FILSPARI® (sparsentan)

Baseline Characteristics of Asian vs Non-Asian Patients in the PROTECT Study

Summary

Background

- Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors[1-3]
- Enrollment of a diverse population of different races, geographical regions, and severity of CKD can elucidate the effectiveness of sparsentan in high-risk patients of varying characteristics[4,5]

Study Data

The labeling data that follows is from the post-hoc analysis, which was limited to fewer patients (the first 281 randomized patients), with follow-up only to 36 weeks. It also includes patients who never started treatment and data after discontinuing treatment.

- The effect of FILSPARI on proteinuria was assessed in a randomized, double-blind, active-controlled, multicenter, global study (PROTECT) in adults with biopsy-proven IgA nephropathy. The primary endpoint was the relative change from baseline in UPCR at Week 36[6]
- After 36 weeks of treatment, patients receiving FILSPARI achieved a mean reduction in UPCR from baseline of 45%, compared to a mean reduction in proteinuria from baseline of 15% for irbesartan-treated patients (P<0.0001). The treatment effect on UPCR at Week 36 was consistent across subgroups such as age, gender, race, and baseline eGFR and proteinuria levels[6]

The efficacy data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

- In the PROTECT study, after 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a mean reduction in proteinuria from baseline of 15.1% for irbesartan-treated patients (P<0.0001)[7]
- Asian and non-Asian study participants were found to differ on a number of baseline characteristics. Patient groups from Asian regions included more females and fewer patients with a history of hypertension and baseline hypertensive medication use compared with patients from non-Asian regions[5]
- Key measures of kidney function, proteinuria, and eGFR were similar between Asian and non-Asian patients in PROTECT[4,5]

Background

Sparsentan is a novel, first-in-class, and the only single molecule antagonist of the ET_A and AT_1 receptors.[1-3] Preclinical studies in rodent models of chronic kidney disease have shown that blockade of both ET_A and AT_1 pathways reduces proteinuria, protects podocytes, and prevents glomerulosclerosis and mesangial cell proliferation.[8-10]

The PROTECT Study

The PROTECT study (NCT03762850) is a phase 3, global, randomized, multicenter, double-blind, parallel-arm, active-controlled clinical trial evaluating long-term antiproteinuric and nephroprotective efficacy and safety of 400 mg of sparsentan compared to 300 mg of irbesartan.[4] The study includes 404 patients ages 18 years and older with biopsy proven IgA nephropathy who experience persistent proteinuria despite available ACEi or ARB therapy. Patients with urine protein ≥1 g/day at screening, eGFR ≥30 mL/min/1.73 m^2, SBP ≤150 mm Hg, and DBP ≤100 mm Hg were eligible.[11] The PROTECT study protocol provides for an unblinded interim analysis of at least 280 patients to be performed after 36 weeks of treatment to evaluate the primary efficacy endpoint, defined as change in proteinuria (UPCR) at Week 36 from baseline. Secondary efficacy endpoints include the rate of change in eGFR following the initiation of randomized treatment over 58-week and 110-week periods, as well as rate of change in eGFR over 52-week and 104-week periods following the first 6 weeks of randomized treatment.[11,12] The PROTECT study also examines change from baseline in UACR based on a 24-hour urine sample at Week 36, and prespecified exploratory endpoints of complete (urinary protein excretion <0.3 g/day) and partial (urinary protein excretion <1.0 g/day) proteinuria remission at least once at any time during the double-blind period. In addition, this study evaluates the proportion of patients in each group reaching a confirmed 40% reduction in eGFR from baseline, KF, or all-cause mortality. KF is defined as initiation of KRT or sustained eGFR value of <15 mL/min/1.73 m^2.[7] Reduction in proteinuria and decline in rate of eGFR are largely accepted as surrogate markers of treatment effect in studies of KF.[7,13]

Baseline characteristics of Asian and non-Asian patients were further described, including demographic attributes, laboratory values, medication use, and parameters of kidney function.[5]

Study Data

The PROTECT Study

The efficacy data that follows is from the pre-specified primary analysis reported at the interim assessment, which includes proteinuria data from all 404 randomized and treated patients in the PROTECT clinical trial at the time of the analysis.

The PROTECT study includes a double-blind period of 114 weeks, after which patients can enter an OLE for up to 156 weeks, for a maximum of 270 weeks.[12] Interim analysis of the PROTECT study found that after 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a mean reduction in proteinuria from baseline of 15.1% for irbesartan-treated patients (P<0.0001).[7]

Randomized patients who received study drug were recruited from both Asian (n=74, 18%) and non-Asian (n=330, 82%) regions. Additionally, baseline characteristics were compared between persons of Asian and non-Asian race, regardless of region. All patients recruited from Asian regions were of Asian race and 13% of patients recruited from non-Asian regions were of Asian race.[5]

Baseline Demographic Characteristics

Patients from Asian and non-Asian regions (regardless of race) were comparable on several demographic characteristics. Numerical differences between Asian and non-Asian patients (regardless of region) were identified (**Table 1**).[4,5]

- There was a higher percentage of male (58%) vs female (42%) patients in Asian regions. In non-Asian regions, the percentage of Asian females (52%) was higher than that of Asian males (48%)
- History of diabetes was higher in Asians from non-Asian regions compared to non-Asians from these regions
- History of hypertension, baseline BP, and BMI were lower in Asians from both Asian and non-Asian countries compared to non-Asians
- Asians from Asian countries were older at time of IgA nephropathy diagnosis compared to patients of all races from non-Asian countries

