ACTION3 – Phase 3 study of DMX-200 (QYTOVRA®) for the treatment of focal segmental glomerulosclerosis (FSGS)

Dimerix

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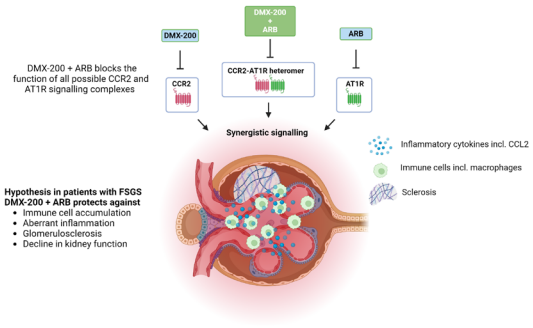
Background

FSGS is a podocytopathy with complications including nephrotic syndrome and progressive kidney failure, and is an area of high unmet medical need with very few effective therapeutic options. Dimerix are developing DMX-200 (repagermanium, QYTOVRA®) as an orally active small molecule inhibitor of the chemokine receptor 2 (CCR2).

CCR2 and angiotensin II receptor type 1 (AT1R) are G-protein coupled receptors expressed on podocytes and other kidney cells. Over-expression of CCR2 and AT1R on podocytes is associated with pathology.[1] High concentrations of the ligands for CCR2 and AT1R (CCL2/MCP-1 & angiotensin II respectively) are also implicated in the pathogenesis of chronic kidney diseases including FSGS.



Mechanism: CCR2 and AT1R form a heteromeric complex (also known as a functional dimer) with signaling cross-talk and transactivation.[1] In a subtotal nephrectomy model in rats, blockage of the CCR2/AT1R dimer with QYTOVRA + an angiotensin receptor blocker (ARB) decreased monocyte infiltration, with lower proteinuria and reduced podocyte loss compared to inhibition with either antagonist alone[1]. Blockade of CCR2 is hypothesized to reduce inflammation and via preventing CCR2 activation in podocytes and immune cells.

Based on data from a Phase 2 study (Fig.1) a global Phase 3 study (ACTION3) was initiated to confirm the proteinuria lowering effects of DMX-200 and assess effects on GFR decline. A blinded futility analysis was conducted in March 2024 and the study was declared non-futile. Here we present the baseline data from the first 92 patients enrolled in ACTION3 as of March 2024.

ACTION3
FSGS CLINICAL STUDY

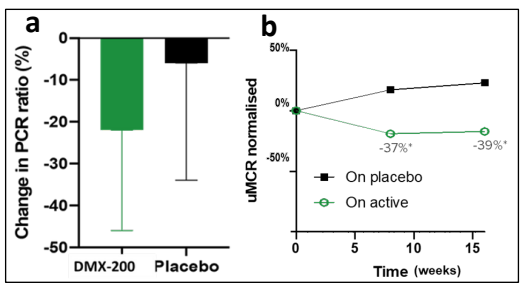


Figure 1 Results from ACTION (FSGS) a Phase 2a proof of concept placebo-controlled cross-over study in N=8 patients with FSGS. **(a)** Change in PCR DMX-200 versus placebo; geometric mean difference -17% (95% CI -43 to +20; p=0.25), repeat measures mixed model. **(b)** Change in urinary MCP-1/creatine ratio for DMX-200 versus placebo.

Eligibility Criteria & Study Objectives

Key Inclusion Criteria

- Age 12 – 80 years
- Biopsy-confirmed FSGS: primary, genetic or FSGS-UC
- Receiving a stable dose of ARB at the maximal tolerated dose and ≥ 50% of the maximum recommended dose
- If taking corticosteroids, dosage must be stable for ≥ 4 weeks prior to screening
- If on aldosterone or direct renin inhibitor, MRA or SGLT2 inhibitor, dose must be stable for 3 months
- Urine PCR >1.5 g/g or 24-hr total protein >1.5 g/d
- Estimated GFR ≥ 25 mL/min/1.73 m²
- BP ≤ 160/100 mm Hg
- BMI ≤ 40 kg/m²

Key Exclusion Criteria

- Secondary FSGS
- Treatment with biological immunosuppressant drugs, CNIs, cyclophosphamide, azathioprine, or mycophenolate mofetil < 12 weeks prior to screening

Study objectives

Primary

To evaluate the efficacy of QYTOVRA in terms of uPCR and eGFR slope in patients with FSGS receiving an ARB

Secondary

To evaluate the safety and tolerability of treatment with QYTOVRA in patients with FSGS receiving an ARB

