

Discussion: IONIS-ANGPTL3 an antisense inhibitor to angiotensin-like protein 3 reduces plasma ANGPTL3 and lipids in healthy volunteers with elevated triglycerides

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# Inhibition of ANGPTL3 with ASO GalNAc Design

Identification of target gene from human genetics (family and population studies)

Testing in both animals and humans for proof of concept

Identification of doses that clearly show impact on atherogenic lipoproteins in phase 1/2a study with small sample size

# Inhibition of ANGPTL3 with ASO GalNAc Design

1. Sustained reductions in ANGPTL3 levels in blood along with reductions in TG, VLDL-C, non-HDL-C, LDL-C, and HDL-C
2. Reductions in TG, VLDL-C, and apo C-III of ~60 that do not appear to be dose dependent
3. Reductions in LDL-C, non-HDL-C, and HDL-C that appear to be dose dependent
4. Reductions in non-HDL-C up to 40% greater than reductions in LDL-C

# Questions

1. What are the effects of targeting ANGPTL3 with ASO on top of high-efficacy statin therapy?
2. Will this mechanism of targeting lipoprotein metabolism provide similar benefit as therapies that increase LDL receptors (statins, ezetimibe, bile acid-binding resins, PCSK9 inhibitors) on ASCVD? Who should be targeted?
3. What are the effects of ANGPTL3 ASO GalNAc on the liver?
4. Are there other adverse effects with long term administration?