THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-0698

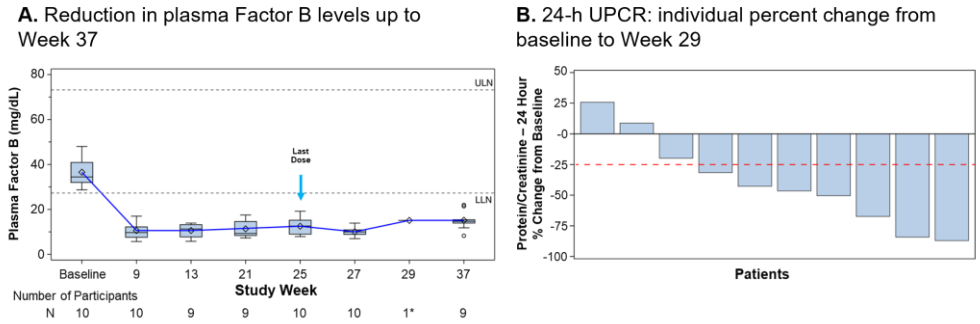
IMAGINATION: A Global Phase 3 Trial of RO7434656, an Antisense Oligonucleotide Inhibitor of Complement Factor B, in IgA Nephropathy

Jonathan Barratt[1], Jurgen Floege[2], Vishal Duggal[3], Nadine Schmit[4], Ji Cheng[5], Jeannette Lo[6], Brad H. Rovin[7]
[1]Department of Cardiovascular Sciences, University of Leicester, United Kingdom
[2]Department of Nephrology, University Hospital, Rheinisch-Westfalische Technische Hochschule (RWTH) Aachen, Germany
[3]Department of Clinical Science, Genentech, Inc., United States
[4]Department of PD Clinical Science, F. Hoffmann-LaRoche Ltd, Switzerland
[5]Department of PD Data Sciences, Hoffmann-La Roche Ltd, Canada
[6]Department of Translational Medicine, Genentech, Inc., United States
[7]Department of Internal Medicine, The Ohio State University College of Medicine, United States

Objectives : RO7434656 (IONIS-FB-L_{Rx}, ISIS 696844), a ligand-conjugated antisense oligonucleotide targeting complement factor B mRNA, was engineered for enhanced delivery to the liver as the primary site of factor B production. In a Phase 2 trial (NCT04014335), RO7434656 inhibited alternative complement pathway activation and demonstrated a clinically meaningful reduction in the urine protein-to-creatinine ratio (UPCR; Fig 1) and stabilization of the estimated glomerular filtration rate (eGFR) in patients with IgA nephropathy (IgAN).
Methods : IMAGINATION (NCT05797610), a Phase 3, randomized, double-blind, placebo-controlled trial will evaluate the efficacy and safety of RO7434656 in adults with biopsy-confirmed primary IgAN (Fig 2). 428 patients will be divided into 2 cohorts: a primary cohort with eGFR ≥30 mL/min/1.73m^2 and an exploratory cohort with eGFR 20-29 mL/min/1.73m^2. Patients on maximally tolerated doses of ACEi/ARB will be randomized 1:1 to receive RO7434656 or placebo subcutaneously (SC) on Days 1, 15 and 29 and every 4 weeks (Q4W) thereafter for 105 weeks, with the option to continue double-blind or open-label treatment. The primary endpoint is change from baseline in 24h UPCR at Week 37. Key secondary endpoints include eGFR slope from baseline at Week 105, time to the composite kidney failure endpoint and patient-reported outcomes. Blood, urine and optional kidney biopsies will be collected throughout the study to assess biomarkers.
Results : Expected upon study completion.
Conclusions : The unique antisense modality and long tissue half-life of RO7434656 enables Q4W SC administration to inhibit the alternative complement pathway. IMAGINATION aims to evaluate the efficacy and safety of RO7434656 in adults with IgAN using a broad range of assessments over 105 weeks. Study and medical writing support funded by F. Hoffmann-La Roche Ltd. This abstract was submitted and accepted for presentation at ASN Kidney Week 2023 and 2024 ISN World Congress of Nephrology. The authors declare that re-submitting the abstract is permitted by the previous meetings.

Figure_1.png

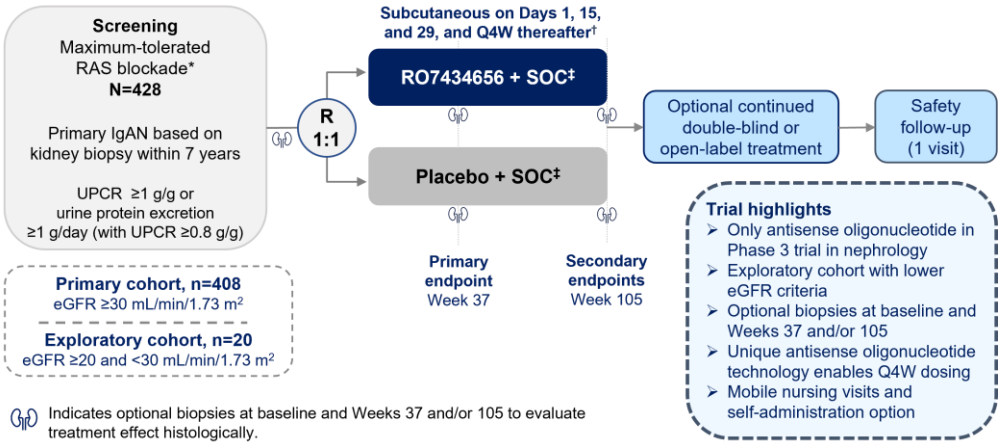
Fig 1. Change in (A) UPCR and (B) Factor B in the Phase 2 Trial of RO7434656 (NCT04014335)



Study sponsor Ionis Pharmaceuticals, Inc.
LLN, lower limit of normal; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio. *Additional complement sampling timepoints following protocol amendment.
Barbour S, et al. Presented at the 2022 American Society of Nephrology (ASN) Annual Meeting. Poster SA-P0714. Reprinted with permission by the author.

Figure_1.png

Fig 2. Study Design of the Phase 3 IMAGINATION trial (NCT05797610)



Indicates optional biopsies at baseline and Weeks 37 and/or 105 to evaluate treatment effect histologically.

*Stable doses of SGLT-2 inhibitors, ERAs and other agents for BP management permitted. †Self-administration by patient or caregiver permitted after first 8 doses. Average on-site visits Q12W, with option of mobile nursing visits. Biomarker, blood and urine samples to be collected throughout the study. ‡SOC includes ACE inhibitor or ARB at maximum tolerated approved dose with or without SGLT-2 inhibitors, ERA, or other agents for BP management.
ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; IgAN, IgA nephropathy; Q4W, every 4 weeks; R, randomized; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2; SOC, standard of care; UPCR, urine protein-to-creatinine ratio.