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

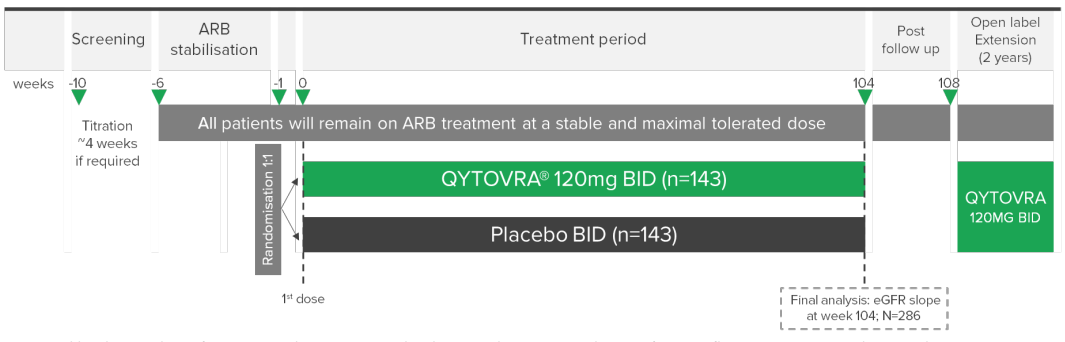
Tertiary

Evaluate biomarkers of kidney function, PK, DMX-200 palatability and QOL

To evaluate the need for initiation of new FSGS directed therapies while on treatment with DMX-200

ACTION3- FSGS Pivotal Study Design & Schema

- ACTION3 is a pivotal, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of QYTOVRA in patients with FSGS on a stable ARB.
- Approximately N=286 adult and adolescent (12-17 years) patients will be enrolled in this study at sites in multiple countries. Enrolment of adolescents is commencing in 2024 in United States/United Kingdom/Argentina/Mexico).
- Background ARB is administered at ≥50% of the maximum labelled dose. Patients not treated with ARB at screening require initiation of this drug.
- All patients completing the 104-week study period will be offered access to an open-label extension study of QYTOVRA for an additional period of up to 2 years.



A stabilization period of 6 weeks prior to randomization applies to all patients. 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.

Futility Analysis – March 2024

In March 2024, an Independent Data Monitoring Committee (IDMC) conduced a futility analysis on data from the first n=72 randomized patients to complete approximately 35 weeks of treatment.

- ACTION3 passed the futility analysis based on a proteinuria efficacy endpoint
- No safety concerns were noted by the IDMC at this analysis with DMX-200 continuing to be very well tolerated with the longest exposure now ~18 months
- ACTION3 is now formally expanding sites from 71 to 185 sites and will now include pediatric patients 12-17 years

Main Endpoints

Primary

- Percent change in uPCR from baseline to week 35 with QYTOVRA vs placebo.
- Change in eGFR slope from baseline to week 104 with QYTOVRA vs placebo.

Secondary

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

Tertiary

- Changes in biomarkers of kidney function from baseline:
  - 24-hour urine chemistry biomarkers: ACR, albumin & protein concentration/excretion.
  - Serum biomarkers: creatinine, creatinine clearance, and cystatin-C.
  - Plasma and urine MCP-1.
- Assessment of plasma QYTOVRA concentration-time profile.
- Change in quality of life from baseline, measured via KDQOL-SF-36
- Proportion of patients on treatment with DMX 200 compared with placebo requiring initiation of new FSGS-directed therapies.

Statistical considerations

- Randomization is stratified by age, entry uPCR (<or> 3.5g/g) and eGFR (<or> 60 mL/min/1.73 m²).
- The uPCR endpoint will be analyzed on the log scale using a Mixed Model Repeated Measures (MMRM) test.
- 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.

Baseline Characteristics

Baseline demographics and characteristics	
Patients enrolled (March 2024)	92
Age	44 median (range 18-78)
Gender	62 (67%) Male 30 (33%) Female
Ethnicity	13 (14.1%) Asian 7 (7.6%) Black 67 (72.8%) White 5 (5.4%) Other
FSGS Diagnosis	75 (78.3%) Primary 10 (10.9%) Genetic 9 (9.8%) Undetermined cause 1 (1.1%) Other
Concomitant SGLT2-inhibitor use	15 (16.3%)
uPCR (g/g)	3.28 ± 2.38
eGFR mL/min/1.73 m²	57.7 ± 27.6
BMI (kg/m²) (median)	25.59 (range 17.68-38.08)
Time since diagnosis months	54.8 ± 66.60
eGFR ml/min/1.73 m²	
≥ 90 ml/min/1.73 m²	14 (15.2%)
≥ 60 to <90 ml/min/1.73 m²	21 (22.8%)
≥ 45 to <60 ml/min/1.73 m²	17 (18.4%)
≥ 30 to <45 ml/min/1.73 m²	31 (33.7%)
<30 ml/min/1.73 m²	9 (9.8%)
uPCR (g/g) by pre-defined strata; n (%)	
≤3.5 g/g uPCR & eGFR ≥ 25 to <60 ml/min/1.73 m²	1.93 ± 0.23 (26%)
≤3.5 g/g uPCR & eGFR >60 ml/min/1.73 m²	2.20 ± 0.94 (39%)
>3.5 g/g uPCR & ≥ 25 to <60 ml/min/1.73 m²	6.03 ± 2.81 (26%)
>3.5 g/g uPCR & eGFR >60 ml/min/1.73 m²	4.38 ± 1.18 (9%)

Study Contacts

- ClinicalTrials.gov Identifier: NCT05183646
- For further information or interest in participating please contact: ACTION3@dimerix.com

QYTOVRA® [REPAGERMANIUM]

Reference: 1. Ayoub, M., et al. (2015) PLOS ONE, 10(3), e0119803

For more information