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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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,[4] 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

KEY TAKEAWAY

Patients with FSGS achieved partial or complete remission of proteinuria earlier and more often with sparsentan vs irbesartan, and those who reached these targets had a lower risk of kidney failure, supporting sparsentan's nephroprotective benefit in FSGS

INTRODUCTION

- 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 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[4]
- Sparsentan 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]

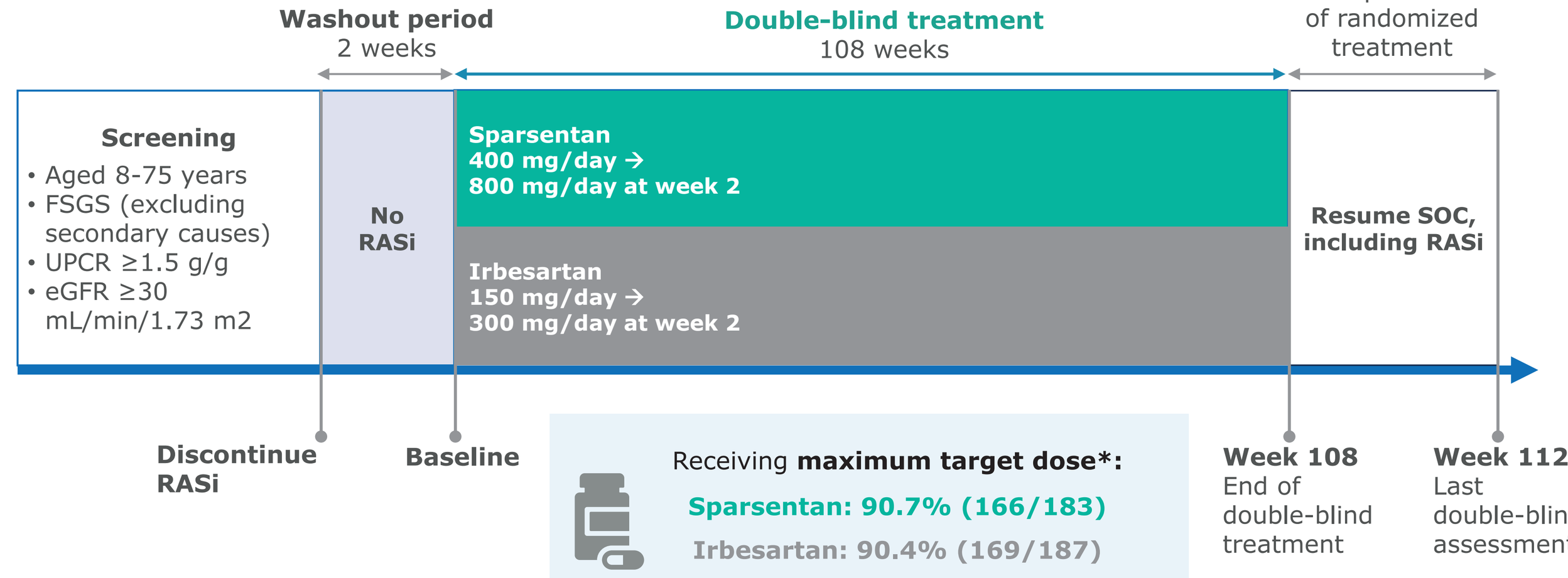
OBJECTIVE

- Expanding on earlier findings from this trial, we investigated the impact of sparsentan vs irbesartan on partial or complete remission of proteinuria and the effect of achieving these targets on progression to kidney failure in DUPLEX

METHODS

- 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 years) with FSGS

Figure 1. DUPLEX Study Design



*Proportion of patients receiving the maximum target dose per treatment arm.

- Analyses by treatment arm evaluated the proportion of patients achieving partial or complete remission of proteinuria at any time through 108 weeks
- Pooled analyses using data from both treatment arms evaluated rates of progression to kidney failure in patients who achieved or did not achieve complete or partial remission of proteinuria

Endpoint definitions

- **Partial remission of proteinuria:** UPCR ≤1.5 g/g and >40% reduction from baseline[8,*]
- **Complete remission of proteinuria:** UPCR <0.3 g/g
- **Kidney failure:** confirmed eGFR <15 mL/min/1.73 m^2 or kidney replacement therapy

*FSGS partial remission endpoint.

