ACTION (AT1R & CCR2 Targets for Inflammatory Nephrosis) Phase 2 Trial for Focal Segmental Glomerulosclerosis

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Background

DMX-200 is the adjunct therapy of propagermanium (organic germanium) and irbesartan for the treatment of patients with proteinuria

G-protein coupled receptors (GPCRs) are a large family of cell membrane receptors responsible for many physiological effects and are accordingly highly important drug targets. There is growing evidence that GPCRs function in complexes of two or more receptors called heteromers, with different pharmacology from the respective monomeric units. The cell-based Receptor-HIT assay (Dimerix Bioscience) identified a heteromer between GPCRs chemokine receptor 2 (CCR2) and angiotensin II receptor type 1 (AT1R) - both known to play roles in the kidney. Formation of the heteromer resulted in transactivation of the CCR2 receptor in response to AT1R activation, and dual agonist-mediated signaling from the complex was only fully reversed by treatment with antagonists for both receptors. Further, simultaneous inhibition with the organometallic small-molecule antagonist of CCR2, propagermanium, and the AT1R antagonist irbesartan in the subtotal nephrectomy rat model of focal segmental glomerulosclerosis (FSGS) led to decreased monocyte infiltration, lower proteinuria, reduced podocyte loss and prevention of renal injury independent of blood pressure. These data suggest a role for simultaneous inhibition of AT1R and CCR2 in proteinuric disease.

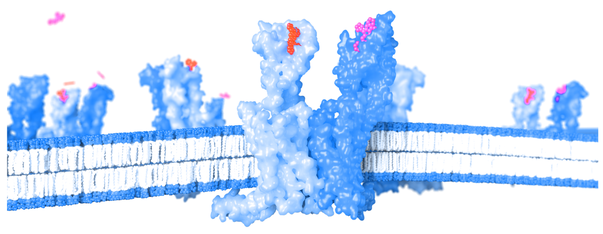

Figure 1: Cartoon of the CCR2 and AT1R heteromer, with ligands propagermanium (orange) and irbesartan (pink).

Use in patients with proteinuria

An initial Phase 2a trial in N=27 patients with proteinuria, showed more than 50% reduction in protein to creatinine ratios in n=6 patients

A prior open-label, Phase 2a study was designed to investigate the safety, tolerability and efficacy of escalating doses of propagermanium (30-240 mg/day) in patients with proteinuria already receiving stable irbesartan (75-300 mg) for at least 3 months prior to enrolment. This study enrolled N=27 patients with proteinuric chronic kidney disease, and showed simultaneous antagonism of AT1R with irbesartan and CCR2 with propagermanium over a period of 32 weeks was safe and well tolerated, with 25% of patients completing the study achieving a greater than 50% reduction in proteinuria.

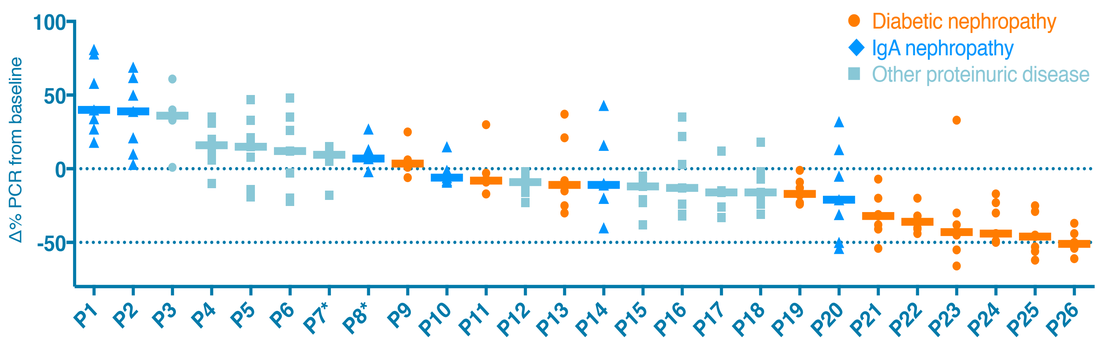

Figure 2: Individual patient (P1-P27) 24-hr PCR values (symbol) as % change from baseline value during treatment with stable irbesartan and increasing doses of propagermanium (30-240mg/day), ordered by median (line) PCR value. Primary renal diagnosis is denoted by symbol shape and color. * withdrawn. One patient not shown as no samples were collected between enrollment and withdrawal.

ACTION for FSGS Study Design

ACTION for FSGS is a prospective phase 2a crossover trial of propagermanium for patients with primary FSGS who are already receiving irbesartan

To determine the effect of combined inhibition of AT1R and CCR2 in patients with the aggressive glomerulonephropathy FSGS, approximately 10 patients with primary FSGS will be enrolled in this study. Patients must be receiving stable irbesartan 300 mg/day for a documented minimum of 3 months prior to and throughout the study including during the washout period. Eligible patients will then be randomised to treatment groups where they will receive propagermanium or placebo in alternate order.

