

Results of the First Major Clinical Trial of An Oral Agent Inducing ApoA-I Synthesis: A New Approach to Raising HDL and CV Risk Modification

The ASSERT Study

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Disclosures

- Honoraria and consultant: AstraZeneca, Abbott, Merck, Anthera, Omthera, Takeda, Roche
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The Challenge of Promoting HDL

- Residual cardiovascular risk persists in many patients despite substantial LDL-C reduction.
- While raising HDL is a theoretically attractive target, the optimal approach remains uncertain.
- An alternative to elevations in HDL-C involves strategies to enhance HDL functionality.
- Although preclinical data suggest that enhancing apoA-I synthesis may be beneficial, finding an effective agent has proven challenging.



RVX-208

- RVX-208 is an oral inducer of apoA-I synthesis.
- Enhanced apoA-I synthesis should generate functional HDL particles that facilitate reverse cholesterol transport.
- In animals and healthy volunteers, RVX-208 treatment is associated with an increase in pre- β HDL and α 1 particles, resulting in increased cholesterol efflux potential.
- Improved HDL quantity and quality may produce other non-lipid-related beneficial effects on inflammation and endothelial function.



Objective of ASSERT Study

The ASSERT study aimed to characterize the short-term (12 weeks) efficacy, safety and tolerability of RVX-208 in statin-treated patients with stable coronary artery disease.



