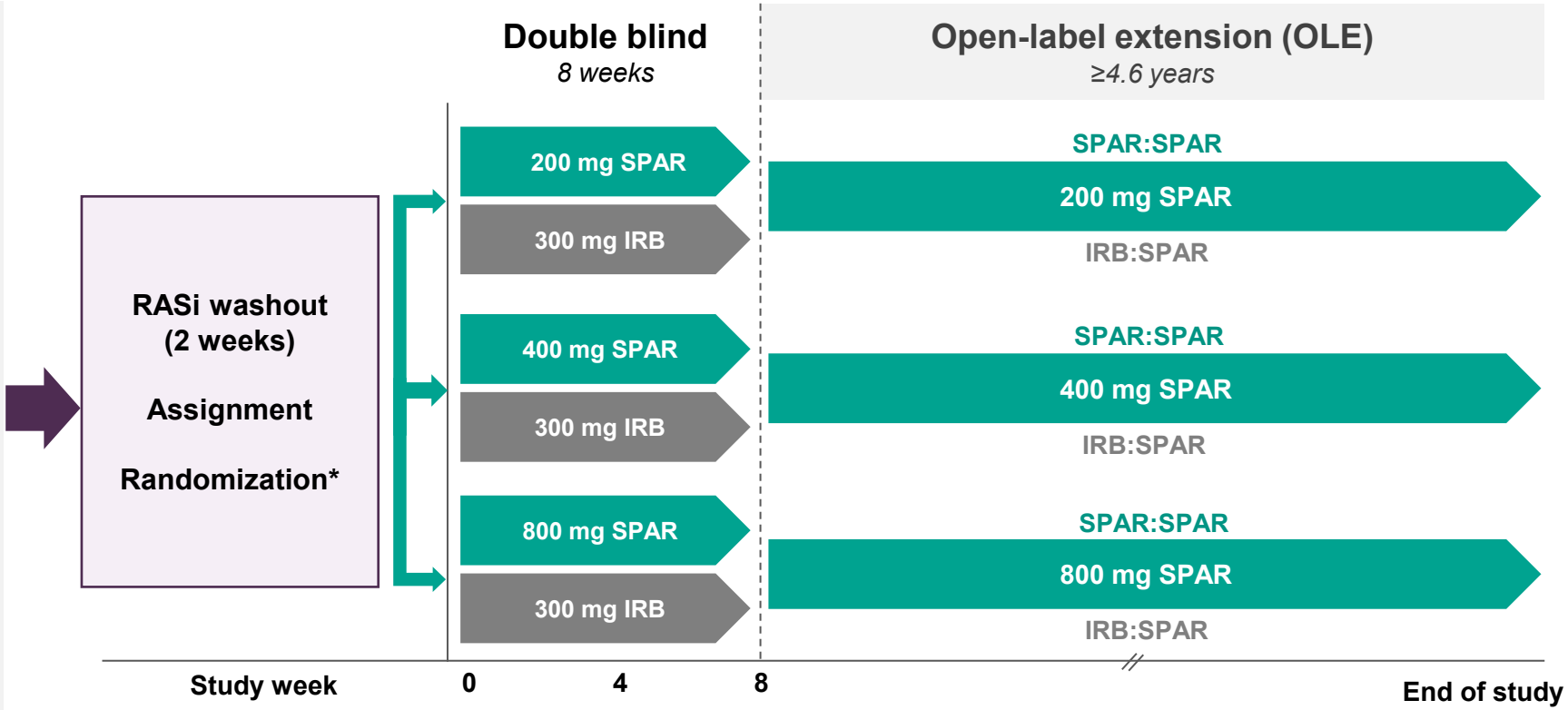
DUET: Study Design

Selection criteria

- Age 8-75 (US) or 18-75 (EU) years
- Biopsy-proven primary FSGS or documented genetic mutation (secondary FSGS excluded)
- UPCR ≥1.0 g/g
- eGFR >30 mL/min/1.73 m^2
- Chronic IST (excluding cyclophosphamide and rituximab) was permitted if dose was stable for 1 month before randomization



Primary endpoint: change in UPCR from baseline to week 8

Secondary endpoint: proportion of patients achieving FPRE† from baseline to week 8

Tertiary endpoints: changes in BP, eGFR, and select laboratory parameters

BP, blood pressure; eGFR, estimated glomerular filtration rate; FPRE, FSGS partial remission endpoint; FSGS, focal segmental glomerulosclerosis; IRB:SPAR, patients randomized to irbesartan who then transitioned to sparsentan in the OLE; IRB, irbesartan; IST, immunosuppressive therapy; OLE, open-label extension; RASi, renin-angiotensin system inhibitor; SPAR, sparsentan; SPAR:SPAR, patients randomized to sparsentan who also received sparsentan in the OLE; UPCR, urine protein-to-creatinine ratio.

*Patients were assigned to dose cohort, then randomized to sparsentan or irbesartan within the dose cohort. Study drug administered orally, once daily. Patients who weighed ≤50 kg received half of the daily dose of sparsentan or irbesartan according to the assigned dose cohort. Randomization after 2 weeks' RASi washout. †FPRE was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline.

