

# Statin-Like Dose-Dependent Reductions in LDL-C and Apolipoprotein B with ISIS 301012 - An Antisense Inhibitor of ApoB in Subjects with Polygenic Hypercholesterolemia -

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**Data Pending**

400 mg/wk data will be included on completed poster for presentation at the meeting.

## Abstract

## ISIS 301012

**Background:** ISIS 301012 selectively inhibits apoB protein synthesis in the liver. Previously, we have shown an LDL-C reduction up to 70% in healthy volunteers in Phase I dose ranging studies with short term dosing. The safety and efficacy profile allowed for longer treatment duration (13 weeks), less frequent dosing (every other week), and a target population of polygenic hypercholesterolemics failing to meet target with diet and exercise alone.

**Methods:** Subjects (n=10 per group) with elevated LDL-C > 130 mg/dL were enrolled into 1 of 5 groups. The first 2 groups received four 200 mg doses of ISIS 301012 in the first 11 days (Days 1, 4, 8, and 11; "Load") followed by 100 mg qow (avg 50 mg/week), or 200 mg qow (avg 100 mg/week). The last 3 groups received 200, 300, or 400 mg every week without a load. Treatment to placebo was 4:1 in each cohort. Study drug was administered subcutaneously.

**Results:** The study is ongoing. A 12, 22, and 42% median reduction in LDL-C and a 22, 23, and 47% median reduction in apoB were observed in the 50, 100, and 200 mg dose groups, respectively, with negligible changes in the pooled placebo group. Preliminary results in the 300 mg/wk cohort showed a 42 and 41% reduction in LDL-C and apoB, respectively following the first 7 weeks of 13 weeks treatment. The most common adverse event has been mild, painless erythema at injection sites. No drug related serious adverse events occurred. The drug was well tolerated. One subject displayed an isolated ALT >3x ULN 80 days after last dose.

**Conclusions:** The initial results show that ISIS 301012 achieves statin-like LDL-C reductions via a complementary mechanism to statins. Furthermore, achieving such LDL-C reductions with a dosing interval of every other week is feasible. Dose escalation to the 400 mg/wk dose group is underway.

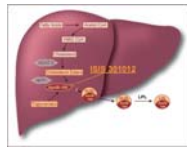
## Background

### Apolipoprotein B & Atherogenic Lipoproteins

- ApoB is an essential component of the principal atherogenic lipoproteins VLDL, IDL, LDL, and Lp(a).
- LDL-C is a risk factor of CVD.
  - LDL-C lowering by statins reduces CVD event rate (TNT, IDEAL, PROVE-IT).
  - Aggressive LDL-C lowering by statins results in regression of atherosclerosis (REVERSAL, ASTEROID).
- Despite statin therapy, 70% of CV events are not prevented.<sup>1</sup>
  - Thus, there is a need for new agents that are complementary in mechanism and additive in effect to statins, and that exert beneficial effects on other risk markers, e.g. elevated triglycerides.<sup>2</sup>

- ISIS 301012 is a 2<sup>nd</sup> generation antisense oligonucleotide<sup>3</sup> complementary to the coding region of the human apoB mRNA.

Selective hybridization (binding) of ISIS 301012 to the cognate mRNA by Watson and Crick base-pairing results in RNase H-mediated degradation of the mRNA to prevent translation of the apoB protein. ApoB is the principal apolipoprotein of LDL and its metabolic precursor, VLDL.



- The effects of ISIS 301012 at doses of 50 to 400 mg in healthy volunteers with primary hypercholesterolemia have recently been published.<sup>4</sup>
- The current study addresses the effects of ISIS 301012 monotherapy in hypercholesterolemic subjects for 13 weeks. Our results presented at this meeting address the effects of ISIS 301012 in combination with statins in subjects of similar disposition.<sup>5</sup>

## Study Design

- This Phase 2 clinical study was designed to examine the dose response of ISIS 301012 as a single agent in subjects with high cholesterol and unable to reach target by lifestyle changes alone.
- Fifty subjects were enrolled in one of five ISIS 301012 dose cohorts (4:1 ratio of active:placebo) at a single site in Germany.
- Study drug was administered by s.c. injection at a dose of 200 mg twice weekly for two weeks followed by 100 (50 mg/wk group) or 200 mg (100 mg/wk group) every other week for 11 weeks; and 200, 300, or 400 mg once per week for 13 weeks (200, 300, or 400 mg/wk groups) without an initial loading dose.
- The primary endpoint was percent reduction in LDL-C from baseline 2 weeks after a 3-month treatment period (Day 99).
- Safety and tolerability were assessed by the incidence, severity, and relationship of adverse events by treatment group. Follow-up period was for 6 months following the last dose.
- Secondary endpoints included % change from baseline in apoB, VLDL-C, HDL-C, non-HDL, total cholesterol, triglycerides, and the apoB/apoA1 ratio.
- Exact Wilcoxon rank-sum tests were used to determine significant differences between placebo and the ISIS 301012-treated groups.

