UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K/A
(Amendment No.1)

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): November 13, 2006

ISIS PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	(IRS Employer Identification No.)

1896 Rutherford Road
Carlsbad, CA 92008
(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01. Other Events.

On November 13, 2006, Isis Pharmaceuticals, Inc. ("Isis") announced new Phase 2 clinical data from ISIS 301012 studies. A copy of the Press Release related to these data is attached hereto as Exhibit 99.1 and is incorporated herein by reference.

In addition, Isis held a web cast conference call regarding these data. A copy of the slides Isis presented as part of the conference call is attached hereto as Exhibit 99.2 and is incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1	Press Release dated November 13, 2006*.
99.2	Slides Presented on the November 13, 2006 Conference Call.

* Previously Filed

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: November 13, 2006

By: /s/ B. Lynne Parshall
B. LYNNE PARSHALL
Executive Vice President,
Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1	Press Release dated November 13, 2006*.
99.2	Slides Presented on the November 13, 2006 Conference Call.

* Previously Filed

ISIS 301012

Phase 2 Results and Program Overview

November 13, 2006

Today's Program

- **Opening Remarks**
  Stanley T. Crooke, MD, PhD
  Chairman and Chief Executive Officer,
  Isis Pharmaceuticals, Inc.

- **ISIS 301012 Clinical Results and Review**
  Mark K. Wedel, MD, JD
  Senior Vice President and Chief Medical Officer,
  Isis Pharmaceuticals, Inc.

- **Clinician's Perspective**
  John J. P. Kastelein, MD, PhD
  Chairman, Department of Vascular Medicine
  Academic Medical Center
  Amsterdam, The Netherlands

Isis Pharmaceuticals
Summary of Key Assets

Three Near Term Product Opportunities
ISIS 301012 ◆ ISIS 113715 ◆ Alicaforsen

Deep Portfolio of Second-Generation Antisense Product Opportunities
Cardiovascular ◆ Metabolic ◆ Inflammation ◆ Ocular ◆ Cancer

Ibis Biosciences Biosensor Products and Technology
Ibis T5000 Instrument ◆ Assay Kits ◆ Assay Services ◆ Research & Development Contracts

Industry Leading RNA-based Estate
Approximately 1,500 patents ◆ Over $84 million generated

Solid Corporate Partner Track Record
Pharmaceutical partners ◆ Biotechnology partners ◆ Satellite companies

Drug Development Pipeline
Isis Internal

Product (form)	Target	Lead Indication	Partner	Preclinical	Phase 1	Phase 2	Phase 3	Marketed
Alicaforsen (E) (ISIS 2302)	ICAM-1	Ulcerative Colitis	Isis					
ISIS 301012 (SC)	ApoB-100	High Cholesterol	Isis*					
ISIS 113715 (SC)	PTP-1B	Diabetes	Isis					
ISIS 369645 (A)	IL-4R α	Asthma	Isis					
ISIS 353512 (SC)	CRP	Cardiovascular / Inflammation	Isis					
ISIS 325568 (SC)	GCGR	Diabetes	Isis*					