1. Komers R, et al. *Kidney Int Rep.* 2017;2:654-664; 2. Trachtman H, et al. *J Am Soc Nephrol.* 2018;29:2745-2754.

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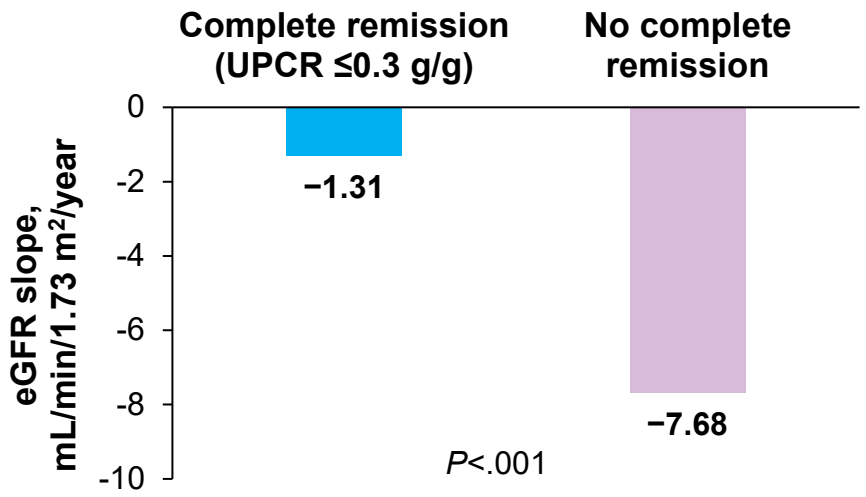
Complete Remission of Proteinuria in DUET Open-Label Period

- In the phase 2 DUET study, sparsentan led to rapid proteinuria reductions in the double-blind period that were sustained throughout the open-label period[1,2]
- **43% of patients achieved complete remission** of proteinuria with sparsentan at any time during the double-blind and open-label period[2]
  - Patients who achieved complete remission in DUET had slower kidney function decline (eGFR slope)[2]
  - Fewer patients who achieved complete remission progressed to kidney failure compared with those without complete remission[2]

43% of patients (46 of 108) achieved complete remission at any time on sparsentan

eGFR slope by CR status



KRT, ESKD, and reduction in eGFR by CR status

Endpoint, n (%)	Complete remission (n=46)	No complete remission (n=62)
KRT or ESKD	3 (6.5)	9 (14.5)
Confirmed 40% reduction in eGFR	10 (21.7)	22 (35.5)
KRT, ESKD, or confirmed 40% reduction in eGFR	10 (21.7)	23 (37.1)

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CR, complete remission of proteinuria; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KRT, kidney replacement therapy; UPCR, urine protein-to-creatinine ratio.

1. Trachtman H, et al. *J Am Soc Nephrol*. 2018;29:2745-2754; 2. Trachtman H, et al. *Kidney Int Rep*. 2023;8:2017-2028.

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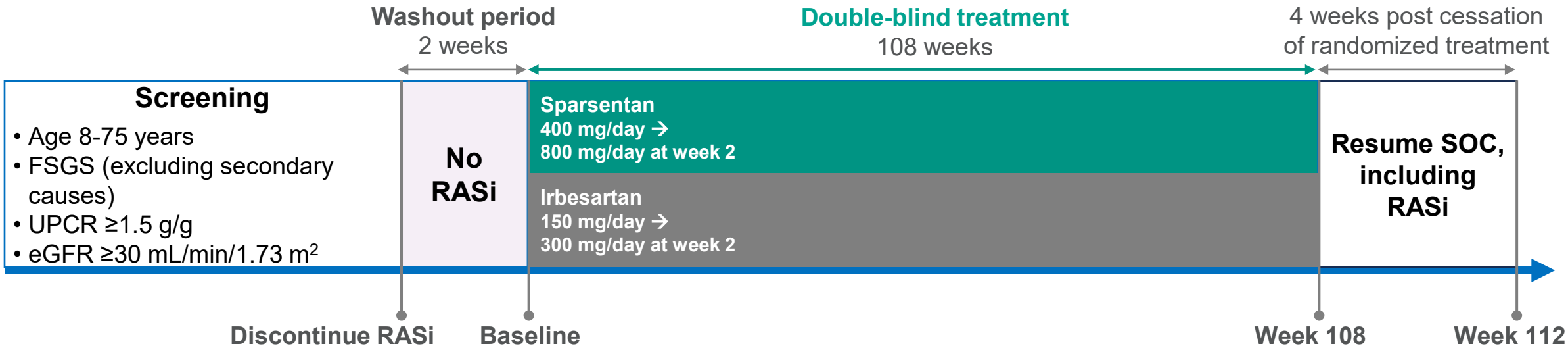
DUPLEX: Study Design

DUPLEX (NCT03493685) is a phase 3, randomized, double-blind trial investigating the safety and efficacy of **sparsentan vs active control, maximum labeled dose irbesartan** in adults and children (aged ≥8 y) with FSGS



Children 8 to <18 years*

Sparsentan: 8.7% (16/184)

Irbesartan: 10.2% (19/187)

Receiving **maximum labeled dose***

Sparsentan: 90.7% (166/183)

Irbesartan: 90.4% (169/187)

- With 371 randomized patients, DUPLEX was the largest randomized clinical trial of FSGS to date

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eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; RASi, renin-angiotensin system inhibitor; SOC, standard of care; UPCR, urine protein-to-creatinine ratio.
*Proportion of patients per treatment arm.