RESULTS

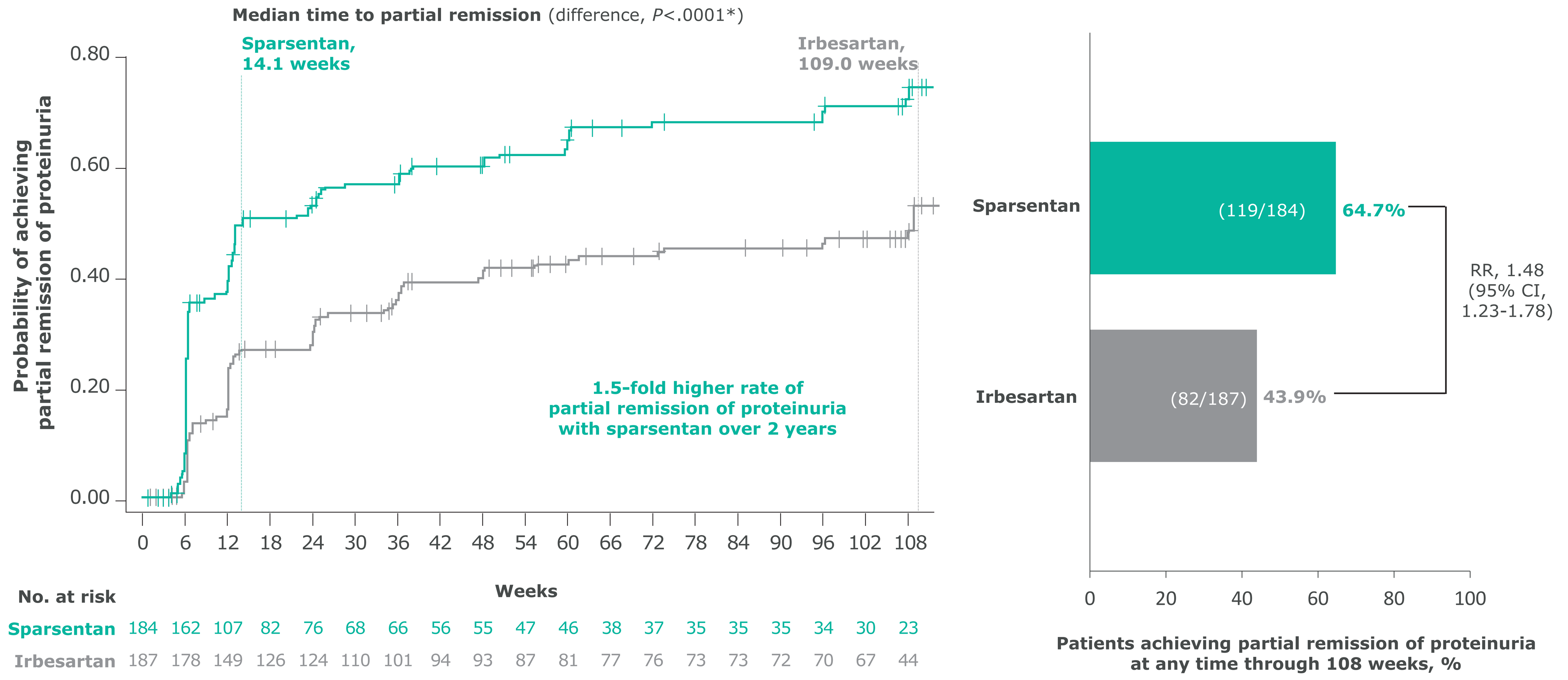
- A total of 371 patients were randomized to receive sparsentan or irbesartan in DUPLEX

Table 1. Patient Demographics and Baseline Characteristics

	Sparsentan n=184	Irbesartan 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 (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	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)

- Patients achieved partial remission of proteinuria earlier and more often with sparsentan vs maximum-labeled-dose irbesartan

