The ACTION (AT1R and CCR2 targets for inflammatory nephrosis) program in focal segmental glomerulosclerosis

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Background

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.

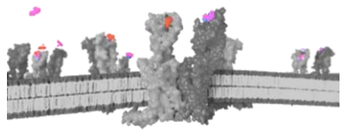


Figure 1: Cartoon of the proposed CCR2 and AT1R heteromer, with antagonists DMX-200 (orange) and irbesartan (pink).

The cell-based Receptor-HIT assay (Dimerix Bioscience) was used to identify a heteromer between GPCRs chemokine receptor 2 (CCR2) and angiotensin II receptor type 1 (AT1R) - both known to play roles in the pathogenesis of various glomerulopathies. 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, DMX-200 (repagermanium), 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. In a Phase 2a study of 27 patients with proteinuric chronic kidney disease, 25% of patients achieved >50% reduction in proteinuria with combined use of DMX-200 and irbesartan. These data suggest a role for simultaneous inhibition of AT1R and CCR2 in proteinuric kidney disease.

FSGS is a disease of podocytes with complications including nephrotic syndrome and progressive kidney failure. There is no approved treatment and FSGS remains an area of high unmet medical need with very few effective therapeutic options. DMX-200 treatment in combination with AT1R blockade aims to address 3 key components of FSGS progression: hyperfiltration with glomerular hypertension, the influx of systemic inflammatory cells into the kidney leading to inflammation and subsequent fibrosis, and the preservation of podocyte number and integrity.

Eligibility Criteria

Key Inclusion Criteria

- Adults 18 – 80 years
- Primary FSGS by renal biopsy
- Stable irbesartan for 3-months (300 mg/d)
- If on ACE, aldosterone, direct renin inhibitor or SGLT2 inhibitors, dose must be stable for 3 months
- If receiving immunosuppressives must be stable for 3 months
- Protein creatinine ratio (PCR) ≥150 mg/mmol
- Estimated glomerular filtration rate (eGFR) ≥ 25 mL/min/1.73 m^2
- Serum potassium < 5.5 mmol/L

Key Exclusion Criteria

- Secondary FSGS secondary
- Type 1 or 2 diabetes mellitus
- 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 known hepatobiliary disease
- ALT or AST >2 times upper limit
- Blood pressure ≥ 160/100 mmHg
- BMI ≥ 35 kg/m2
- Breastfeeding or pregnant

Objectives & Endpoints

Primary Objectives

- To evaluate the safety and tolerability of DMX-200 in patients with FSGS receiving a stable dose of irbesartan.

Primary Endpoints

- Incidence and severity of AEs during treatment with DMX-200 as compared to placebo;
- Incidence of clinically significant changes in the safety profile of patients treated with DMX-200 as compared to placebo.

Secondary Objectives

- Change in PCR during treatment with DMX-200 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 DMX-200 as compared to placebo;
- Proportion of patients who achieve a response during treatment with DMX-200 as compared to placebo.

Study Design

ACTION-FSGS (DMX-200-202) is a Phase 2a randomised, placebo-controlled, two-way crossover study in primary FSGS patients receiving irbesartan, exploring the safety and efficacy of DMX-200 in reducing proteinuria.

Approximately 10 patients with primary FSGS were planned for enrolment.. All patients had to 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 were randomised to treatment groups where they received DMX-200 or placebo in alternate order. DMX-200 was administered as twice daily capsules, 120mg bid.

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

21 patients were screened, 8 were randomized. All 8 patients were included in the main analysis populations (ITT, safety and pharmacodynamic).

Figure 2: 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)

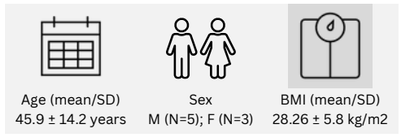
Primary Endpoint: Safety

- Combined therapy with DMX-200 and irbesartan was well tolerated.
- Adverse events were consistent with underlying patient and population co-morbidities.
- There were no DMX-200-related treatment-emergent adverse events (TEAEs).
- There were no clinically relevant findings or observations of note in clinically laboratory parameters, vital signs, or ECG results.

	Placebo (n=8)	DMX-200 (n=8)	Unassigned (n=8)
TEAE (n/E)	6/20	7/18	4/7
TEAE by severity (n/E): Mild Moderate Severe	 5/13 2/4 0	 7/14 2/3 1/1	 3/5 1/2 0
IP-related TEAE (n/E)	0	0	1/1
Irbesartan-related TEAE (n/E)	1/1	0	0
TEAE leading to IP or study discontinuation (n/E)	0	0	0
Serious AE (n/E)	0	1/1	0

Unassigned TEAEs are defined as those TEAEs with (1) Start Date more than 28 days after last dose in Treatment Period 1 (and before the start dose in Period 2), OR (2) Start Date more than 28 days after last dose in Treatment Period 2.
n= number of patients with at least one TEAE. E= number of events.