ASSERT Study Design

299 Statin-Treated Patients with Stable Coronary Artery Disease at 35 sites in the US

12 Week Treatment Period

2 Week
Screening
Period

RVX-208 50 mg bid

RVX-208 100 mg bid

RVX-208 150 mg bid

Placebo

4 Week
Follow-up
Period



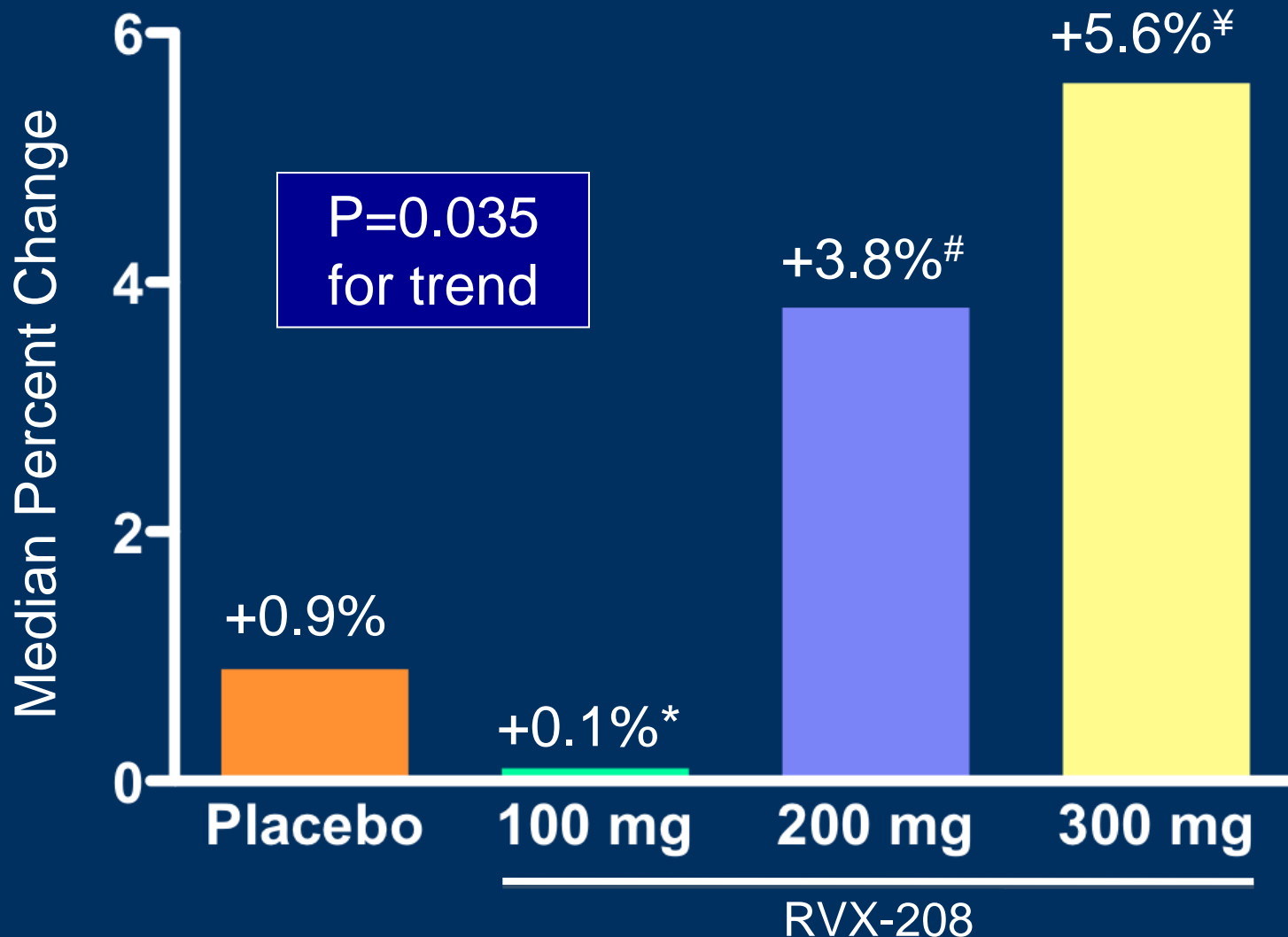
Baseline Patient Characteristics

Parameter	Cohort (n=299)
Age (years)	65.8
Males (%)	75.3
Caucasian (%)	93.3
Body Mass Index (kg/m ²)	30.7
Hypertension (%)	87.6
Diabetes (%)	29.4
Smoker (%)	17.1

Baseline Biochemical Values

Parameter	Cohort (n=299)
Total Cholesterol (mg/dL)	150
LDL Cholesterol (mg/dL)	76
HDL Cholesterol (mg/dL)	44
Triglycerides (mg/dL)	115
Apolipoprotein B (mg/dL)	76
Apolipoprotein A-I (mg/dL)	141
hsCRP (mg/L)	1.8

Median Change in ApoA-I from Baseline



*P=0.09, #P=0.10 and ¥P=0.06 compared with placebo



Median Percent Change in Biochemical Markers

Parameter	Placebo (n=74)	RVX-208			P Value
		100 mg (n=76)	200 mg (n=75)	300 mg (n=74)	
HDL-C	0	3.2	6.3*	8.3**	0.02
LDL-C	4.2	0.7	1.6	1.0	0.79
Triglycerides	1.6	2.2	4.5	6.5	0.85
apoB	-3.8	-6.6	-6.7	-2.0	0.45
hs-CRP	2.5	-13.0	-17.5	-22.0	0.33

* P<0.05 and ** P<0.01 compared with placebo



Median Percent Change in NMR Lipid Markers

Parameter	Placebo (n=74)	RVX-208			P Value
		100 mg (n=76)	200 mg (n=75)	300 mg (n=74)	
Total HDL	1.2	4.0	2.8	5.1	0.80
Large HDL	-0.5	11.1	20.2**	21.1***	0.003
Small HDL	2.6	-0.4	-2.6	-4.0	0.07
HDL size	0	1.1*	1.2***	1.1***	<0.001
Total LDL	3.8	3.8	0.8	4.1	0.25
LDL size	-1.0	0	-0.5	-0.5	0.59

* P<0.05, ** P<0.01 and *** P<0.001 compared with placebo

Increase in Larger α 1 HDL Particles: 2-D Gel Analysis

Least Square Mean Percent Change from Baseline

Parameter	Placebo (n=68)	RVX-208			P Value
		100 mg (n=69)	200 mg (n=68)	300 mg (n=64)	
Pre- β 1 HDL	-7.3	-10.6	-0.4	-4.4	0.17
α 1 HDL	-2.3	3.7	8.0*	8.8*	0.12

