PROTECT in Immunoglobulin A Nephropathy (IgAN): Study Design of a Phase 3, Randomized, Double-blind, International, Active-controlled Study of the Efficacy and Safety of Sparsentan

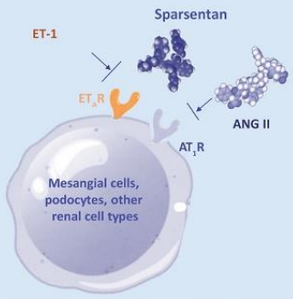
Jonathan Barratt, PhD[1]; Brad Rovin, MD[2]; Kevin Carroll, PhD[3]; Rosanna Coppo, MD[4]; Ulysses Diva, PhD[5]; Richard Lafayette, MD[6]; Francesco Locatelli, MD[7]; Bart Maes, MD, PhD[8]; Alex Mercer[9]; Vlado Perkovic, MBBS, PhD, FRACP, FASN[10]; Manuel Praga, MD[11]; Pierre-Louis Tharaux, MD, PhD[12]; James Tumlin, MD[13]; Radko Komers, PhD, MD[5]

[1]University of Leicester & Leicester General Hospital, Leicester, UK; [2]The Ohio State University Wexner Medical Center, Columbus, OH, USA; [3]KJC Statistics Ltd, Cheshire, UK; [4]Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy; [5]Retrophin, Inc., San Diego, CA, USA; [6]Stanford University Medical Center, Stanford, CA, USA; [7]Ospedale Alessandro Manzoni, ASST Lecco, Lecco, Italy; [8]AZ Delta, Roeselare, Belgium; [9]Consultant to Retrophin, Inc., San Diego, CA, USA; [10]The George Institute for Global Health, Sydney, Australia; [11]Hospital 12 de Octubre, Madrid, Spain; [12]Paris Cardiovascular Centre-PARCC, French Institute of Health and Medical Research – Inserm, Paris, France; [13]Emory University, Atlanta, GA, USA

Introduction

- Renin-angiotensin-aldosterone system inhibitors (RAASIs) have been associated with a reduction in proteinuria and improvement in kidney function in patients with immunoglobulin A nephropathy (IgAN)[1,2]
- The Kidney Disease: Improving Global Outcomes guidelines recommend antiproteinuric and antihypertensive therapy through renin-angiotensin system blockade as first-line therapy for IgAN patients with proteinuria >1 g/day[3]
- Despite optimized RAASI therapy, 20-40% of patients progress to end-stage renal disease (ESRD) within 20 years[4]
- There is an unmet need for efficacious and well-tolerated medications for patients with IgAN who remain at risk for ESRD despite optimized treatment with RAASIs[4,5]
- Sparsentan (**Figure 1**) is a first-in-class, orally active, dual-acting selective antagonist of angiotensin II Type 1 and endothelin type A receptors in development for treatment of glomerular diseases,[5,6] including IgAN and focal segmental glomerulosclerosis[7-9]

Figure 1. Sparsentan: dual mechanism of action[5,6]



ANG II = angiotensin II; AT_1R = angiotensin II Type 1 receptor; ET-1 = endothelin 1; ET_AR = endothelin type A receptor.

Objectives

- **Efficacy:** To determine the effect of sparsentan on proteinuria and renal function, as compared with an angiotensin receptor blocker (ARB), in patients with IgAN
- **Safety:** To assess the safety and tolerability of sparsentan by double-blind monitoring of safety endpoints