Table 1. Baseline Demographic Characteristics and Relevant Medical History by Asian and Non-Asian Race Within Geographic Regions

Characteristic	Asian Geographic Regions	Non-Asian Geographic Regions		
	Asian Race (n=74)	Overall (n=330)	Asian Race (n=42)	Non-Asian Race (n=288)
Age at informed consent, years, median (IQR)	49 (40-56)	46 (36-56)	46 (38-57)	46 (36-56)
Sex, n (%)				
Male	43 (58)	239 (72)	20 (48)	219 (76)
Female	31 (42)	91 (28)	22 (52)	69 (24)
Age at IgAN diagnosis, years, median (IQR)*	42 (33-51)	38 (29-49)	37 (31-46)	38.0 (29-49)
Time from initial kidney biopsy to informed consent, years, median (IQR)†	3.0 (1.0-9.0)	4.0 (1.0-10.0)	4.5 (2.0-9.0)	4.0 (1.0-10.0)
History of diabetes, n (%)	8 (11)	35 (11)	6 (14)	29 (10)
History of hypertension, n (%)	43 (58)	266 (81)	26 (62)	240 (83)
Blood pressure, mmHg, mean±SD				
Systolic	124±14	130±13	125±10	131±13
Diastolic	80±11	83±11	81±9	83±11
BMI, kg/m², mean±SD	27±5	29±6	28±5	29±6

Asian geographic regions include Hong Kong, Taiwan, and South Korea. Non-Asian geographic regions include all other countries. For patients who selected multiple races, if one of the races was Asian, the patient was included as Asian. All patients enrolled from Asian regions were of Asian race.
*Age at IgAN diagnosis is derived based on the year of IgAN diagnosis and year of birth.
†Time from initial biopsy is derived based on the year of the initial kidney biopsy and year of signed informed consent.

Baseline Laboratory Parameters

Patients from Asian and non-Asian regions (regardless of race) were comparable on several key lab values and liver function parameters at baseline.[5] Key measures of kidney function, proteinuria, and eGFR were similar in Asian and non-Asian patients.[4,5]

Numerical differences were identified between Asian and non-Asian patients (regardless of region).[5]

- Some laboratory parameters were lower in Asians from both Asian and non-Asian regions[5]
  - Nephrotic range proteinuria
  - Urinary albumin excretion
  - Hemoglobin
  - Serum creatinine
  - Hematuria/microscopic hematuria
  - Urine sodium
- LDL cholesterol was lower in Asians from Asian countries compared to all patients from non-Asian countries. However, LDL cholesterol was higher in Asians from non-Asian regions compared to the overall patient sample[5]
- Despite differences in total and LDL cholesterol in the regional comparison, there were no apparent differences in lipid profile when comparing Asian vs non-Asian patents within the non-Asian geographic regions[5]

Medication Use

Regional differences between groups were also found in baseline medication use.[5]

- Asian patients in non-Asian regions had higher percentages of ACEi-only or ACEi plus ARB use, MLD of ACEi or ARB, and diuretics compared to patients in Asian regions
- Conversely, Asian patients in non-Asian regions showed lower use of ARB-only, antihypertensives, beta-blockers, alpha-blockers, calcium channel blockers, and lipid-lowering medications compared to patients in Asian regions

Differences between Asian and non-Asian patients were further identified, regardless of region.[5]

- Compared to non-Asians, Asian patients had lower use percentages of ACEi-only, ACEi plus ARB, antihypertensives, diuretics, and beta-blockers
- Asian patients had a higher proportion of use of ARB-only and lipid-lowering medications

Impact of Asian Ethnicity on Long Term Outcomes in IgA Nephropathy

The UK National Registry of Rare Kidney Diseases (RaDaR) includes a cohort of patients with IgA nephropathy (2299 adults, 140 children), with 228 patients (9%) of Asian ethnicity. Follow up of the IgA nephropathy sample (median 5.9 years) identified generally poor outcomes, with most patients progressing to kidney failure within 10-15 years.[14] Asian ethnicity was found to be a significant risk factor for disease progression in both univariable (HR=1.26; *P*=0.02) and multivariable (HR=1.36; *P*=0.002) analyses. Overall, Asian patients had significantly poorer 10-year survival rates and more rapid eGFR loss compared to White patients.[15]

Asian Ethnicity as a Predictor of Adverse Kidney Disease Events

A study of health records data from the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry at Providence and UCLA Health systems examined predictors of MAKDE among patients with IgA nephropathy (N=1105). Asian race was a significant predictor for adverse kidney events, with a HR (95% CI) of 1.51 (1.00-2.27); *P*=0.048.[16]

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT_1, angiotensin II type 1; BMI, body mass index; BP, blood pressure; CURE-CKD, Center for Kidney Disease Research, Education, and Hope; eGFR, estimated glomerular filtration rate; ET_A, endothelin-1 type A; HR, hazard ratio; IgA, immunoglobulin A; IgAN, IgA nephropathy; IQR, interquartile range; ISAS, interim sensitivity analysis set; KF, kidney failure; KRT, kidney replacement therapy; LDL, low-density lipoprotein; MAKDE, major adverse kidney disease events; MLD, maximum labeled dose; NDA, new drug application; OLE, open-label extension; PAS, primary analysis set; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; UACR, urine albumin-creatinine ratio; UCLA, University of California, Los Angeles; UPCR, urine protein-creatinine ratio.

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