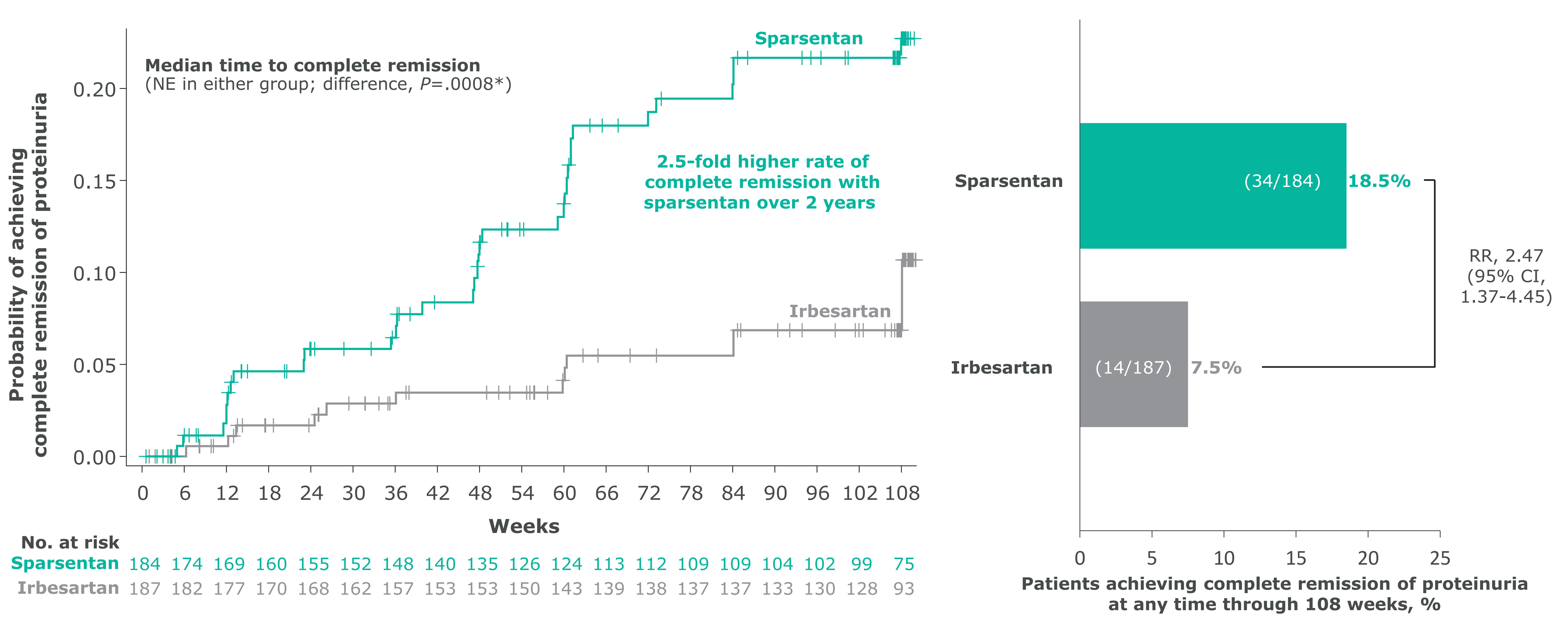
Figure 2. Probability of Achieving Partial Remission of Proteinuria Through 108 Weeks



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

- Patients achieved complete remission of proteinuria earlier and more often with sparsentan vs maximum-labeled-dose irbesartan

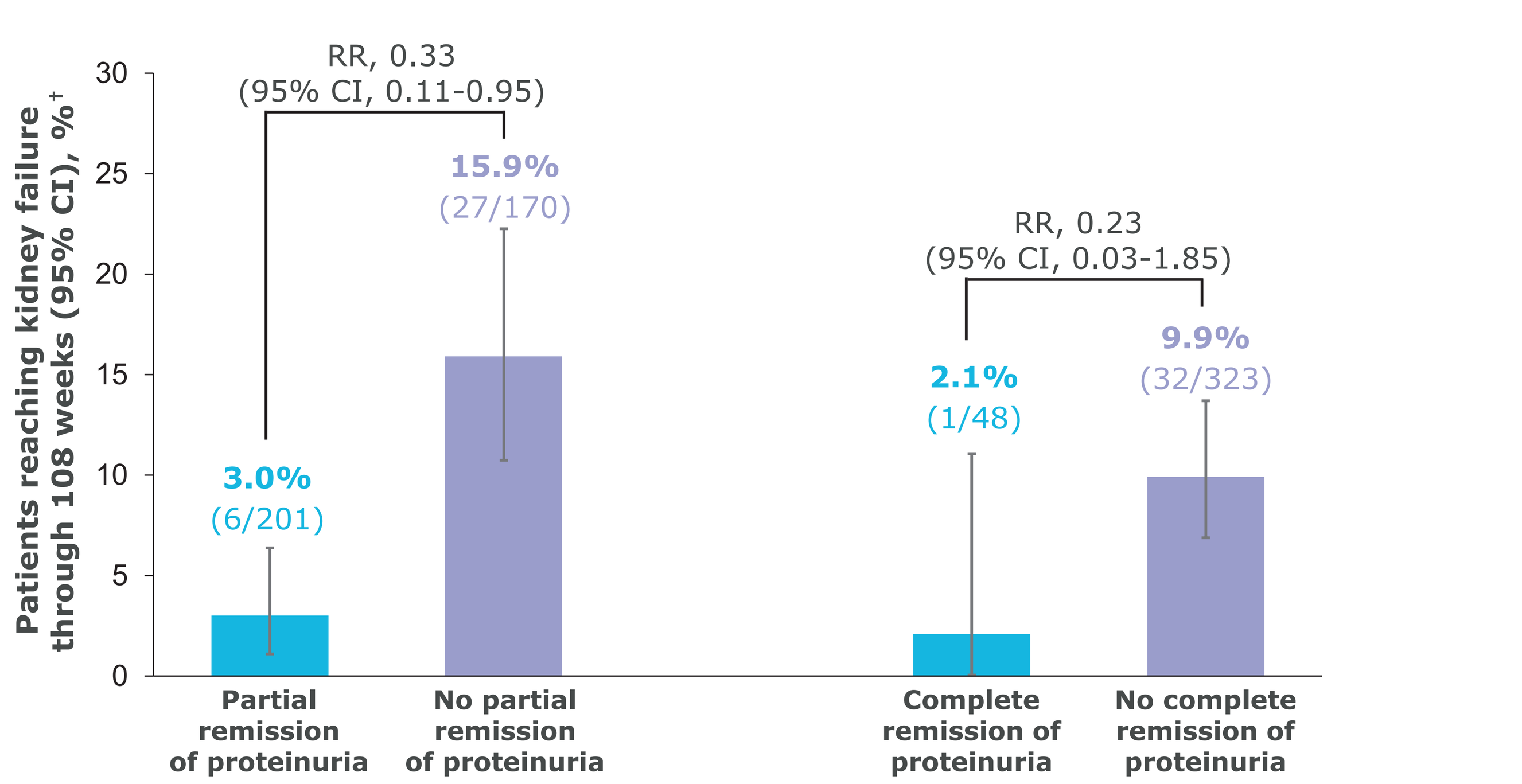
Figure 3. Probability of Achieving Complete Remission of Proteinuria Through 108 Weeks



