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-0865

Safety, Tolerability, and Pharmacodynamics of ARO-C3, a Subcutaneously Administered Investigational RNA-interference Therapeutic Targeting Complement C3 in Adult Healthy Volunteers: Interim Findings from the AROC3-1001 Study

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Objectives : Despite the established role of complement dysregulation in the pathogenesis of C3 Glomerulopathy (C3G) and IgA Nephropathy (IgAN), no therapies targeting complement have been approved for either condition.
Methods : AROC3-1001 (NCT05083364) is an ongoing Phase 1/2a dose-escalating study evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ARO-C3, an RNA-interference therapeutic targeting complement component 3 (C3), in healthy volunteers (HV) and patients with C3G or IgAN. Interim PD and safety data from Part 1 of the study, evaluating single and multiple ascending doses of ARO-C3 in HV, are described.
Results : 42 adult HVs were randomized to ARO-C3 (n=28) or placebo (n=14). ARO-C3 doses between 25-400mg, administered as one or two subcutaneous injections, resulted in durable, dose-dependent decreases in serum complement C3 levels [Fig 1], total complement activity (CH50), and alternative pathway (AP) activity (AH50 and Wieslab AP) [Fig 2]. Following a single 400mg dose of ARO-C3, mean(±SD) C3 reduction of 81±10% from baseline was observed at week 4, with sustained reduction of 79±11% at week 16 [Fig 1a]. Repeat 400mg doses (on Days 1 and 29) led to mean C3 reductions of 88±6% by week 8 and 85±7% at week 16 [Fig1b]. Corresponding decreases of 63±8%, 91±15%, and 98±2% from baseline in CH50, AH50, and Wieslab AP, respectively, were seen 4 weeks after the second dose of ARO-C3 [Fig2]. Decreases in complement activity were sustained through week 16. ARO-C3 was well-tolerated, with no drug-related serious adverse events (SAEs), dose-limiting adverse events (AEs), or AEs resulting in study drug discontinuation. Most AEs were mild in severity.
Conclusions : ARO-C3 is well tolerated and achieves sustained reductions in complement C3 and suppression of total and alternative pathway activity after single and repeat subcutaneous doses, supporting a quarterly dosing regimen. Part 2 of the study, enrolling patients with C3G and IgAN, is ongoing.

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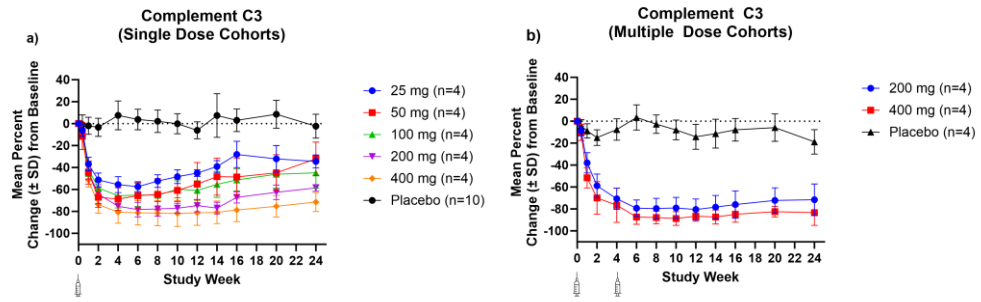

Fig 1. Measured serum complement C3 levels (expressed as percent of baseline) in **(a)** single ascending dose (SAD) healthy volunteer cohorts and **(b)** multiple ascending dose (MAD) healthy volunteer cohorts.

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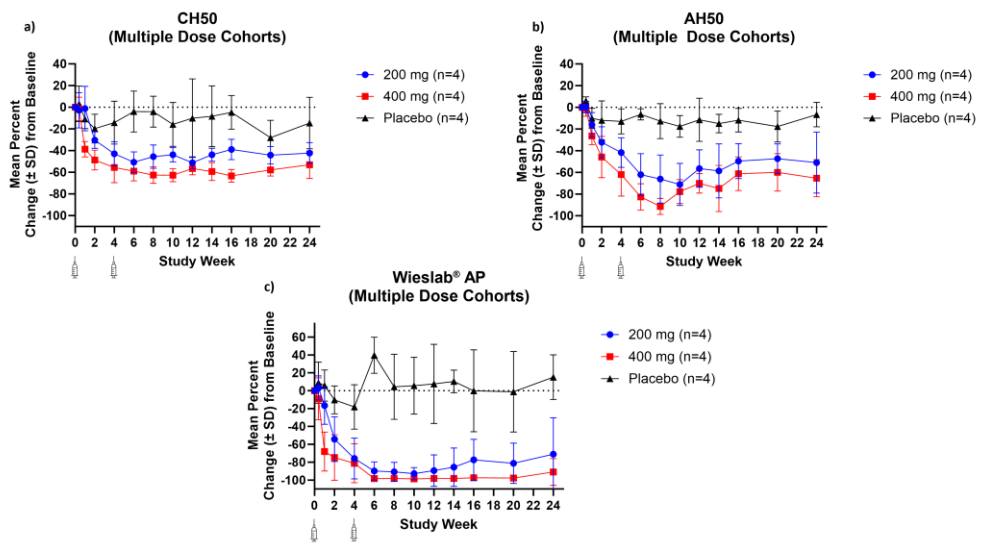

Fig 2. Measures of Complement Activity (expressed as percent of baseline) in multiple ascending dose (MAD) healthy volunteer cohorts: **(a)** Total Complement Activity (CH50), **(b)** Alternative Pathway Activity (AH50), and **(c)** Wieslab® Alternative Pathway (AP) Activity.