ACTION3- pivotal Phase 3 study assessing the CCR2 inhibitor DMX-200 in patients with focal segmental glomerulosclerosis

FSGS CLINICAL STUDY

Dimerix

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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 highly important drug targets.
- GPCRs function in complexes of two or more receptors called dimers or heteromers with different pharmacology from the respective monomeric units.
- The cell-based Receptor-HIT assay (Dimerix Bioscience) identifed a heteromer between the GPCRs chemokine receptor 2 (CCR2) and angiotensin II receptor type 1 (AT1R) - both known to play roles in the pathogenesis of glomerulopathies.Formation of the CCR2/AT1R heteromer resulted in transactivation of the CCR2 receptor in response to AT1R activation, and dual ligand-mediated signaling complex was only reversed by treatment with antagonists for both receptors.
- 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 compared to inhibition with either antagonist alone.
- 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.
- A previous Phase 2a proof of concept study (ACTION-FSGS) explored the safety and efficacy of DMX-200 (120mg bid) in reducing proteinuria.
  - This was a randomised, placebo-controlled, two-way crossover study in N=8 patients with primary FSGS receiving stable irbesartan treatment (300 mg/day for a minimum of 3 months prior to and throughout the study).
  - The duration of each treatment period duration was 16-weeks, separated by a 6-week washout period.
  - There were no clinically relevant findings with the safety or tolerability of DMX-200 in this patient population. In addition, there was evidence of efficacy with clinically relevant reduction in protein creatinine ratio (PCR) when DMX-200 was added to irbesartan.
  - The mean decrease (improvement) in urine PCR from study baseline was greater when patients were administered DMX-200 (Δ = -84.3 mg/mmol) compared to when they received placebo (Δ = -5.1 mg/mmol), with a difference of -79.2 mg/mmol between groups.

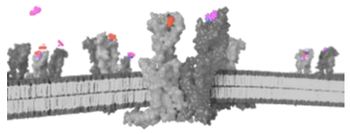


Figure 1: Cartoon of the CCR2 and AT1R heteromer, with ligands DMX-200 (orange) and irbesartan (pink).

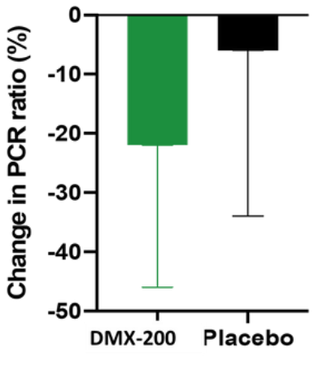
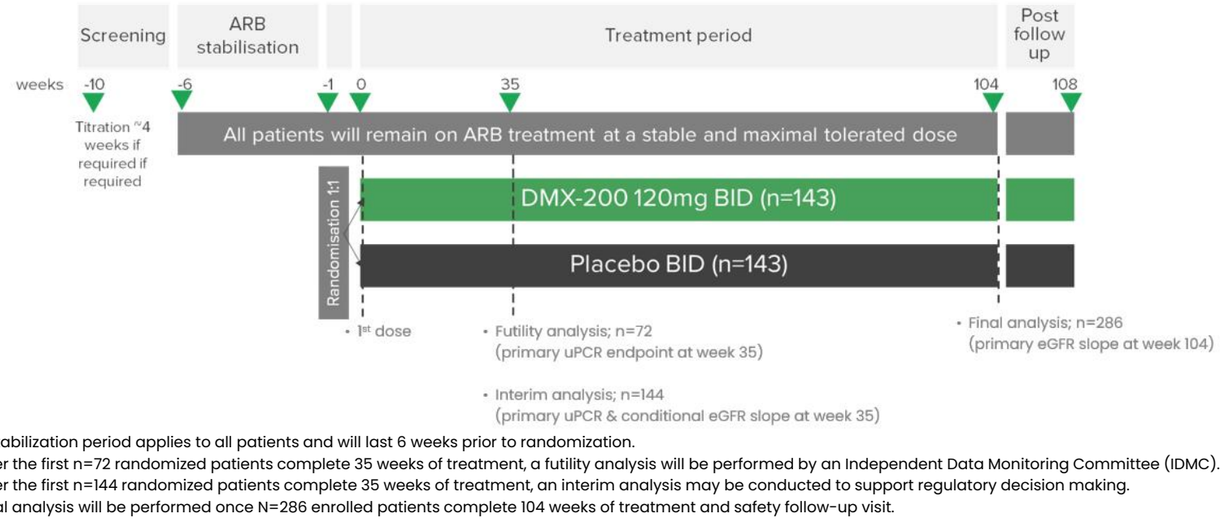


Figure 2. Change in PCR DMX-200 versus placebo; geometric mean difference -17% (95% CI -43 to +20; p0.25), repeat measures mixed model.

These findings have led to the initiation of the pivotal Phase 3 trial (ACTION3).

ACTION3- FSGS Pivotal Study Design & Schema

- ACTION3 is a pivotal, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of DMX-200 in patients with FSGS on a stable ARB
- Approximately N=286 adult patients will be enrolled in this study at sites in multiple countries.
- The study utilizes a decentralized model with a mix of on-site and optional remote visits.
- DMX-200 120 mg capsules are administered bid.
- Background ARB treatment is administered at ≥50% of the maximum recommended dose. Patients not treated with ARB at screening require initiation of this drug.



