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VASCULAR DISEASE

RVX-208 DECREASES PROGRESSION OF ATHEROSCLEROSIS IN APOE NULL MICE

ACC Poster Contributions
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Background: RVX-208 is an orally active small molecule that increases apoA-I production in vitro and in vivo. Preclinical tests in several animal models including the African Green Monkey showed that RVX-208 raises plasma apoA-I, HDL, prebeta1-HDL, large alpha-HDL and ex vivo cholesterol efflux mediated by SR-B1, ABCA1, and ABCG1. Data from phase 1a and 1b/2a human trials showed RVX-208 to be safe and well tolerated.

Methods: Doses of RVX-208 were given orally to humans and mice as indicated.

Results: In the 1b/2a lasting 28 days, at trial end, the apoA-I rose significantly by 6.5 and 10.4% in subjects given 2 or 6 mg/kg/day of RVX-208, respectively vs. placebo. In low HDL-c subjects (<40 mg/dL), apoA-I induced increases were more robust at 7.8 and 10.6%, respectively. HDL changes mirrored the apoA-I and rose by 7.4 and 15.1% in subjects given 2 and 6 mg/kg/day, respectively, of RVX-208 vs placebo. Again low HDL-c subjects responded to RVX-208 with enhanced HDL rises of 10.4 and 15.8%, respectively. These biomarker changes suggested potential benefit on atherosclerosis. To test this possibility, a model of atherosclerosis, the apoE null mice were fed a high-fat diet and 150 mg/kg of RVX-208 or vehicle b.i.d. for 12 weeks. In treated mice the plasma HDL-c levels were 2-fold ($p<0.01$) higher vs. vehicle. Atherosclerotic lesions were 27% ($p<0.01$) and 17% ($p<0.05$) less in aortic sinus and thoracic aorta, respectively in treated mice. Additionally, biomarkers of inflammation; VCAM-1, MIP-1 , IL-18 and SAP were 17, 15, 21 and 18% lower, respectively in treated vs. vehicle. Next apoE null mice were fed a high fat diet for 10 weeks to induce atherosclerosis before starting RVX-208 for 12 weeks. In treated mice, the lesion number within whole aorta was 40% less vs. vehicle.

Conclusions: In summary, the 1b/2a trial extends RVX-208 human safety data to 28d and the RVX-208 induced rise in apoA-I and HDL is both dose and time dependent. Actions of RVX-208 in subjects with low HDL to raise apoA-I and HDL appear more robust suggesting potential usefulness of the compound in this population at high risk for CVD. Data in apo E null mice show the ability of RVX-208 to not only limit but suggests possible regression of atherosclerosis.