Methods

Patient Selection

- Key inclusion and exclusion criteria are shown in **Table 1**

Table 1. Key inclusion and exclusion criteria

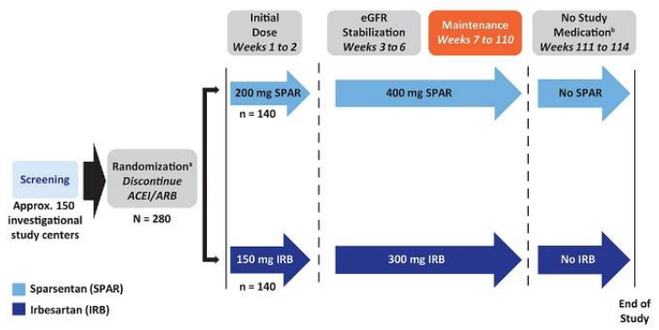
Key Inclusion Criteria	Key Exclusion Criteria
• Patients aged ≥18 years • Biopsy-proven primary IgAN • Urine total protein ≥1.0 g/day • eGFR ≥30 mL/min/1.73 m² • ACEI and/or ARB therapy for ≥12 weeks at a stable maximum tolerated dose and at least one-half of the maximum dose according to local approved labeling • SBP ≤150 mm Hg and DBP ≤100 mm Hg and managed according to standard of care	• Patients with IgAN secondary to another condition • Presence of cellular crescents in >25% of glomeruli on renal biopsy within 6 months prior to screening • Use of systemic immunosuppressive medications for >2 weeks within 3 months of screening • Potassium >5.5 mEq/L • Significant medical conditions related to cardiac, hepatic, or immune function • Documented history of heart failure • Type 1 diabetes mellitus, uncontrolled type 2 diabetes mellitus, or nonfasting blood glucose >180 mg/dL • Hematocrit <27% or hemoglobin <9 g/dL

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; IgAN = immunoglobulin A nephropathy; SBP = systolic blood pressure.

Study Design

- PROTECT in IgAN is a global, phase 3, randomized, multicenter, double-blind, parallel-group, active-controlled study of the efficacy and safety of sparsentan for the treatment of IgAN
- Eligible patients are randomized to receive an initial dose of sparsentan 200 mg or active control (irbesartan 150 mg) upon discontinuation of prior angiotensin-converting enzyme inhibitor (ACEI) and/or ARB therapy (**Figure 2**)

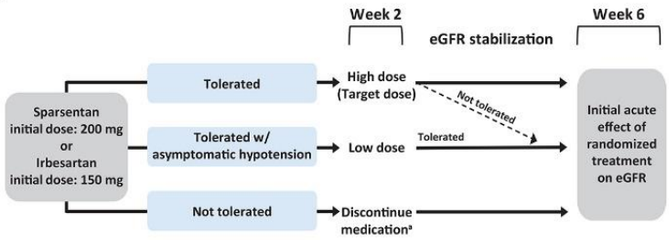
Figure 2. PROTECT in IgAN study design



[a]On Day 1, patients will be randomized 1:1 to SPAR or IRB, stratified by eGFR (30 to <60 mL/min/1.73 m² and ≥60 mL/min/1.73 m²) and total urine protein (≤1.75 g/day and >1.75 g/day).
[b]Patients will resume standard-of-care treatment including RAASIs (excluding irbesartan).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; eGFR = estimated glomerular filtration rate; IgAN = immunoglobulin A nephropathy; IRB = irbesartan; RAASI = renin-aldosterone-angiotensin system inhibitor; SPAR = sparsentan.

- The target dose of sparsentan 400 mg or irbesartan 300 mg will be titrated at Week 2 (**Figure 3**)
  - Patients who tolerate the initial dose but show asymptomatic blood pressure values ≤100/60 mm Hg or present with orthostatic hypotension at Week 2 will continue the initial dose
  - Patients who cannot tolerate the initial dose at Week 2 may discontinue the study medication

Figure 3. Blinded dose titration



Note: Dose tolerance was defined as SBP >100 mm Hg and DBP >60 mm Hg after 2 weeks and no AEs (eg, worsening edema) or abnormal laboratory findings (eg, serum potassium >5.5 mEq/L).
[a]Patients who do not tolerate the initial dose will be encouraged to restart study medication throughout the study. Patients who do not tolerate study medication should continue in the study even if they permanently discontinue study medication.
AEs = adverse events; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure.

