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Title [all caps; not counted]
SPARSENTAN REDUCES PROTEINURIA IN PATIENTS WITH IMMUNOGLOBULIN A NEPHROPATHY (IGAN): INTERIM RESULTS OF THE PROTECT STUDY

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Introduction: [886 characters+spaces]
IgAN is the most common glomerular disease worldwide. Despite optimized standard of care treatment, up to 40% of individuals with IgAN develop kidney failure requiring dialysis or kidney transplantation, consequently seriously affecting their quality of life and mortality. Treatments that reduce proteinuria and risk of kidney disease progression are urgently needed for IgAN. Sparsentan is a novel, orally active, single molecule that is a dual endothelin and angiotensin receptor antagonist being investigated for IgAN and focal segmental glomerulosclerosis. The Phase 3 PROTECT study is examining the long-term antiproteinuric and nephroprotective potential and safety of sparsentan compared with an active control, angiotensin receptor blocker (ARB) irbesartan, in adults with IgAN. Reported here are the PROTECT pre-specified interim primary efficacy endpoint and safety outcomes.

Methods: [1463 characters+spaces]
PROTECT is an ongoing, global, Phase 3, multicenter, randomized, double-blind, parallel-group, active controlled study designed to evaluate the efficacy and safety of sparsentan versus the active control irbesartan in adults with IgAN with overt proteinuria despite receiving maximized treatment with an angiotensin converting enzyme inhibitor (ACEi) and/or ARB. The study duration is 270 weeks (double-blind period of 114 weeks; open-label extension period up to

156 weeks). Adult patients with biopsy-proven IgAN (excluding IgAN secondary to another condition or IgA vasculitis), urine protein excretion value ≥1.0 g/day, eGFR ≥30 mL/min/1.73m^2, systolic/diastolic blood pressure ≤150/≤100 mmHg, and on a stable dose of ACEi and/or ARB therapy for at least 12 weeks prior to screening that is both the patient's maximum tolerated dose and at least one-half of the maximum labeled dose were eligible for inclusion. Patients took their last ACEi and/or ARB dose the day before randomization. Patients were randomized 1:1 to sparsentan or irbesartan (target dose 400 and 300 mg/day, respectively), stratified by screening eGFR and urine protein excretion values. The pre-specified interim primary efficacy endpoint of change from baseline in urine protein/creatinine ratio (UP/C, based on a 24-hour urine sample) at Week 36 was analyzed using a mixed model repeated measures analysis. The safety evaluation included assessment of treatment emergent adverse events.

Results: [614 characters+spaces]
A total of 671 patients were screened; 406 patients from clinical sites in 18 countries, including sites in North America, Europe, and Asia Pacific, met eligibility criteria and were enrolled and randomized into PROTECT. Two randomized patients withdrew from the study prior to initiating study treatment. The 404 randomized patients who received study drug were included in the primary analysis population. The mean reduction in UP/C from baseline at 36 weeks was significantly greater in the patients who received sparsentan (-49.8%) versus irbesartan (-15.1%, P<0.0001). Sparsentan was generally well-tolerated.

Conclusion: [411 characters+spaces]
The interim results of the PROTECT study show that in adult patients with IgAN and persistent proteinuria above 1 g/day despite being treated with ACEis and/or ARBs, once-daily treatment with sparsentan compared to irbesartan produces a robust and clinically meaningful reduction in proteinuria. The safety of sparsentan was comparable to previous studies in FSGS and no new drug-related safety signals emerged.

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