* P<0.05 compared with placebo

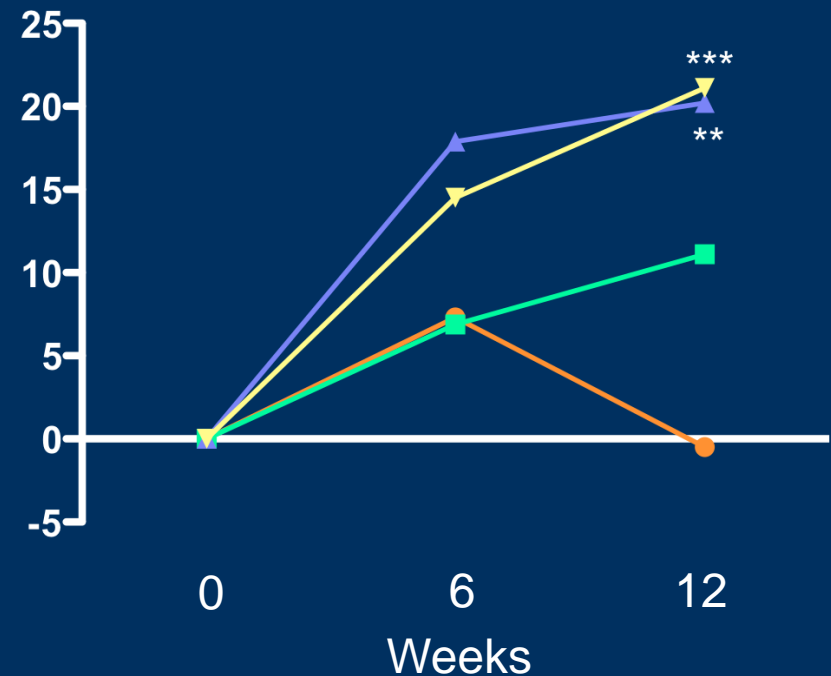
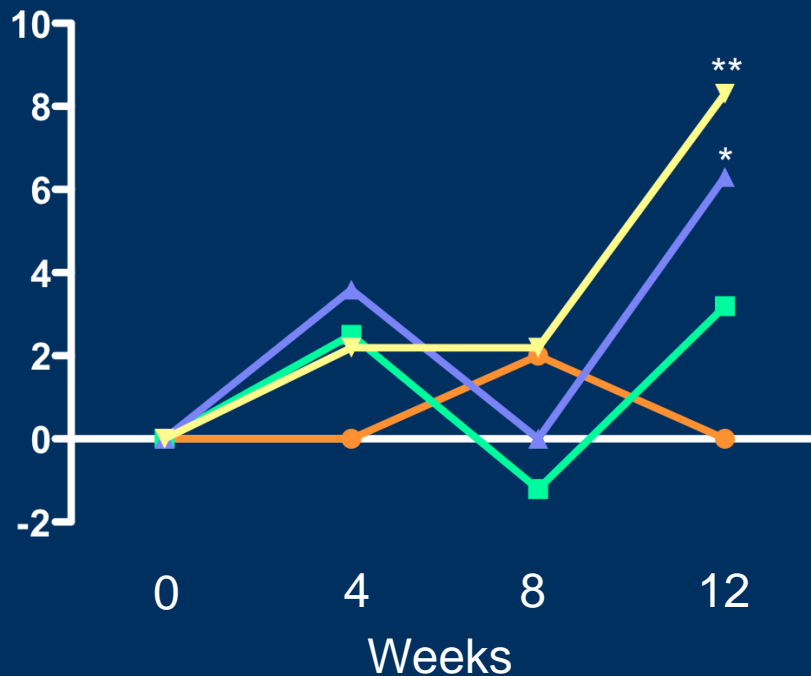


