IDENTIFICATION AND CHARACTERIZATION OF SOLBINSIRAN, A GALNAC-CONJUGATED SIRNA TARGETING ANGIPOIETIN-LIKE 3

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Presenter Disclosure

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Hypothesis: Blocking ANGPTL3 activity or preventing its expression is a therapeutic approach to reduce atherogenic apoB-containing lipoprotein particles.
ANGPTL3 Genetic Deficiency Protects Against Coronary Artery Disease

Deep phenotyping in a Mendelian family with complete ANGPTL3 deficiency

Complete ANGPTL3 deficiency

First degree related controls

Quantify Atherosclerotic Plaque

No coronary atherosclerosis detected in complete ANGPTL3 deficiency

Large-scale Association of Heterozygous ANGPTL3 deficiency

N=22K CAD
N=158K Controls

Loss of Function Mutations

Test for Association with CAD

Functional Analysis of Missense Mutations in Mouse Models

34% risk of CAD in heterozygous ANGPTL3 deficiency
Triglycerides: -17%
LDL-C: -12%

Circulating ANGPTL3 levels and Risk of MI

N=1500 Cases
N=3200 Controls

Cases with MI
Control

Measure Plasma ANGPTL3 Protein Concentration

35% risk of MI in lowest tertile of ANGPTL3 concentrations

3 Lines of Evidence: ANGPTL3 Deficiency Protects Against CAD

Stitziel et al., JACC (2017)
Solbinsiran is a GalNAc-conjugated siRNA that targets hepatic ANGPTL3 expression

- Solbinsiran (LY3561774) is an angiopoietin like protein 3 (ANGPTL3)-specific Dicer substrate small interfering RNA (DsiRNA) conjugated to N-Acetylgalactosamine (GalNAc)
  - Convenient, subcutaneous administration
  - Long duration of action
  - Target specificity
Solbinsiran reduces human ANGPTL3 mRNA in Huh7 cells

- 275 siRNA screened by transient transfection in immortalized Huh7 human hepatocytes
- Data are mean of 5’ and 3’ RT-PCR assays, arranged by location
Solbinsiran reduces human ANGPTL3 mRNA in Huh7 cells

- 275 siRNA screened by transient transfection in immortalized Huh7 human hepatocytes
- Data are mean of 5’ and 3’ RT-PCR assays, arranged by activity
Solbinsiran reduces human *ANGPTL3* mRNA in mice

- Day 1: 1 mg/kg subcutaneous (SC) doses of solbinsiran were administered to CD1 mice
- Day 4: Human ANGPTL3 expression was induced by hydrodynamic tail vein injection of a plasmid containing the full-length human *ANGPTL3* cDNA under control of a ubiquitous promoter sequence.
- SC dose of 1 mg/kg solbinsiran resulted in a statistically significant reduction of 65% in human *ANGPTL3* mRNA

* p <0.0001 vs vehicle by unpaired t test
Solbinsiran reduces hepatic ANGPTL3 mRNA durably in cynomolgus monkeys

- Female and male Mauritius cynomolgus monkeys were enrolled in the study, n=5/group
- Solbinsiran was formulated in phosphate buffered saline and delivered at 3 mg/kg dose levels by subcutaneous injection at day 0
- On Study Days -5, 28, 56, 84, and 113 liver tissue samples were collected by percutaneous biopsy for ANGPTL3 mRNA measurement

* p <0.05 vs vehicle by unpaired t test
Solbinsiran reduces circulating ANGPTL3 protein durably in cynomolgus monkeys

![Graph showing the reduction of ANGPTL3 protein over time with Solbinsiran compared to vehicle. The graph indicates a significant decrease in serum ANGPTL3 Protein with Solbinsiran, with an asterisk indicating statistical significance at certain time points.

-68.6% reduction by study day 14 with Solbinsiran compared to vehicle.

* p < 0.01 vs vehicle by unpaired t test.
SUMMARY

- Through a large-scale in vitro screen of the anti-ANGPTL3 library in human cells, solbinsiran was identified as an efficacious siRNA.

- When given a single dose at 1 mg/kg subcutaneously, solbinsiran reduced human ANGPTL3 mRNA by 65% in mouse hepatocytes.

- A single dose of solbinsiran reduced liver ANGPTL3 mRNA expression by up to 72.9% and reduced serum ANGPTL3 protein expression by 68.6% in cynomolgus monkeys.

- Solbinsiran displayed a long duration of activity in cynomolgus monkeys, as indicated by a greater than 50% mRNA knockdown remaining 12 weeks after a single dose.
CONCLUSIONS

- These data supported the advancement of solbinsiran to Phase 1 and 2 clinical testing in participants with mixed dyslipidemia (ClinicalTrials.gov Identifiers: NCT04644809 and NCT05256654)

- Solbinsiran may become a therapeutic option for different indications, such as homozygous and heterozygous familial hypercholesterolemia, severe hypertriglyceridemia, mixed dyslipidemia, statin intolerance and, ultimately, to reduce the risk of cardiovascular events in patients with or at high risk for atherosclerotic cardiovascular disease.
THANK YOU