- Decreases in target dose and titrations up to the target dose are permitted at any time
- Additional treatment for hypertension is encouraged during the study, excluding the use of ACEIs, ARBs, aldosterone blockers, and aliskiren
- Study visits are conducted at 2, 4, 6, and 12 weeks after randomization, and at approximately 12-week intervals thereafter
- Efficacy and safety endpoints are shown in **Table 2**. Study medication will be discontinued at Week 110, and patients will continue to be followed on an intent-to-treat basis to Week 114
- Proteinuria and estimated glomerular filtration rate (eGFR) will be assessed at scheduled visits during treatment and at Week 114 (4 weeks off treatment)

Table 2. Efficacy and safety endpoints

Efficacy Endpoints	Safety Endpoints
• Primary – Change in UP/C from baseline at Week 36 (based on a 24-hour urine sample) • Key secondary – Rate of change in eGFR over 52-week period (from Week 6 to Week 58) – Rate of change in eGFR over 104-week period (from Week 6 to Week 110) – Change in eGFR from baseline to 4 weeks post-cessation of randomized treatment (Week 114)	• Incidence of TEAEs • Changes from baseline in: – Body weight – Vital signs – Physical examinations – Peripheral edema – Clinical laboratory parameters

eGFR = estimated glomerular filtration rate; TEAEs = treatment-emergent adverse events; UP/C = urine protein/creatinine ratio.

Conclusions

- The PROTECT in IgAN trial is a pivotal phase 3 study that is expected to provide important evidence regarding the antiproteinuric effects of sparsentan and its potential utility in slowing eGFR deterioration
- The study will also include evaluation of the safety profile of sparsentan in patients with IgAN
- If data are positive, the study will allow for registration of sparsentan for the treatment of IgAN
- Enrollment is anticipated to begin in Q4 2018

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Disclosures

Jonathan Barratt, PhD, is an employee of the University of Leicester; holds consultancy agreements with Ablynx, Anthera Pharmaceuticals, Inc., EMD Serono, Omeros, PharmaLink, and Retrophin, Inc.; has received research funding from Anthera Pharmaceuticals and honoraria from UCB Celltech; and is a member of the Editorial Boards of *Kidney International* and *Clinical Science*.

Brad Rovin, MD, Kevin Carroll, PhD, Rosanna Coppo, MD, Manuel Praga, MD, Pierre-Louis Tharaux MD, PhD, and James Tumlin, MD, have a consulting service agreement with Retrophin, Inc.

Radko Komers, PhD, MD, and Ulysses Diva, PhD, are employees of Retrophin, Inc.; may have an equity or other financial interest in Retrophin, Inc.

Richard Lafayette, MD, has a consulting service agreement with and has received personal fees as a member of an advisory board for Retrophin, Inc.; has received grants and personal fees from Mallinckrodt, Inc., Omeros, Calliditas Therapeutics, and Rigel Pharmaceuticals; has received a grant from Pfizer; and has been issued a patent for "Use of Biomarkers in IgA Nephropathy."

Francesco Locatelli, MD, has a consulting service agreement with and is a member of an advisory board for Retrophin, Inc.

Bart Maes, MD, PhD, has a consulting service agreement with Retrophin, Inc., and holds a national leadership role in the GSK Ascend-ND and Ascend-D trails.

Alex Mercer is a consultant to Retrophin, Inc.

Vlado Perkovic, MBBS, PhD, FRACP, FASN, has a consulting service agreement with Retrophin, Inc., and has received personal fees for advisory boards or scientific presentations from Retrophin, Inc., Janssen, Merck, and Servier; he has served on steering committees for trials funded by Abbvie, Boehringer Ingelheim, GSK, Janssen, and Pfizer; and participated in scientific presentations/advisory boards with Abbvie, Astellas, AstraZeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GSK, Novartis, Novo Nordisk, Pfizer, PharmaLink, Relypsa, Sanofi, and Vitae, with fees paid to his institution.

Writing and editorial support for this poster was provided by Kristen W. Quinn, PhD, of Peloton Advantage, LLC, and was funded by Retrophin, Inc.

Presented at the 15th International Symposium on IgA Nephropathy, September 27–29, 2018, Buenos Aires, Argentina