Patient Demographics and Baseline Characteristics

	Sparsentan n=184	Irbesartan n=187	All patients N=371
Age, mean (SD), years[1]	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 (interquartile range)	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[2]	13 (7)	18 (10)	31 (8)
COL4A3-5 variants[3]	11 (6)	14 (7)	25 (7)
High-risk *APOL1* variants[1]	9 (5)	5 (3)	14 (4)
Prior RASi use (stopped before washout), n (%)[1]	152 (83)	143 (76)	295 (80)
Baseline use of immunosuppressive agents, n (%)[1]	50 (27)	46 (25)	96 (26)
Baseline use of diuretics, n (%)[1]	68 (37)	73 (39)	141 (38)

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eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; RASi, renin-angiotensin system inhibitor; UPCR, urine protein-to-creatinine ratio.

1. Rheault MN, et al. *N Engl J Med.* 2023;389:2436-2445 (incl suppl). 2. Yee J, et al. *J Am Soc Nephrol.* 2014;35(suppl 10):10.1681. Abstract TH-PO1199. 3. Data on file. Travere Therapeutics, Inc.

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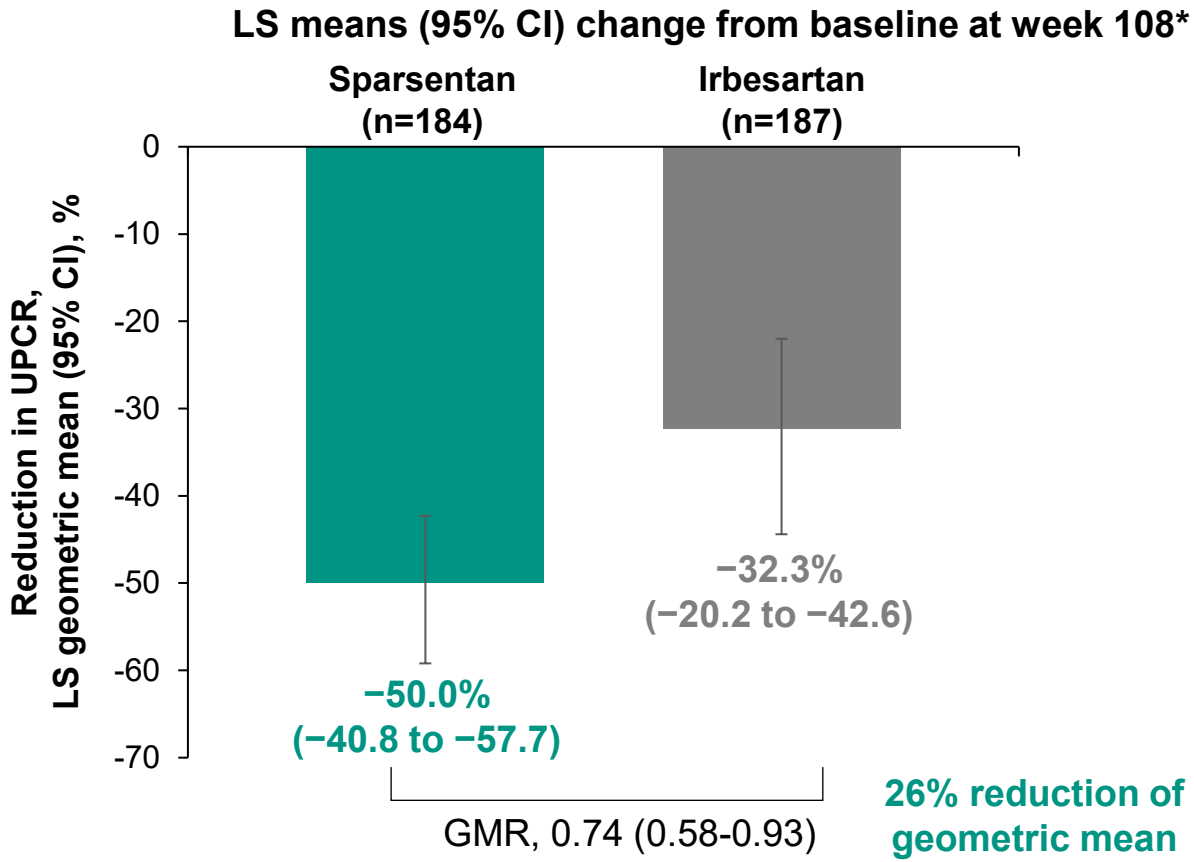
DUPLEX: Reductions in Proteinuria

In the phase 3 DUPLEX study, sparsentan was well tolerated and led to **rapid (as early as 6 weeks) and sustained (up to 108 weeks) reductions in proteinuria** compared with the active control irbesartan in patients with FSGS[1]



- In a week-36 interim analysis, more patients achieved the surrogate endpoint of partial remission† with sparsentan vs irbesartan (*P*=.009)[1]

- At the 108-week final analysis, the **geometric mean reduction in UPCR from baseline** was[1]:

  50% with sparsentan
  32% with irbesartan

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CI, confidence interval; FSGS, focal segmental glomerulosclerosis; GMR, geometric mean reduction; LS, least squares; UPCR, urine protein-to-creatinine ratio.
*Full analysis set. †FSGS partial remission endpoint (UPCR ≤1.5 g/g and >40% reduction from baseline).
Rheault MN, et al. *N Engl J Med*. 2023;389:2436-2445.