A = Aerosol E = Enema SC = Subcutaneous

* Developed by Isis as part of the Symphony GenIsis collaboration

ISIS PHARMACEUTICALS

Drug Development Pipeline
Partners

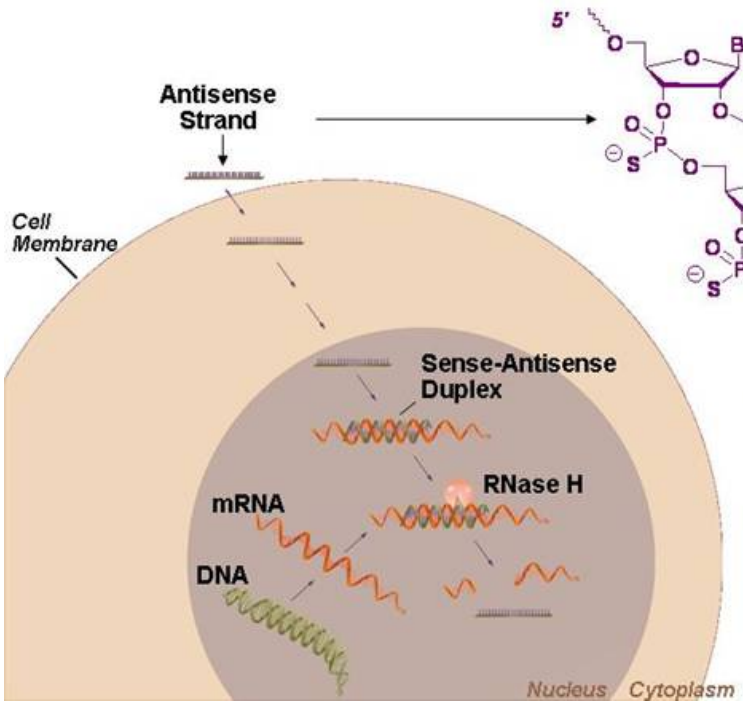
Product (form)	Target	Lead Indication	Partner	Preclinical	Phase 1	Phase 2	Phase 3	Marketed
Vitravene® (I)	CMV	CMV Retinitis	Novartis					
ATL1102 (SC)	VLA-4	MS	ATL					
OGX-011 (IV)	Clusterin	Cancer	OncoGenex					
LY2181308 (IV)	Survivin	Cancer	Lilly					
LY2275796 (IV)	eIF-4E	Cancer	Lilly					
iCo 007 (I)	C-Raf kinase	Ocular Diseases	iCo					
OGX-427 (IV)	Hsp27	Cancer	OncoGenex					
ISIS 333611 (IT)	SOD1	ALS	ALSA					
ISIS 5320 (T) **	HIV	AIDS	ImQuest					

I = Intravitreal IT = Intrathecal IV = Intravenous SC = Subcutaneous T = Topical
** Aptamer

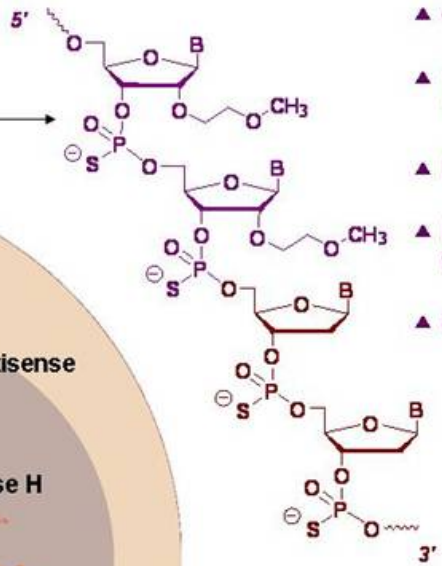
ISIS PHARMACEUTICALS

Antisense: A Novel Approach to Drug Discovery Through Inhibition of Translation of a Specific Targeted Protein

RNase H Dependent Mechanism of Action



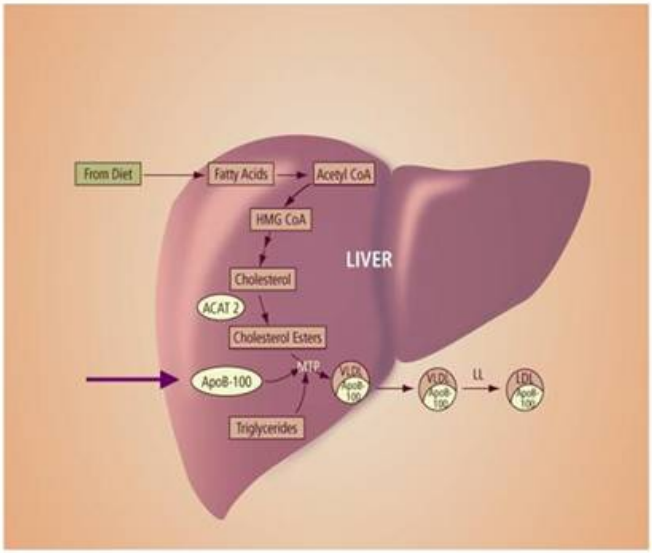
2nd Generation Antisense Drugs



- ~20X more potent
- 1X/week to 1X/quarter dosing
- Better tolerated
- Lower cost of therapy
- Orally bioavailable