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

- Irrespective of treatment arm, patients who achieved partial or complete remission of proteinuria were less likely to reach kidney failure vs those who did not

Figure 4. Probability of Reaching Kidney Failure Through 108 Weeks*



*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.

- 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

Table 2. Adverse Events

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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ABBREVIATIONS

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **eGFR**, estimated glomerular filtration rate; **FSGS**, focal segmental glomerulosclerosis; **NE**, not estimable; **RASi**, renin-angiotensin system inhibitor; **RR**, relative risk; **SD**, standard deviation; **SOC**, standard of care; **TEAE**, treatment-emergent adverse event; **ULN**, upper limit of normal; **UPCR**, urine protein-to-creatinine ratio.

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DISCLOSURES

JT reports grants and/or consulting fees from Akebia Therapeutics, Alexion Pharmaceuticals, Argenx, AstraZeneca, Aurinia Pharmaceuticals Inc., Biogen 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; and advisory board or speak bureau participation for Alexion Pharmaceuticals, Otsuka Pharmaceuticals, Vera Therapeutics, and Vertex Pharmaceuticals. **VT** reports consulting fees and/or honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Calliditas Therapeutics, GSK, Eli Lilly, Novartis, Otsuka Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics; and clinical trial steering committee membership for Calliditas Therapeutics, Novartis, Otsuka Pharmaceuticals, Travere Therapeutics, Inc., and Vera Therapeutics. **HT** reports grants and/or consulting fees from AstraZeneca, Bayer, BioCryst Pharmaceuticals, Biogen Inc., Calliditas Therapeutics, Chinook Therapeutics, Dimerix, George Clinical, Novartis, Omeros, Otsuka Pharmaceuticals, Takeda Pharmaceuticals, Timberlyne Therapeutics, Travere Therapeutics, Inc., and Vera Therapeutics; honoraria and/or travel support from AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, George Clinical, Novartis, and Travere Therapeutics, Inc.; and data safety monitoring or advisory board participation for AstraZeneca, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Novartis, and Travere Therapeutics, Inc. **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. **ERG** reports non-financial 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.

ACKNOWLEDGMENTS

This study was funded by Travere Therapeutics, Inc.

Medical writing support was provided under the direction of the authors by Taryn Ralph, PhD, and CJ Henley-Smith, PhD, of Nucleus Global, an Inizio company, in accordance with Good Publication Practice guidelines, and was funded by Travere Therapeutics, Inc.

The authors thank all the patients, families, and investigators who made this study possible.

Presented at the National Kidney Foundation (NKF) Spring Clinical Meetings 2025; April 10-13, 2025; Boston, MA, USA

MA-SP-25-0044 04/2025

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