Phase 1/2 Trial of PS-002, an AAV-based Therapy Delivering the Complement Factor I Gene to Podocytes in IgA nephropathy

Pille Harrison[1], Richard Layfayette[2], Smeeta Sinha[3], Ian Roberts[4], Moin Saleem[5], Charlotte J Smerdon[1], Alicia Rowland[1], Fredrik Erlandsson[1], Jonathan Barratt[6]

Introduction

IgA nephropathy (IgAN) is a chronic, progressive autoimmune disease. Data from the UK Registry of Rare Kidney Diseases show that most adults have a considerable lifetime risk of developing kidney failure, based on a young age at presentation and established impaired kidney function at the time of diagnosis(1).

Recent drug development in IgAN has seen major advancements in addressing chronic kidney disease and immunological dimensions. Next to systemic approaches, a medical need remains to target the disease-specific processes locally.

PS-002 Mechanism of Action

Systemic complement inhibition has demonstrated clinical benefit in IgAN, coincidentally requiring vaccinations against infections with encapsulated bacteria(2). PS-002 is a gene therapy designed to deliver a transgene encoding for human complement factor I (hCFI) into podocytes, resulting in local production of CFI in glomeruli and subsequent amelioration of glomerular complement activation.

In the grouped ddY mouse model of IgAN, a PS-002 analogue clears glomerular C3 deposition and improves histopathological characteristics including fibrosis. In pigs, administration of PS-002 results in the highly localised expression of hCFI within glomeruli in the kidney cortex.

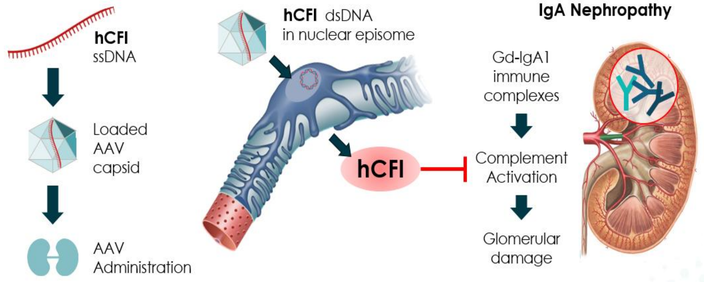

Figure 1. PS-002 modulates complement activation locally

Study Design and Methodology

Here we describe the design and methodology for the phase 1/2 study in adult primary IgAN patients (NCT07182227).

Primary objective
To assess safety and tolerability of PS-002 in study participants with IgAN

Key secondary objective
To evaluate the effect of PS-002 in IgAN study participants on proteinuria reduction at prespecified timepoints

Secondary objectives
Includes measurement of the effect of PS-002 on key biochemistry and complement parameters, evaluation of the progression of IgAN based on clinical events, evaluation of the impact on quality of life and immune responses to AAV

Exploratory objectives
Includes histopathology, complement, clinical and general safety assessments

Participant eligibility

Inclusion:

- Adult participant with a diagnosis of primary IgAN
- A kidney biopsy with ongoing complement system activity
- UPCR at least 1g/g
- SBP < 140mmHg, DBP <90
- eGFR (CKD-EPI) at least 45 ml/min/1.73m^2 etc

Exclusion:

- Presence of nephrotic syndrome
- History of malignancy or bone marrow or organ transplant
- Washout required from immunosuppressive treatments

Study overview

Part 1 will consist of up to 3 dose escalation cohorts with a minimum of 3 evaluable participants in each cohort.

Part 2 will consist of dose expansion with up to 20 participants evaluated at a biologically optimal dose.

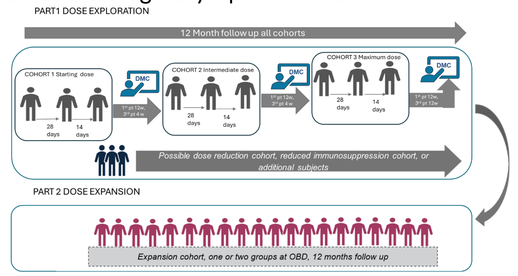

Figure 2. Study schematic

Study key assessments

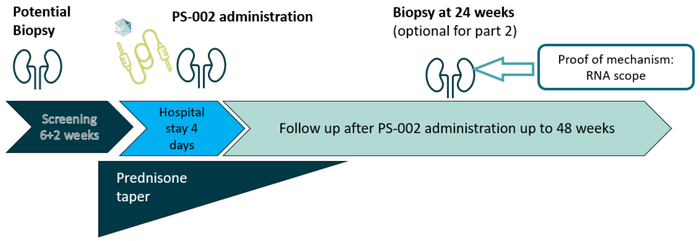

Figure 3. Time course for assessments

References

Pitcher et al. CJASN 2023 1;18(6):727–738;
Percovic et al. NEJM 2025; 392(6): 532–543

[1] *Purespring Therapeutics Ltd,* [2] *Stanford University Medical Center,* [3] *Salford Royal NHS Trust,* [4] *Cellular Pathology at the University of Oxford,* [5] *Bristol Children's Hospital,* [6] *University of Leicester*