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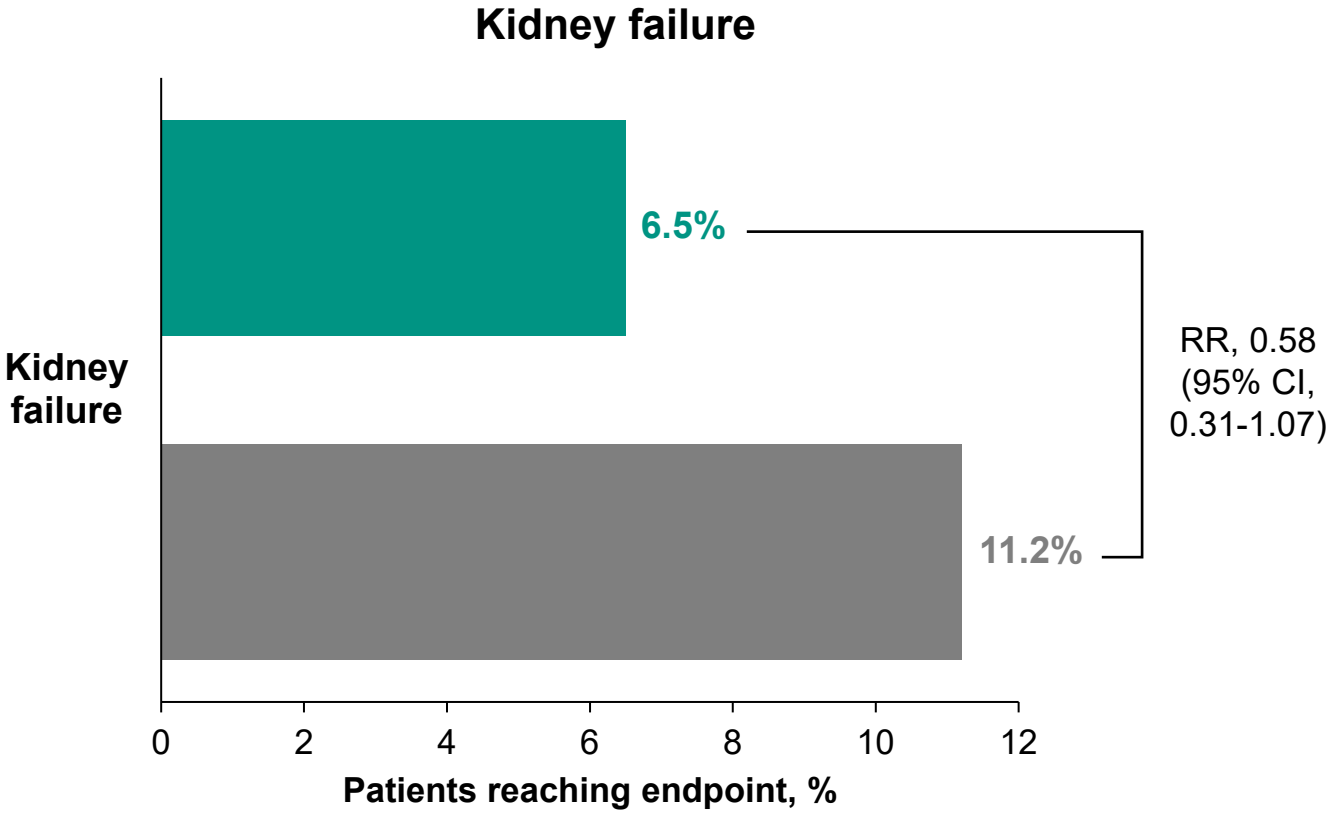
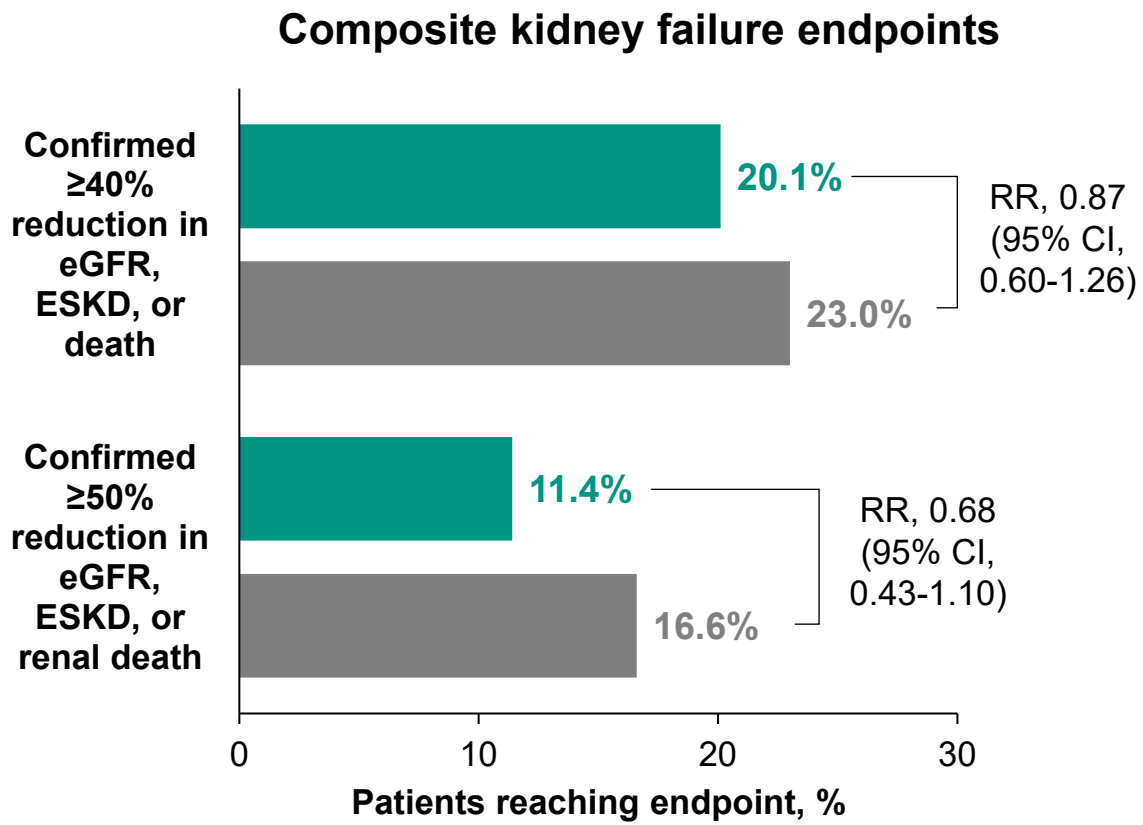
DUPLEX: Risk of Kidney Failure

