HTA306

Surrogate Endpoints in German Health Technology Assessment: *Post Hoc* Analyses of the Phase III PROTECT Study Highlights the Efficacy of Sparsentan in Slowing Down the Loss of Kidney Function in IgAN Patients

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Introduction

Immunoglobulin A nephropathy (IgAN) is a rare kidney disease with poor prognosis and high unmet medical need. Sparsentan (SPAR) is the first EMA approved non-immunosuppressive therapy for IgAN. SPAR's positive effects on proteinuria and estimated glomerular filtration rate are clinically relevant. However, those biochemical endpoints are not recognized as patient relevant in the German health technology assessment (HTA) process. Here we demonstrate that SPAR prevents patients from entering the chronic kidney disease (CKD) stage 4 or 5. A *post hoc* analysis that led to the recognition of an evidence based "additional benefit" in Germany's HTA.

Methods

The randomized, double-blind, active-controlled, multicenter Phase III PROTECT[1] study examined the efficacy and safety of SPAR (n=202) vs. maximum-labeled dose IRB (n=202) in adult patients with biopsy-proven IgAN over 110 weeks (Figure 1). As a study inclusion criterion, patients had to have CKD stage 1-3 at screening. However, some patients progressed to CKD stage 4 prior to baseline visit (SPAR: n=15, IRB: n=5). We analyzed the proportion of patients who progressed to CKD stage 4 or 5 by Week 110 and the time to progress to CKD stage 4 or 5. The entire study population (CKD 1-4) as well as patients with CKD stages 1-3 at baseline (CKD 1-3) were analyzed.

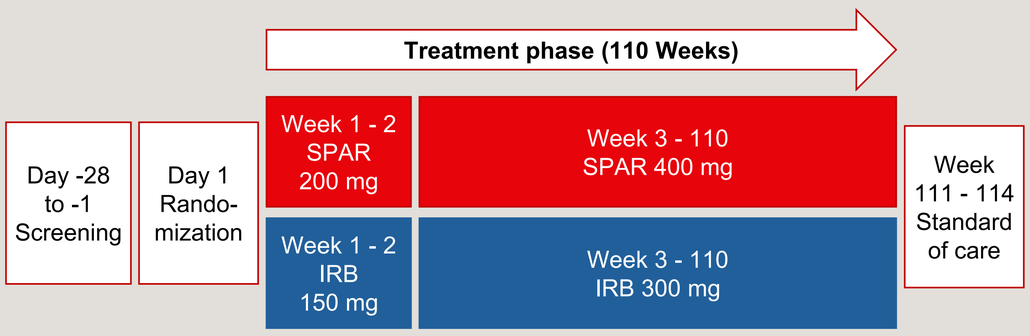

Figure 1: Study design of the Phase III PROTECT[1] study.

Conclusions

SPAR significantly slowed renal function decline, reducing progression to CKD stage 4 or 5. These findings underscore the overall randomized clinical trial and the importance of clinically relevant endpoints. The German HTA process should consider surrogate endpoints for CKD as patient relevant as they reflect critical diagnostic and prognostic indicators to derive an additional benefit.

Results

In the Phase III PROTECT[1] study, SPAR demonstrated a greater decrease in proteinuria and improved preservation of eGFR compared to IRB. By slowing disease progression, SPAR treatment thus achieved a key therapeutic goal in the management of patients with IgAN.

Table 1: Patients with CKD stage 4 or 5 by Week 110.

CKD stages at baseline	Progression to CKD stage 4 or 5		Patients with CKD stage 4 or 5	Time to progress to CKD stage 4 or 5
	SPAR n/N (%)	IRB n/N (%)	RR* [95 % CI] p-value	HR** [95 %-CI] p-value
CKD 1-4	47/202 (23.3)	65/202 (32.2)	0.731 [0.555; 0.964] **0.026**	0.666 [0.458; 0.971] **0.034**
CKD 1-3	43/187 (23.0)	65/197 (33.0)	0.735 [0,558; 0,969] **0.029**	0,672 [0,457; 0,989] **0.044**

* RR and p-value were derived by a log binomial model with factors treatment and randomization strata. ** HR and p-value were derived by a Cox proportional model with factors treatment and randomization strata.

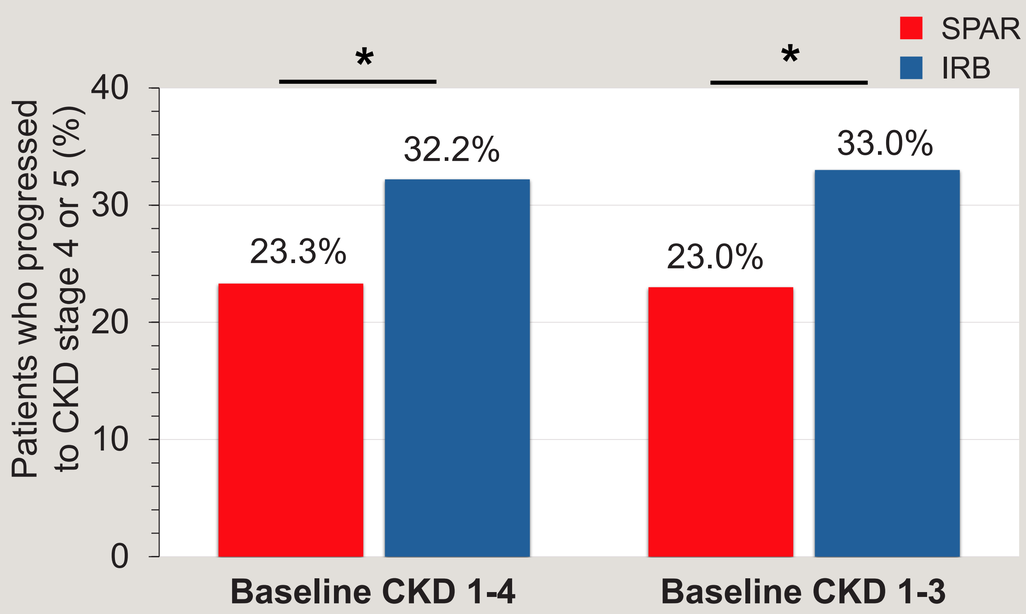

Figure 2: Percentages of patients who progressed to CKD stage 4 or 5 by Week 110.

Significantly fewer patients treated with SPAR progressed to CKD stage 4 or 5 compared to IRB. This benefit of SPAR treatment was shown for patients with CKD stages 1-4 as well as for patients with CKD stages 1-3 at baseline (Table 1, Figure 2). Moreover, the time to progress to CKD stage 4 or 5 was significantly longer under SPAR treatment indicating a reduced risk to progress to CKD stage 4 or 5 by 33.4% (CKD 1-4: HR=0.666) and 32.8% (CKD 1-3: HR=0.672) (Table 1).

REFERENCES: [1] Rovin B. et al. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. Lancet. 2023 Dec 2;402(10417):2077-2090. doi: 10.1016/S0140-6736(23)02302-4. **DISCLOSURES:** The PROTECT study was sponsored by Travere Therapeutics. *Post hoc* analyses were sponsored by Vifor Pharma Deutschland GmbH. Jürgen Floege received consulting fees from Vifor Pharma Deutschland GmbH. Matthias Roll, Thomas Hardt, and Amadeus Gladbach are full-time employees of Vifor Pharma Deutschland GmbH. **ACKNOWLEDGEMENT:** Medical writing assistance and editorial support was provided by Johanna Müller and Saskia Carstensen-Aurèche of Cencora, financed by Vifor Pharma Deutschland GmbH.