Patient Characteristics



(N=8)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	eGFR (mL/min/1.73 m2)	Baseline PCR (mg/mmol)	Serum potassium (mmol/l)	IP compliance (mean %)	Irbesartan compliance (mean %)
Placebo	127.2 (9.5)	79.8 (4.1)	55.8 (34.6)	285.60 (90.43)	4.47 (0.54)	93.9	99.0
DMX-200	131.5 (10.1)	79.2 (5.8)	53.8 (33.4)	361.01 (215.73)	4.47 (0.54)	98.3	98.3

Secondary Endpoint: Efficacy (proteinuria)

Following 15/16 weeks of treatment with DMX-200 or placebo:

- The mean decrease (improvement) in urine PCR (Treatment Periods 1 and 2 combined) from Baseline was greater in the DMX-200 group (Δ = -84.3 mg/mmol) compared with the placebo group (Δ = -5.1 mg/mmol), with a difference of -79.2 mg/mmol between groups.
- The median change from baseline was also higher in the DMX-200 group (Δ = -55.4 mg/mmol) compared with the placebo group (Δ = +11.8 mg/mmol), with a median difference of -32.8 mg/mmol between groups.

In the unpowered analysis of treatment effect using a random effects mixed model and the log-transformed urine PCR values, the placebo-corrected ratio (DMX-200 versus placebo) of the PP protocol (n=7) was 0.83. The placebo-corrected ratio was less than 1, indicating a greater reduction in urine PCR in the DMX-200 group compared with the placebo group. The difference was not statistically significant (nominal p-value >0.05). No sequence effect or period effect were observed (nominal p-values >0.05)

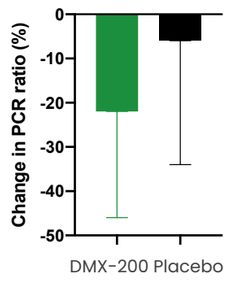
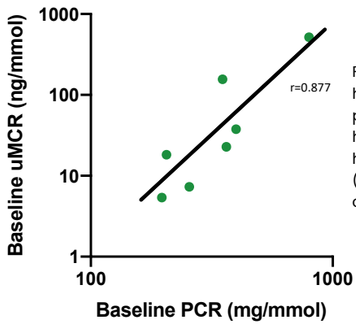


Figure 3. Change in PCR DMX-200 versus Placebo; geometric mean difference -17% (95% CI -43 to +20; p0.25)

Of 8 treated patients, 4 patients had at least a secondary modified partial uPCR-based response (≥30% reduction) at 15/16 weeks; more patients (2 patients) had a response to DMX-200 alone than to placebo alone (1 patient); 1 patient had a response to both DMX-200 and placebo. Three patients achieved a modified partial response (≥40% reduction in PCR from baseline) during the study, and the frequency of patients with responses to the IP alone was similar between groups (1 patient each); 1 patient had a response to both DMX-200 and placebo. Two patients achieved a partial response (≥50% reduction in PCR from baseline) during the study (1 patient to placebo alone and 1 patient to both DMX-200 and placebo). No patients achieved a complete response.

Exploratory Endpoint: MCP-1

MCP-1 = monocyte chemoattractant protein-1 or CCL-2, the ligand for CCR2.



FSGS patients with high baseline proteinuria (PCR) had corresponding high urine MCR (urine MCP-1 to creatinine ratio)

Figure 4. Baseline PCR versus baseline uMCR n=7

Figure 5. Change in uMCR DMX-200 versus placebo

Conclusions

- Simultaneous inhibition of AT1R and CCR2 demonstrated a reassuring safety profile and was well tolerated in patients with primary FSGS.
- There was evidence of promising efficacy with clinically relevant reduction in uPCR when DMX-200 was added to irbesartan.
- The uPCR reduction with DMX-200 was in addition to the proteinuria decline that would be expected with AT1R blockade alone in FSGS.
- An anti-inflammatory effect of DMX-200 was supported by evidence of reduction in a clinically relevant biomarker, MCP-1.
- These findings have led to the initiation of an international Phase 3 randomised double-blind, placebo-controlled study (ACTION3) to further evaluate the efficacy of DMX-200 in patients with FSGS receiving angiotensin receptor blockade. (ClinicalTrials.gov Identifier: NCT05183646)

References

Ayoub, M., et al. (2015). Functional Interaction between Angiotensin II Receptor Type 1 and Chemokine (C-C Motif) Receptor 2 with Implications for Chronic Kidney Disease. PLOS ONE, 10(3), e0119803