Pivotal Phase 3 study assessing the CCR2 inhibitor QYTOVRA® in adult & adolescent patients with focal segmental glomerulosclerosis

ACTION3 FSGS CLINICAL STUDY

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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.

Chemokine receptor 2 (CCR2) and angiotensin II receptor type 1 (AT1R) are G-protein coupled receptors (GPCRs) 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.

CCR2 & AT1R form a heteromeric complex (functional dimer) with signaling cross-talk and transactivation.[1] In vitro studies showed that the dual ligand-mediated signaling complex was only reversed completely by treatment with simultaneous antagonism of both receptors.

QYTOVRA® (repagermanium; DMX-200) is an orally active small molecule CCR2 antagonist.

In a subtotal nephrectomy model in rats, QYTOVRA + angiotensin receptor blockade (ARB) decreased monocyte infiltration, with lower proteinuria and reduced podocyte loss compared to inhibition with either antagonist alone[1].

A Phase 2a proof of concept placebo-controlled cross-over study in N=8 patients explored the safety & efficacy of QYTOVRA in maximal ARB (irbesartan)-treated primary FSGS, with evidence of an antiproteinuric effect (17% placebo-adjusted reduction in uPCR; p=NS).

This uPCR reduction with QYTOVRA was in addition to the proteinuria decline that would be expected with AT1R blockade alone. The combination of ARB and QYTOVRA was well-tolerated and demonstrated a reassuring safety profile.

An anti-inflammatory effect of QYTOVRA was supported by evidence of reduction in the ligand of CCR2, monocyte chemokine attractant protein (MCP-1).

These findings led to development of the ACTION3 Phase 3 FSGS trial.

Eligibility Criteria

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-hour total protein > 1.5 g/d
- Estimated GFR ≥ 25 mL/min/1.73 m2
- BP ≤ 160/100 mm Hg
- BMI ≤ 40 kg/m^2

Key Exclusion Criteria

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

Study Objectives

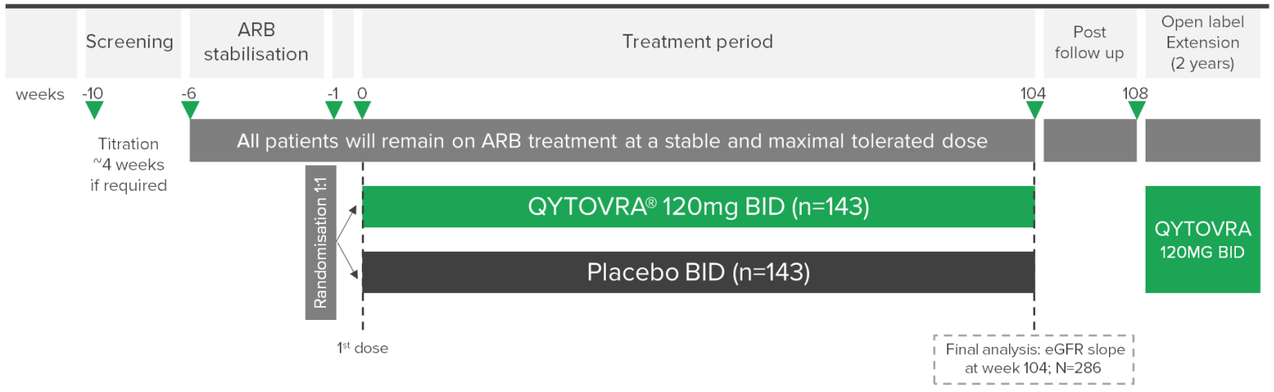
Primary:
To evaluate the efficacy of QYTOVRA in terms of uPCR and eGFR slope in patients with FSGS receiving an ARB

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, pharmacokinetics, and QOL

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 (aged 12-17 years) patients will be enrolled in this study at sites in multiple countries. Enrolment of adolescents will commence following first interim analysis and will be in selected countries (United States/United Kingdom/Argentina/Mexico).
- QYTOVRA 120 mg capsules are administered bid.
- 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 applies to all patients and will last 6 weeks prior to randomization.
- After the first n=72 randomized patients complete approximately 35 weeks of treatment, a blinded futility analysis will be performed by an Independent DMC.
- 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.

ACTION3 Clinical Locations

QYTOVRA® [REPAGERMANIUM]

Primary Endpoints

- 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 Endpoints

- Incidence and severity of AEs following treatment with QYTOVRA vs placebo.
- Incidence of clinically significant changes in the safety profile as measured by 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 Endpoints

- 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.

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.

Study Contacts

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

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