ISIS PHARMACEUTICALS

Human ApoB-100 is an Ideal Target for a 2nd Generation Antisense Drug



- Expressed in the liver
- Essential for the synthesis and transport of VLDL and LDL-C
- Plays a crucial role in lipid management
- Biologically validated, but undruggable target for small molecules
- An apoB-100 inhibitor should have a unique lipid lowering profile
- Complementary mechanism with potential for additive effects when co-administered with statins
- Status
  - Phase 2 program in progress
  - Symphony Genlsis collaboration

ISIS PHARMACEUTICALS

ISIS 301012
Summary of Preclinical Properties

- Potent dose-dependent reduction of liver mRNA and protein levels, and serum apoB-100 in normal and hyperlipidemic animals
- 50 to 90% reduction of apoB mRNA in all species evaluated
- Attractive safety profile in mice and other species
- Antisense inhibition of apoB-100 produces secondary effects on genes associated with lipid synthesis & fatty acid oxidation
- Excellent PK/PD correlation (elimination half-life > 30 days)
- Reduction of atherosclerotic plaques in two animal models

ISIS PHARMACEUTICALS

ISIS 301012
Clinical Development Strategy

- We intend for ISIS 301012 to be:
  - The drug of choice for patients at risk who are unable to achieve target levels when added to statins & ezetimibe
    - initially in patients with Familial Hypercholesterolemia (FH)
    - ultimately in patients with polygenic hypercholesterolemia
  - An alternative to statins for those who are intolerant of statins
  - An alternative to statins period

ISIS PHARMACEUTICALS

ISIS

Mark Wedel, MD, JD

ISIS 301012 Clinical Results and Review

ISIS 301012
Clinical Program Overview

- Phase 1
  - Healthy volunteers
  - Drug-drug interaction
- Phase 2
  - Hypercholesterolemic subjects
    - Monotherapy
    - Co-administration with statins
  - High-risk populations
    - Homozygous familial hypercholesterolemia (HoFH)
    - Heterozygous familial hypercholesterolemia (HeFH)

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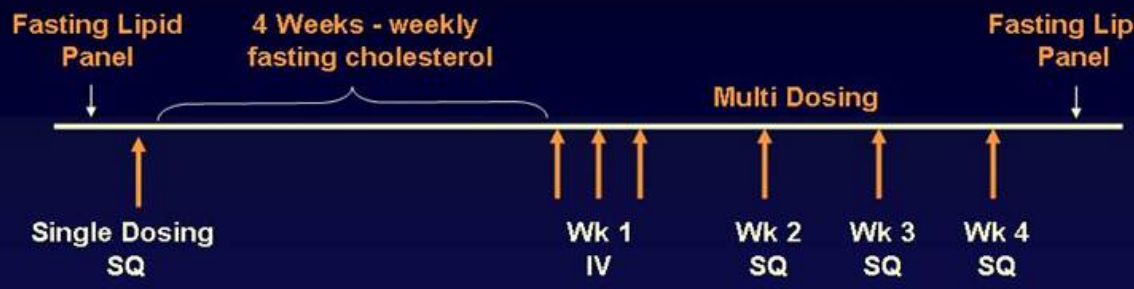
ISIS 301012 – Phase 1 Design
Normal Volunteers with Mild Hypercholesterolemia