Timing of Increase in HDL Measures

Median Percentage Change from Baseline

HDL Cholesterol

Large HDL



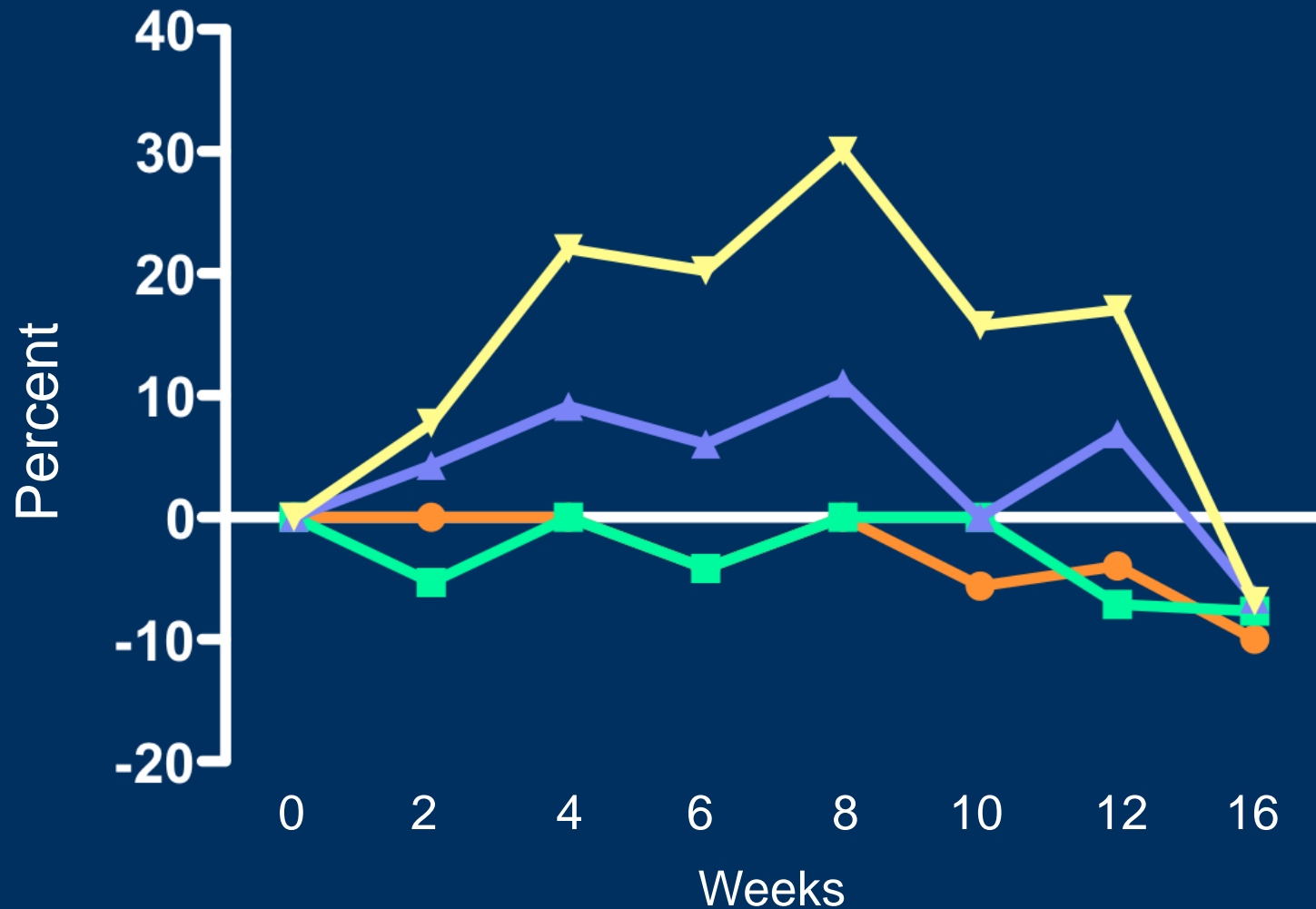
Placebo RVX 100 mg RVX 200 mg RVX 300 mg