In DUPLEX study, **fewer patients progressed to kidney failure** or composite kidney failure endpoints with sparsentan vs maximum labeled dose irbesartan





Sparsentan (n=184) Irbesartan (n=187)

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CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease, RR, relative risk.
Rheault MN, et al. *N Engl J Med.* 2023;389:2436-2445 (incl suppl).

Achieving Proteinuria Remission

What is the impact of sparsentan on partial or complete remission of proteinuria, and what is the effect of achieving these outcomes on progression to kidney failure?

Analyses

Analyses by treatment arm

- Proportion of patients achieving partial or complete remission of proteinuria at any time through 108 weeks
- Time to first partial or complete remission of proteinuria

- **Partial remission of proteinuria:** UPCR ≤1.5 g/g and >40% reduction from baseline[1]*
- **Complete remission of proteinuria:** UPCR <0.3 g/g

Analyses using pooled data from both treatment arms

- Rates of progression to kidney failure in patients who achieved vs did not achieve complete or partial remission of proteinuria

- **Kidney failure:** eGFR <15 mL/min/1.73 m^2 or kidney replacement therapy

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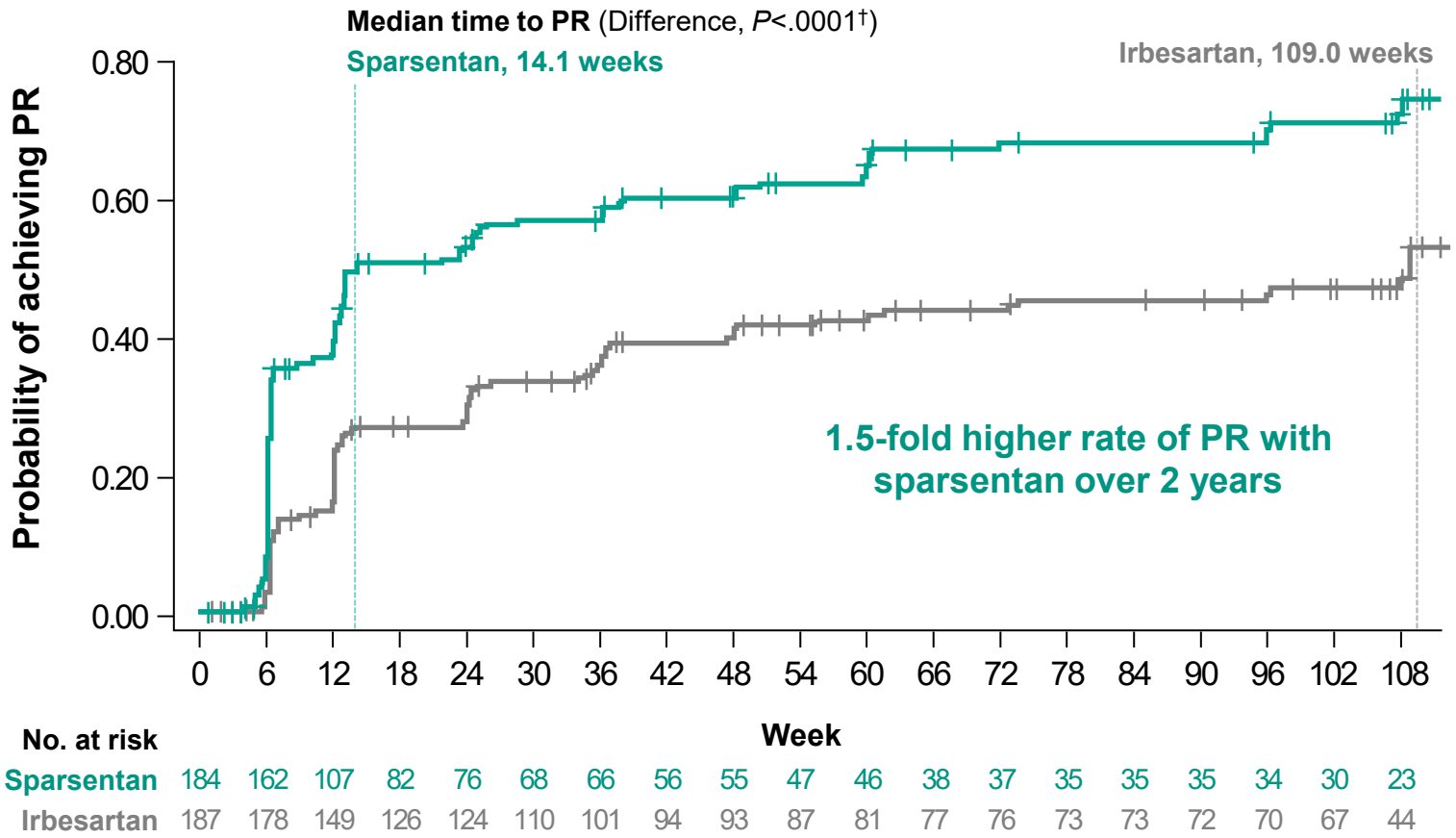
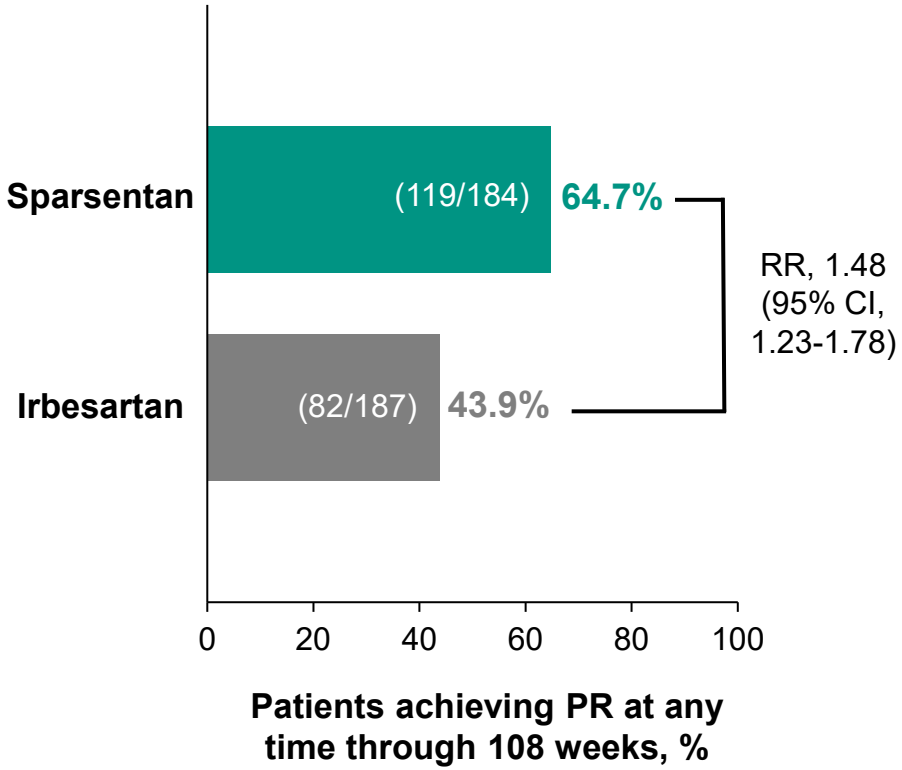
eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; UPCR, urine protein-to-creatinine ratio.
*FSGS partial remission endpoint (FPRE).

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

Patients Achieved Partial Remission (PR) of Proteinuria Earlier and More Often With Sparsentan vs Maximum Labeled Dose Irbesartan*





CI, confidence interval; FSGS, focal segmental glomerulosclerosis; NE, not estimable; PR, partial remission of proteinuria; RR, relative risk; UPCR, urine protein-to-creatinine ratio.

*Partial remission of proteinuria was defined as UPCR of ≤1.5 g/g and >40% reduction from baseline (FSGS partial remission endpoint).

†*P* value generated from a stratified Cox proportional hazards model with treatment and baseline log (UPCR) as covariates, stratified by randomization stratification factors.

