ACTION (AT1R & CCR2 Targets for Inflammatory Nephrosis) Phase 2 Trial for Diabetic Kidney Disease

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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 glomerulosclerosis 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 including diabetic kidney disease (DKD).

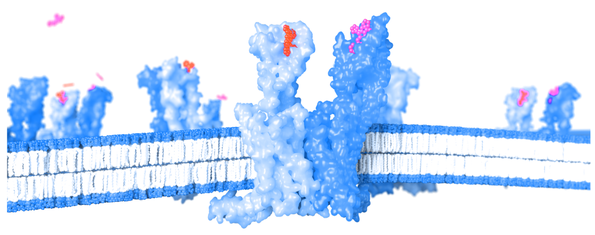

Figure 1: Cartoon of the CCR2 and AT1R heteromer, with ligands propagermanium (orange) and irbesartan (pink).

Use in diabetic kidney disease patients

An initial Phase 2a trial in N=27 patients with proteinuria, showed a reduction in protein to creatinine ratio (PCR) in n=10 diabetic patients

An open-label, Phase 2a study was conducted 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, including n=10 patients with a primary renal diagnosis of diabetic nephropathy. Simultaneous antagonism of AT1R with irbesartan and CCR2 with propagermanium over a period of 32 weeks was safe and well tolerated in all patients, with diabetic nephropathy patients showing a statistically significant reduction in PCR (24hr) of 31.9% between baseline and the last two periods of treatment (p=0.0014).

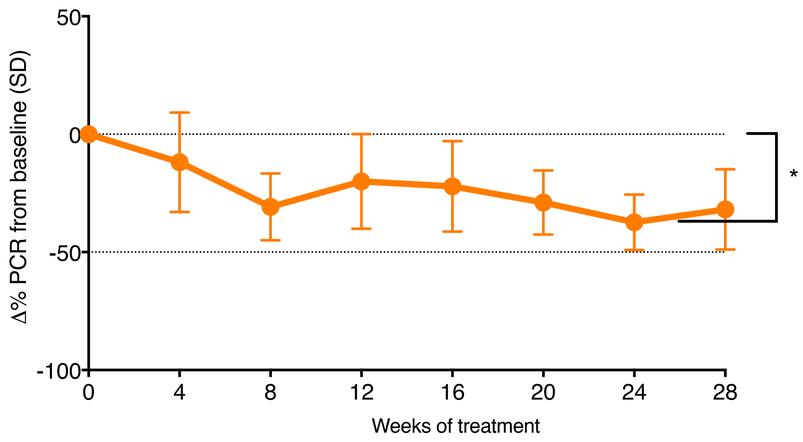

Figure 2: Group mean (SD) of diabetic nephropathy patient PCR (24hr) values as % change from baseline during treatment.

* Two-way, ratio paired t-test between baseline and mean of week 24 and 28, p=0.0014, n=10.

ACTION for DKD Study Design

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

Approximately 40 patients with DKD will be enrolled in a randomised, placebo-controlled study to confirm the effect of combined inhibition of AT1R and CCR2 in patients with DKD. Patients must be receiving stable irbesartan 300 mg/day for a minimum of 3 months prior to and throughout the study including during the washout period. Eligible patients will be randomised to treatment groups to receive propagermanium and placebo in alternative order.

The study consists of a screening visit and baseline assessment prior to randomisation, 2 treatment periods (each treatment period duration is 12-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 37 weeks.

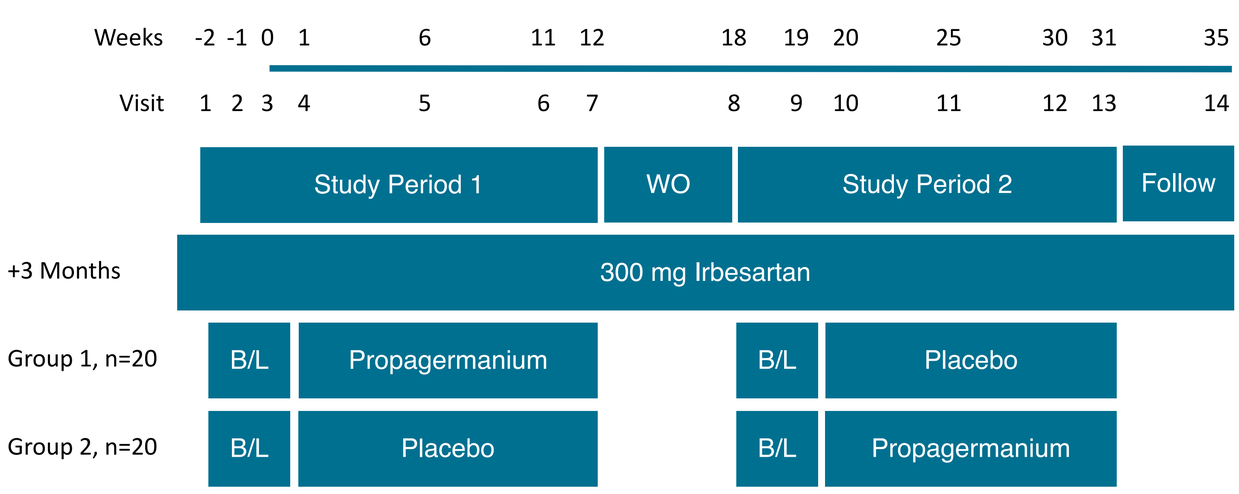

Figure 3: Schematic of study design. Abbreviations: B/L = baseline (1 week), WO = washout (6 weeks), Follow = follow up period (4 weeks after last dose of treatment)

Study Population

Key Inclusion Criteria

- Adults 18 – 80 years
- Type 2 diabetes mellitus
- Baseline HbA1c between 6-11%
- Fasting plasma glucose ≤ 15 mmol/L
- Stable irbesartan for 3-months (300mg/d)
- If on ACE, aldosterone or SGLT2 inhibitors then must be stable for 3 months
- ACR 30 – 500 mg/mmol
- eGFR 25 – 90mL/min/1.73 m^2
- Serum potassium <5.5 mmol/L

Key Exclusion Criteria

- Type 1 diabetes mellitus
- Non-diabetic kidney disease
- Prior organ or stem cell transplant
- Major adverse cardiac event within 6 months
- Receiving immunosuppressive medications
- Rapid eGFR rate decline
- 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 ≥ 40 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 change in albumin to creatinine ratio (ACR) with treatment of propagermanium in patients with DKD who are also receiving stable irbesartan. Study powered to detect 30% change

Primary Endpoints

- Percent change from baseline (mean of 2 values) in 24-hour ACR after 11/12-weeks of treatment (mean of two values) with propagermanium as compared to placebo

Secondary Objectives

- To evaluate the effect of treatment with propagermanium on measures of albuminuria, proteinuria and kidney function
- To evaluate the safety and tolerability of the treatment with propagermanium in patients with DKD who are receiving stable irbesartan

Secondary Endpoints

- Assessment of frequency of patients who achieve an albuminuria-based response during treatment (reduction of ≥ 30% geometric mean ratio), and charge from baseline in renal function
- Incidence and severity of AEs, and changes in safety profile of patients

Discussion

- The use of propagermanium and irbesartan has a strong preclinical and clinical rationale for efficacy in DKD, including a previous study where the majority of DKD patients experienced a reduction in proteinuria with a significant decrease in mean PCR of 31.9% from baseline
- The *ACTION for DKD* study is powered to determine a 30% reduction in albuminuria from baseline, an endpoint significantly correlated with improved renal outcomes
- 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

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