* $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ compared with placebo



Biochemical Safety Measures

Median Percentage Change in ALT



Placebo RVX 100 mg RVX 200 mg RVX 300 mg

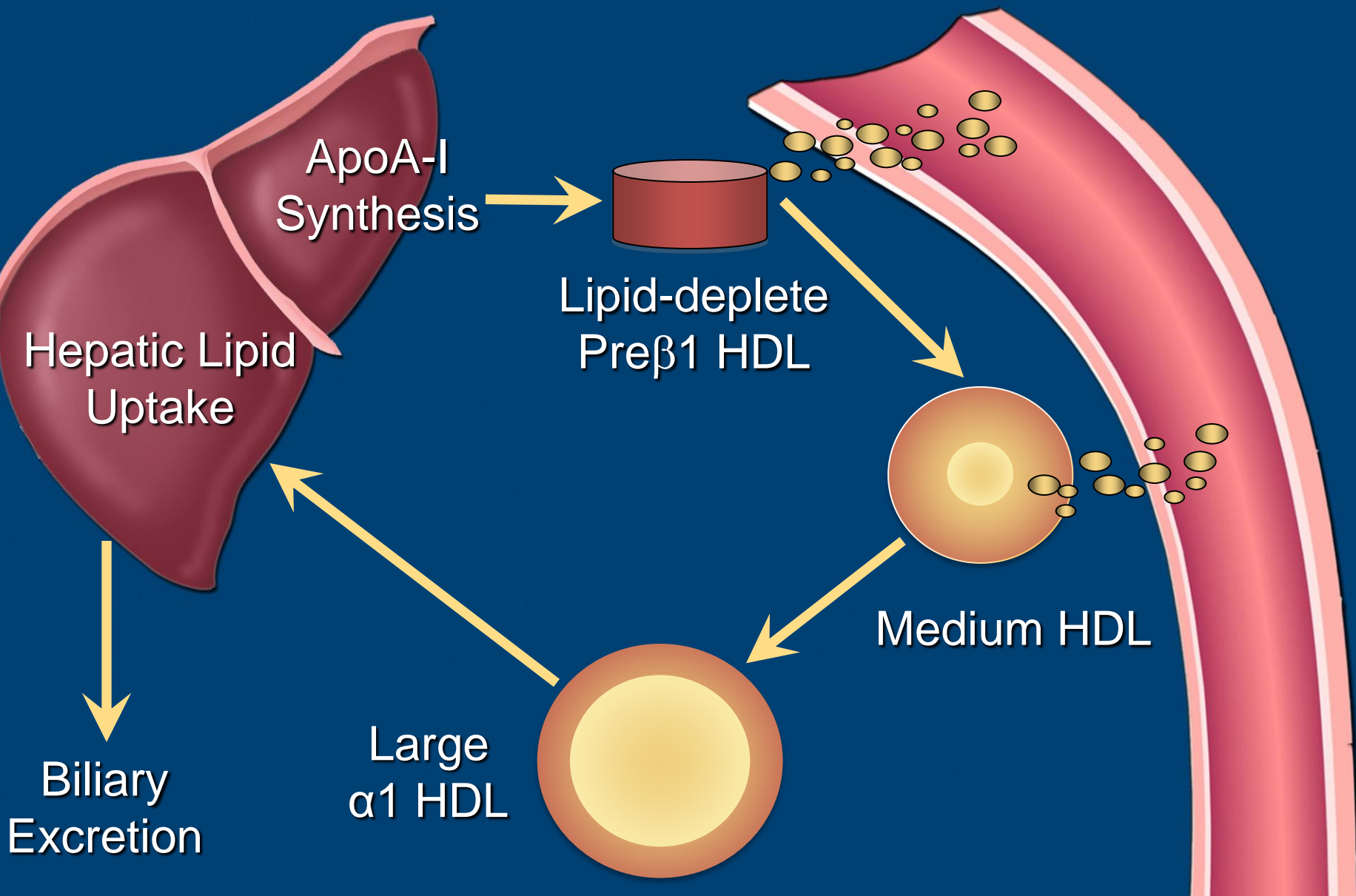


Biochemical Safety Measures

Number of Patients

Parameter	Placebo (n=74)	RVX-208			P Value
		100 mg (n=76)	200 mg (n=75)	300 mg (n=74)	
ALT/AST >3xULN	0	3	8	7	0.009
ALT/AST >8xULN	0	2	4	2	0.28
Tot Bili >2x ULN	0	0	0	0	1.00
CK >3x ULN	4	1	0	3	0.10
Creatinine >1.5x baseline	0	0	3	3	0.07

Proposed Mechanism Underlying Findings



Summary

- While not achieving the primary endpoint, RVX-208 was associated with dose-dependent increases in levels of apoA-I, HDL-C and large HDL particles.
- These changes are consistent with enhanced mobilization of lipid into functional HDL particles.
- The time course of changes suggest that a greater benefit may be observed with longer treatment.
- Reversible transaminase elevations without evidence of impaired liver function were observed.



Conclusion

- Induction of apoA-I synthesis represents a novel approach to HDL therapy targeting functionality rather than quantitative measures of HDL.
- The impact of RVX-208 on plaque burden and cardiovascular outcomes remains to be determined in future studies.