## Baseline Characteristics

Characteristic	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk	400 mg/wk
n	10	8	8	8	8	8
Age	53	50	40	48	55	58
MW	82	77	71	71	80	80
ApoB	130	156	129	130	139	150
	(119-154)	(106-184)	(100-189)	(93-150)	(109-160)	(118-172)
LDL-C	162	172	154	173	178	206
	(127-181)	(132-216)	(133-216)	(132-216)	(119-232)	(162-241)
Non-HDL-C	108	212	195	196	199	225
	(116-238)	(118-289)	(133-276)	(150-228)	(153-239)	(163-260)
VLDL-C	23	17	19	17	23	30
	(9-57)	(10-57)	(7-58)	(8-58)	(6-49)	(14-52)
HDL-C	54	55	57	54	50	52
	(39-61)	(45-63)	(40-65)	(40-59)	(40-59)	(39-62)
Apo A1	133	137	142	127	114	120
	(116-159)	(123-171)	(115-159)	(114-141)	(92-135)	(86-149)
Apo B:A1	1.0	1.1	0.8	1.0	1.1	1.2
	(0.8-1.3)	(0.8-1.4)	(0.7-1.3)	(0.7-1.3)	(1.0-1.7)	(0.8-1.9)
TC	240	271	240	252	248	272
	(195-299)	(205-307)	(203-308)	(208-279)	(194-289)	(211-322)
TG	177	161	125	129	182	219
	(89-174)	(79-238)	(64-200)	(62-200)	(87-240)	(101-293)

Lipids and lipoproteins are presented in mg/dL.

## Lipid Profile Two Weeks After Treatment

Characteristic (Median %Δ)	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk	400 mg/wk
ApoB	7%	-22% P=0.07	-23% P=0.001	-47% P=0.0002	-41% P=0.0003	-51% P=0.0003
LDL-C	2%	-12% P=0.33	-22% P=0.002	-42% P=0.0002	-62% P=0.0003	-62% P=0.0003
Non-HDL-C	4%	-17% P=0.25	-21% P=0.02	-44% P=0.0002	-54% P=0.0003	-54% P=0.0003
VLDL-C	-17%	-14% P=0.43	-14% P=0.98	-54% P=0.0002	-52% P=0.0003	-52% P=0.0003
HDL-C	2%	9% P=0.28	5% P=0.40	1% P=0.72	-1% P=0.93	-15% P=0.0002
Apo A1	0%	8% P=0.01	5% P=0.19	-2% P=0.96	-14% P=0.06	-14% P=0.06
Apo B:A1	11%	-22% P=0.007	-26% P=0.0002	-46% P=0.0002	-51% P=0.0003	-51% P=0.0003
TC	6%	-12% P=0.33	-15% P=0.09	-34% P=0.0002	-46% P=0.0003	-46% P=0.0003
TG	-13%	-7% P=0.68	-22% P=0.04	-46% P=0.0002	-43% P=0.0003	-43% P=0.0003

\*Data Pending - Will be included on the poster at time of meeting.

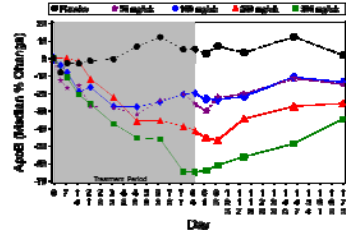
<sup>†</sup>HDL-C measurements for this study were performed using a direct method that can be inaccurate when LDL-C levels are low. Parallel evaluation of the 200 mg/wk cohort in this study using a common precipitation method showed an 11% increase in HDL-C.

## Liver Transaminase

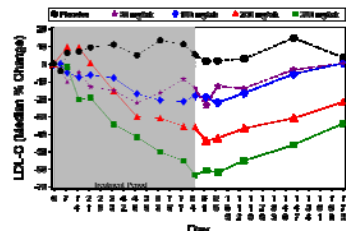
ALT Elevations	Placebo (n=9) <sup>†</sup>	50 mg (n=8)	100 mg (n=8)	200 mg (n=8)	300 mg (n=8)	400 mg (n=8)
Dosing	0	0	0	0	0	0
Follow-up	0	0	0	1	1	1

<sup>†</sup>ALT elevation ≥ 3xULN on two consecutive measures at least 7 days apart.  
<sup>‡</sup>2 subjects not included. †Cohort in fu period. ‡Cohort in dosing period.

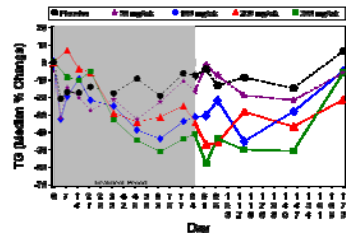
## ApoB\*



## LDL-C\*



## TG\*



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## Safety Observations

- One SAE (meningoencephalitis) occurred that was considered unrelated to drug.
- The most common adverse event was mild, painless erythema at site of injection.
- One subject had consecutive ALT elevations ≥ 3x ULN during follow-up, with no elevation in total bilirubin.
- Recently dosed cohorts continue in their 6-month post-dosing follow-up period.

## Summary of Results

- Potent, dose-dependent reductions in atherogenic lipids and lipoproteins with maximum XX% (P=xxx) and YY% (P=xxx) reduction in apoB and LDL-C at 400 mg/wk respectively.
- Prolonged effects consistent with > 30-day terminal elimination half-life.
- Clinically significant reductions in TG and VLDL-C levels with maximum XX% (P=xxx) and YY% (P=xxx) reductions at 400 mg/wk respectively.

## Conclusions

- Reductions in apoB-containing lipoproteins exceed those reported for statins in other studies
- Clinically significant reductions in triglycerides
- No unexpected toxicities
- Further studies are required to determine the generalizability of these results.

## References

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- Kastelein JJP, et al. Circulation 2006;114:1729-35.
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