The study consists of a screening visit and baseline assessment prior to randomisation, 2 treatment periods (each treatment period duration is 16-weeks) separated by a 6-week washout period and a follow up visit. Measurements of patient health and treatment efficacy, including blood and urine-based assessment of kidney function and biomarkers of inflammation will be performed. Total study duration is approximately 45 weeks.

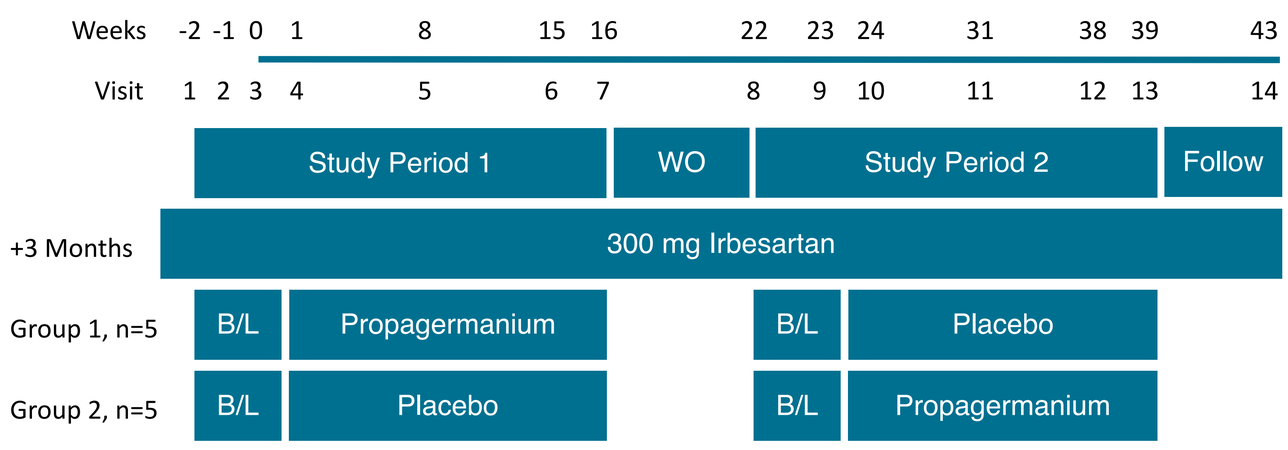

Figure 3: Schematic of study design. Abbreviations: B/L = baseline (1 week), WO = washout (6 weeks), Follow = follow up period (4 weeks after last dose of treatment)

Study Population

Key Inclusion Criteria

- Adults 18 – 80 years
- Primary FSGS by renal biopsy
- Stable irbesartan for 3-months (300 mg/d)
- If on ACE, aldosterone or SGLT2 inhibitors, dose must be stable for 3 months
- If receiving immunosuppressive medications inhibitors then must be stable for 3 months
- PCR ≥ 150 mg/mmol
- eGFR ≥ 25 mL/min/1.73 m^2
- Serum potassium < 5.5 mmol/L

Key Exclusion Criteria

- Has FSGS secondary to another condition
- Type 1 or 2 diabetes mellitus or non-fasting blood glucose > 10 mmol/L
- Prior organ or stem cell transplant
- Major adverse cardiac event within 6 months
- Lymphoma, leukaemia or other malignancy in past 5 years
- Jaundice, active hepatitis or hepatobiliary disease
- ALT or AST > 2 times upper limit
- Blood pressure ≥ 160/100 mmHg
- BMI ≥ 35 kg/m^2
- Active treatment for a major depressive order, or past hospitalisation for a major depressive episode
- Breastfeeding or pregnant

Study Endpoints

Primary Objectives

- To evaluate the safety and tolerability of the adjunct use of propagermanium in patients with FSGS who are also receiving stable irbesartan

Primary Endpoints

- Incidence and severity of AEs during treatment with propagermanium as compared to placebo
- Incidence of clinically significant changes in the safety profile of patients treated with propagermanium as compared to placebo

Secondary Objectives

- Change in protein to creatinine ratio (PCR) during treatment with propagermanium in patients with FSGS who are receiving stable irbesartan

Secondary Endpoints

- Percent change from baseline (mean of 2 values) in 24-hour PCR after 15/16-weeks of treatment (mean of two values) with propagermanium as compared to placebo
- Proportion of patients who achieve a response during treatment with propagermanium as compared to placebo

Discussion

- The use of propagermanium and irbesartan has a strong preclinical and clinical rationale for efficacy in FSGS, including a previous study where approximately 25% of patients experienced a reduction of their level of proteinuria by more than 50%
- The *ACTION for FSGS* study is designed to determine the treatment effect of using propagermanium and irbesartan simultaneously in patients with primary FSGS
- The crossover study provides improved statistical power to resolve treatment effect as each patient is their own control, and also ensures all patients receive treatment

Contacts

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