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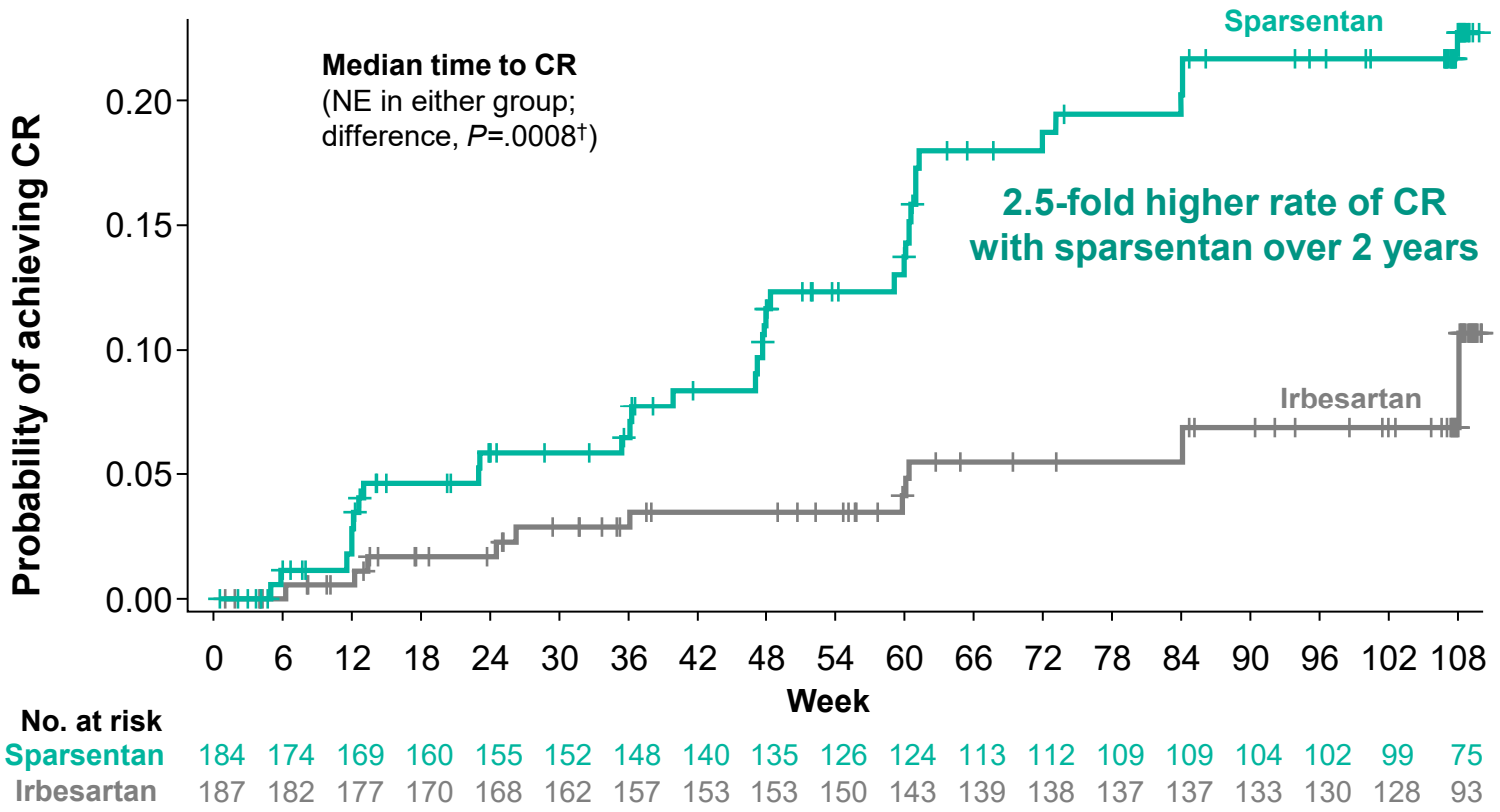
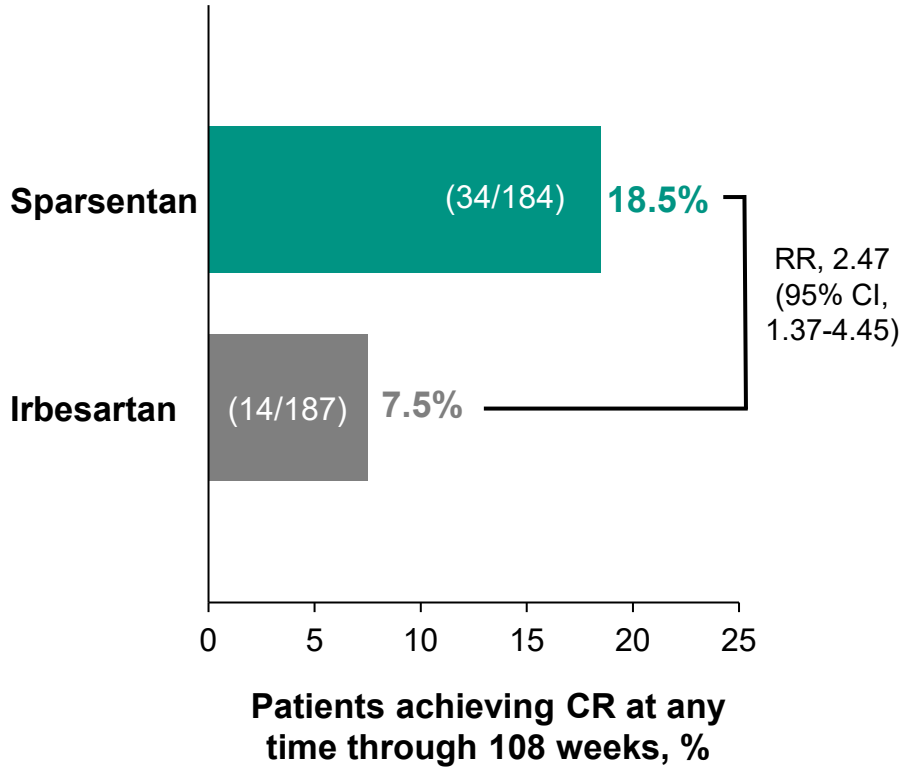
Patients Achieved Complete Remission (CR) of Proteinuria Earlier and More Often With Sparsentan vs Maximum Labeled Dose Irbesartan*





CI, confidence interval; CR, complete remission of proteinuria; NE, not estimable; RR, relative risk; UPCR, urine protein-to-creatinine ratio.
*Complete remission 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.

