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An Exploratory Trial of an Investigational RNA Therapeutic, IONIS-FB-LRx, for Treatment of IgA Nephropathy: New Interim Results

Jason Choo[2], Sean Barbour[3], Michelle Hladunewich[5], Angela Makris[4], Sven Jean Tan[7], MG Wong[8], Lixuan Yin[1], Terry Barrett[1], Eugene Schneider[1], **Jason Choo**[1]
[1]Department of Internal Medicine-Nephrology, Singapore General Hospital, Singapore
[2]Department of Renal Medicine, Singapore General Hospital, Singapore
[3]Department of Nephrology, University of British Columbia, Canada
[4]Department of Nephrology, Liverpool Hospital, Australia
[5]Department of Nephrology, Sunnybrook Research Institute, Canada
[6]Department of Nephrology, Exsera Biolabs, United States
[7]Department of Nephrology, Royal Melbourne Hospital, Australia
[8]Department of Nephrology, University of Sydney, Australia

Objectives : Overactivity of the complement Alternative Pathway (AP) has been proposed to contribute to pathogenesis of IgA nephropathy (IgAN). An antisense oligonucleotide to complement factor B (FB), IONIS-FB-L_{Rx} (ISIS696844, RO7434656) targets FB mRNA in the liver leading to inhibition of AP and reduction in proteinuria in IgAN patients.
Methods : A single-arm, open-label Ph2 study (NCT04014335) recruited patients with biopsy-confirmed IgAN, proteinuria>1.5g/d, eGFR>40mL/min/1.73m^2, and hematuria despite maximum tolerated RAAS blockade. Patients received monthly SC administration of IONIS-FB-L_{Rx} for 24 weeks. Primary outcome was change in 24-hr proteinuria at Wk29 (4 weeks after last dose) compared to baseline(BL).
Results : 13 subjects have completed study to date, 25-62 yr, 40% Female, 7 Asian, and 6 White. There was a selective reduction of plasma complement FB levels, serum AP activity, urinary Ba and urinary sC5b-9 (mean % change of -69%, -36%, -92%, and -26% respectively). Median 24-hr proteinuria at BL was 1.80 g/g (IQR 1.23, 2.33 g/g). At Wk29, a 47% geometric mean ratio reduction was observed. There was no change in eGFR at Wk29 compared to BL (mean±SD; BL 70±25; Wk29 72±22 mL/min/1.73m2). One subject opted to extend treatment and continued to receive treatment through Wk61, demonstrating a sustained reduction in proteinuria. One subject discontinued study drug after 4 months of treatment to initiate SGLT-2 inhibitors. 24-hr urine samples collected 3 weeks after the last dose of IONIS-FB-L_{Rx}, but prior to use of SGLT-2 inhibitors (Wk27), demonstrated a 41% reduction in proteinuria. IONIS-FB-L_{Rx} demonstrated an acceptable safety profile with no Treatment Emergent SAE. A transient and reversible ALT elevation without a change in bilirubin was observed in one subject.
Conclusions : This Ph2 open-label study provides continuing evidence that IONIS-FB-L_{Rx}, reduces complement levels and proteinuria in patients with IgAN, supporting Ph3 development (NCT05797610) to determine the potential to reduce progression of IgAN.