ACTION3 Phase 3 Clinical Trial Assessing the Efficacy and Safety of DMX-200 (Repagermanium): Mid-trial Safety Assessment and Pharmacometric Model-Informed Pediatric Dose Selection

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ACTION3 FSGS CLINICAL STUDY

Background

FSGS is a podocytopathy with complications which may include 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). ACTION3 is a global Phase 3 study designed to confirm the proteinuria lowering effects of DMX-200 in combination with an angiotensin receptor blocker (ARB) and to assess effects on GFR decline. The initial stage of ACTION3 enrolled adult patients with FSGS with enrolment of adolescent patients to commence following an initial interim analysis and confirmation of dose selection.

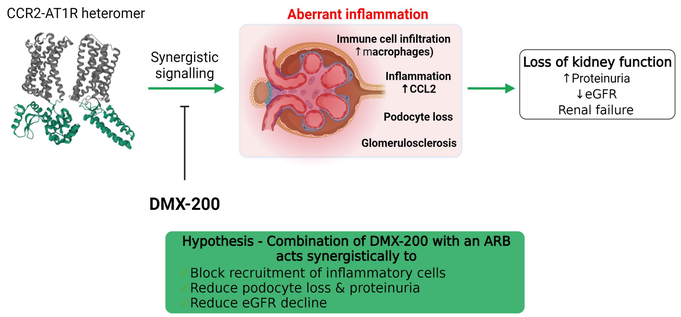


Fig 1: Mechanism of action and rationale for DMX-200 use in patients with FSGS

DMX-200 pharmacokinetic model

DMX-200 has no known metabolites, a low potential for drug-drug interactions and is mainly renally cleared. DMX-200 has a half-life of 3.6 hours in renal impairment and shows large fluctuations in plasma concentrations following BID administration. Using data from prior Phase 1 and Phase 2 studies Dimerix developed a population pharmacokinetic model (popPK) consisting of a two-compartment disposition model combined with zero- and first-order absorption.

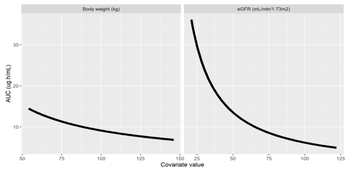
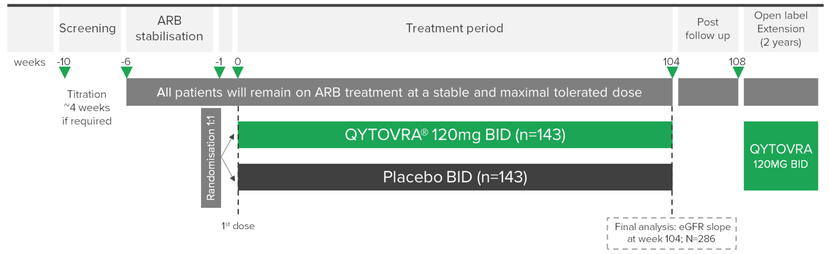


Fig 2: Population PK modelling indicated dependence of drug exposure (AUC) on body weight and renal function

ACTION3 - FSGS pivotal study design & schema



A blinded futility analysis was performed in March 2024 by an IDMC after approximately the first n=72 randomized patients had completed approximately 35 weeks of treatment.

Results - safety analysis

- Median duration of exposure to DMX-200 or placebo was 9.1 months (range 0.5-17.3) with median total exposure of 65.7 g (range 3.6 -124.5 g)
- 277 individual adverse events (AEs) were reported by 72/91 (79%) patients. 80% of AEs were rated as “mild” and reflected the underlying disease (FSGS) and associated comorbidities.
- ACTION3 PK data were comparable with previous data and support use of the previous developed popPK model.