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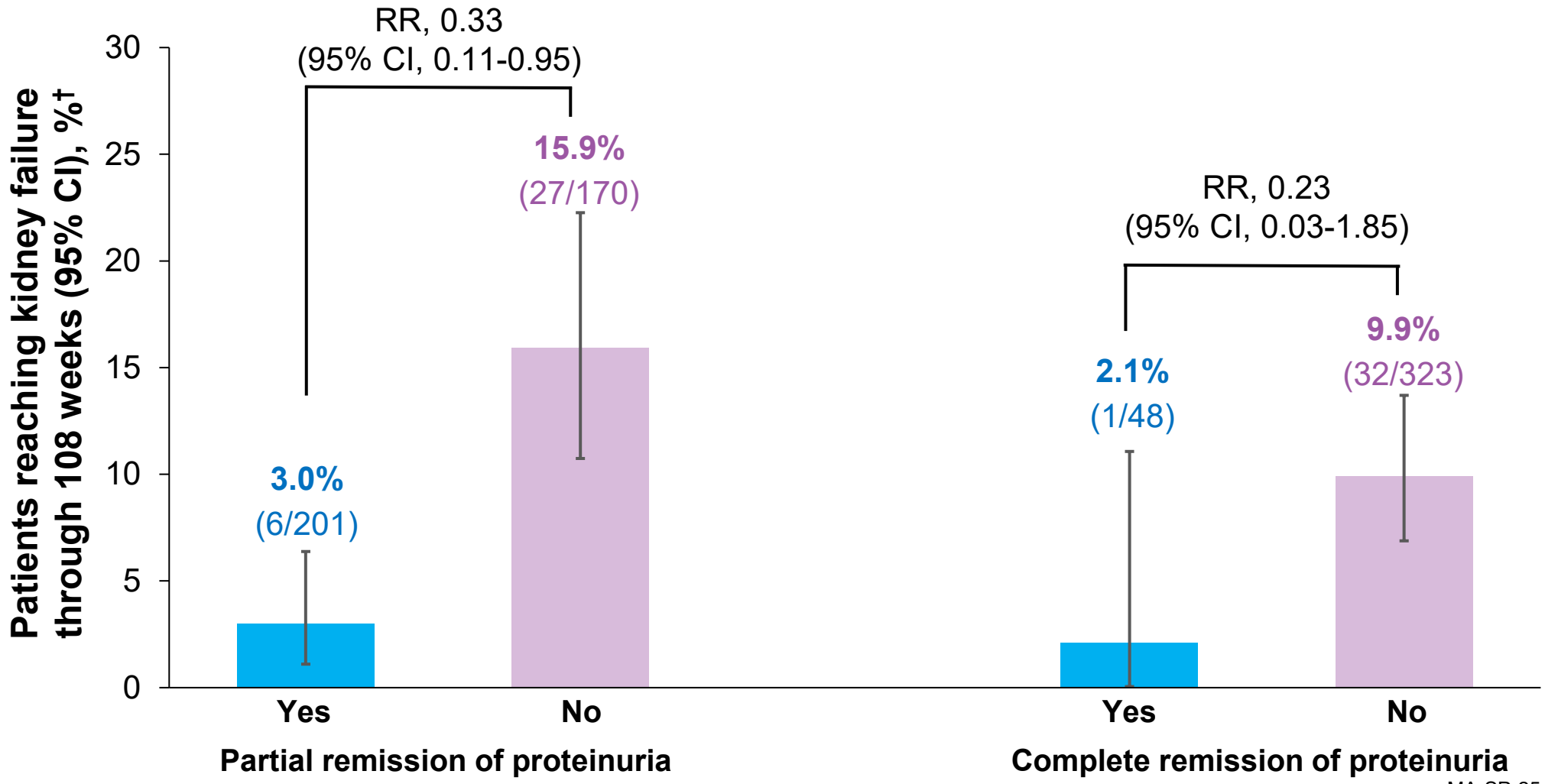
Irrespective of Treatment, Patients Who Achieved Partial or Complete Remission Were Less Likely to Reach Kidney Failure



CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk.
*Results from post hoc analyses using pooled data irrespective of treatment arm.
†Confirmed eGFR of <15 mL/min/1.73 m^2 or kidney replacement therapy.

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Sparsentan Was Well Tolerated, With a Safety Profile Comparable to That of Irbesartan

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

Patients With TEAEs, n (%)	Sparsentan n=184	Irbesartan 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

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

Conclusions

- Dual endothelin angiotensin receptor blockade with sparsentan led to partial or complete remission of proteinuria earlier and more often in patients with FSGS than did angiotensin receptor blockade alone with irbesartan
- Consistent with recently reported results from PARASOL,[1] patients who reached partial or complete remission of proteinuria showed markedly reduced risk of progression to kidney failure
- Sparsentan was generally well tolerated over 108 weeks of treatment, with a safety profile comparable to that of irbesartan
- **Taken together, these findings from the DUPLEX trial support the antiproteinuric and nephroprotective benefits of sparsentan in patients with FSGS**

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FSGS, focal segmental glomerulosclerosis.

1. Smith AR, et al. ASN 2024. Translational session. Abstract INFO10-SA.

Polling question

Patients with FSGS receiving sparsentan are ____ likely to reach complete remission of proteinuria and therefore are ____ likely to progress to kidney failure

- A) Less, less
- B) Less, more
- C) More, less
- D) More, more

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Questions?