- A stabilization period applies to all patients and will last 6 weeks prior to randomization.
- After the first n=72 randomized patients complete 35 weeks of treatment, a futility analysis will be performed by an Independent Data Monitoring Committee (IDMC).
- After the first n=144 randomized patients complete 35 weeks of treatment, an interim analysis may be conducted to support regulatory decision making.
- Final analysis will be performed once N=286 enrolled patients complete 104 weeks of treatment and safety follow-up visit.

Primary Endpoints

- Percent change in urine PCR (based on 24-hour urine collection) from baseline to week 35 following treatment with DMX-200 compared with placebo.
- Change in eGFR slope from baseline to week 104 following treatment with DMX-200 compared with placebo

Secondary Endpoints

- Incidence and severity of AEs following treatment with DMX-200 compared with placebo.
- Incidence of clinically significant changes in the safety profile of patients treated with DMX-200 compared with placebo, as measured by changes from baseline in clinical laboratory evaluations, ECGs, vital signs, and physical examinations.
- Proportion of responders and non-responders following treatment with DMX-200 compared with placebo, defined as:
  - Complete response: 24-hour urine PCR reduction to < 0.3 g/g [< 33.9 mg/mmol].
  - Modified partial remission: 24-hour urine PCR reduction ≥ 40% from baseline and < 1.5 g/g
  - No response (failure to meet any response criteria).
- Proportion of patients on treatment with DMX-200 compared with placebo that meet a composite endpoint of worsening in kidney function.

Tertiary Endpoints

- Changes in biomarkers of kidney function from baseline after treatment with DMX-200 compared with placebo:
  - 24-hour urine chemistry biomarkers: ACR, albumin concentration, total protein concentration, total albumin excretion, and total protein excretion.
  - Serum biomarkers: creatinine, creatinine clearance, and cystatin-C.
  - Plasma and urine MCP-1.
- Assessment of plasma and urine DMX-200 concentration-time profiles.
- Change in quality of life from baseline, measured via KDQOL-SF-36 .

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

Study Objectives

Primary:
To evaluate the efficacy of DMX-200 in terms of urine PCR and eGFR slope in patients with FSGS receiving an ARB

Secondary:
To evaluate the safety and tolerability of treatment with DMX-200 in patients with FSGS receiving an ARB

To evaluate the effect of DMX-200 on kidney function parameters including proteinuria in patients with FSGS receiving an ARB

Tertiary:
Evaluate biomarkers of kidney function, DMX-200 pharmacokinetics, and quality of life

Statistical Considerations

- Randomization is stratified according to entry urine PCR (< or > 3.5g/g) and eGFR (< or > 60 mL/min/1.73 m2).
- A sample size of 286 patients provides ≥80% power at the 1-sided 1.5% alpha level to detect a treatment effect of ≥1.68 mL/min/1.73 m2 per year in annualized eGFR slope.
- The urine PCR endpoint will be analyzed on the log scale assessed using a Mixed Model Repeated Measures (MMRM) analysis.
- The primary long-term annualized eGFR rate of change endpoint will be assessed via mixed model random coefficients analysis.
- Secondary and tertiary efficacy endpoints will be summarized descriptively.

Eligibility Criteria

Key Inclusion Criteria

- Adults 18 – 80 years
- Biopsy-confirmed FSGS: primary, genetic or FSGS of undetermined cause
- Receiving a stable dose of an ARB at the maximal tolerated dose and ≥ 50% of the maximum recommended dose per the product label for 6 weeks prior to screening, or willing to transition to this treatment during titration and stabilization period.
- If taking corticosteroids, the dosage must be stable for ≥ 4 weeks prior to screening
- If on aldosterone mineralocorticoid receptor antagonists, direct renin inhibitors or SGLT2 inhibitors, dose must be stable for 3 months
- Urine PCR >1.5 g/g (> 169.5 mg/mmol) or 24-hour total protein > 1.5 g/day based on 24-hour urine collection
- Estimated GFR ≥ 30 mL/min/1.73 m2
- BP ≤ 160/100 mm Hg
- BMI ≤ 40 kg/m²

Key Exclusion Criteria

- Secondary FSGS
- Type 1 or uncontrolled Type 2 diabetes
- Active malignancy in the last 2 years
- Active hepatitis or known hepatobiliary disease
- NYHA Class III/IV heart failure or major adverse cardiac event in prior 12 weeks
- Prior organ transplant
- Positive for HIV, HBsAg, HCV
- Serum potassium >5.5mmol/L
- AST and ALT > 2 times upper limit normal
- Treatment with immunosuppressant biological drugs, calcineurin inhibitors, cyclophosphamide, azathioprine, or mycophenolate mofetil within 12 weeks prior to screening

Study Status & Contacts

The study is currently recruiting patients in 11 countries (US, South America, Europe and Asia-Pacific regions) at approximately 70 investigational sites. Expansion of countries and sites is expected following futility analysis.

- **ClinicalTrials.gov Identifier: NCT05183646**
- **For further information please contact: Dr Ash Soman; Ph: 1300 813 321; Email: ACTION3@dimerix.com**