Table 1: Frequently reported adverse events

Preferred Term	Patients (n=91)
Headache / migraine	12 (13%)
Hypotension	10 (11%)
COVID	9 (10%)
URTI	9 (10%)
Oedema	8 (9%)
Hypertension	7 (8%)
Influenza	6 (7%)
Nausea	6 (7%)
Deterioration renal function	5 (5%)
Dizziness	5 (5%)
Fatigue	5 (5%
Nasopharyngitis	5 (5%)
Back pain	4 (4%)

Results - pharmacokinetic modelling

Multiple-dose simulation in adults and adolescents

- Exposure in healthy adolescents (12-17yrs) at steady-state is expected to be within/below the range observed in adults
- Exposure in adolescents with renal impairment may be higher than in adults but is covered by DMX-200 safety margins and good tolerability in adults

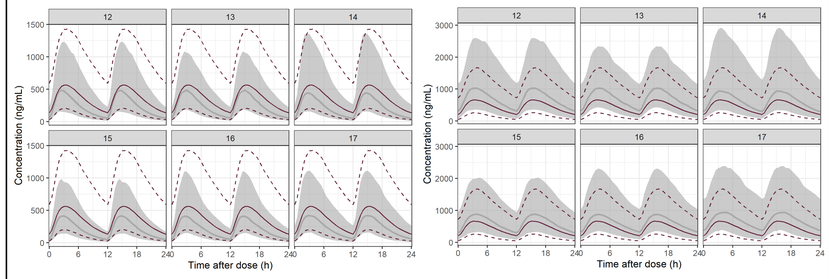


Fig 3: Comparison multi-dose (120mg DMX-200 BID) simulations in healthy **(left group)** or renally impaired **(right group)** adolescents (grey lines shaded area) & adults purple lines.

Simulated steady-state exposure in adults and adolescents

- Renally impaired patients with low body weight may have slightly higher exposure than adults with mild renal disease

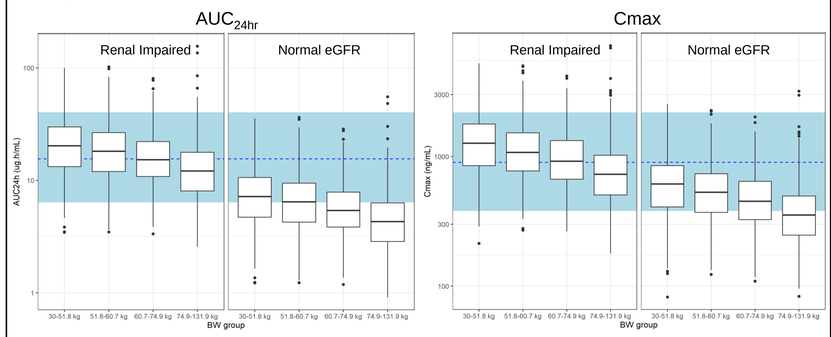


Fig 4: Simulated steady-state AUC_{24hr} **(right)** and Cmax **(left) i**n adults and adolescents by body weight and renal impairment. Blue area/dashed line represents the simulated exposure range in adults with mild to moderate renal disease. Simulated adolescent data are shown as box plots (IQR and median) with whiskers representing min/max.

Methods

In March 2024, an independent data monitoring committee (IDMC) conducted an interim safety analysis on the first n=91 patients randomised in ACTION3 (see study schema).

Blinded pharmacokinetic data from n=46 DMX-200 evaluable patients was assessed in the popPK model and was also used to simulate DMX-200 exposure in adolescent patients.

Conclusions

- No safety signals of concern were noted by the IDMC and the study was allowed to continue unchanged. The safety profile reflected the underlying disease and associated comorbidities.
- ACTION3 PK data were very comparable with previous data and support using the population PK model for dose simulations.
- A dose adjustment is considered not needed for 12-17 years olds

Study locations and contacts

Adolescent sites opening

Argentina, Mexico, United Kingdom, and USA

ClinicalTrials.gov Identifier

NCT05183646

For further information please contact **ACTION3@dimerix.com**

Dimerix