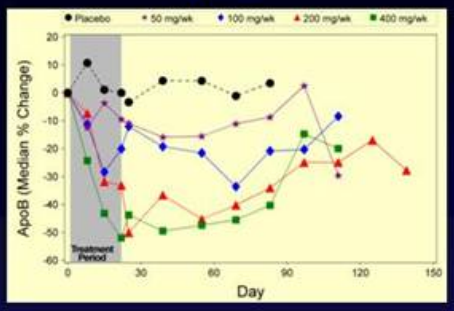


ISIS

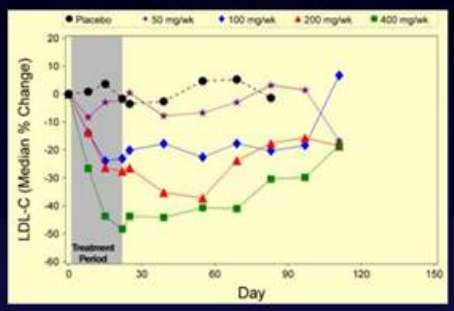
ISIS 301012 – Phase 1

Dose-Dependent Prolonged Reduction in Serum ApoB & LDL-C*

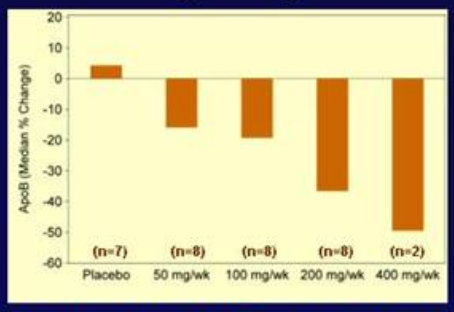
ApoB



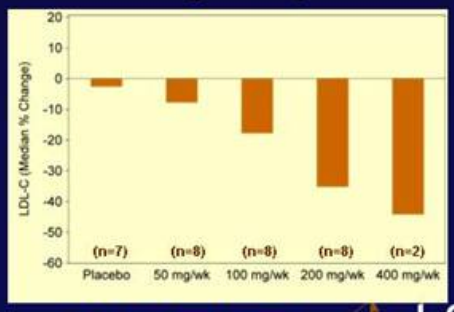
LDL-C



% Change at Day 39**



% Change at Day 39**



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

** 14 days post dosing

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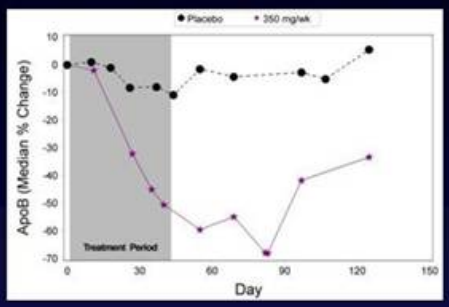
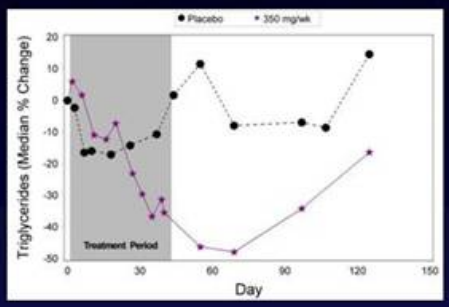
ISIS 301012 – Phase 1

Reductions in Serum ApoB, LDL-C and TG *(dose: 350 mg/wk, 1 month)*

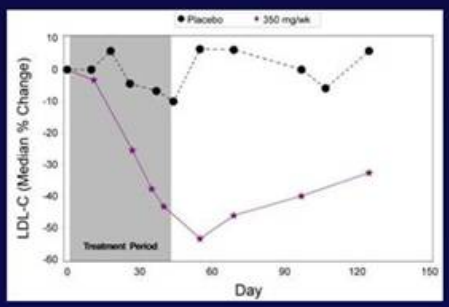
ApoB



Triglycerides



LDL-C



Median Reductions	
ApoB	60%
LDL-C	54%
Triglycerides	46%

N = 6 treated
N = 12 placebo

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ISIS 301012 – Drug-Drug Interaction Study

Study Design

ISIS 301012: 200 mg IV

Day: 1 4 6 8 11

Simvastatin: 40 mg

ISIS 301012: 200 mg IV

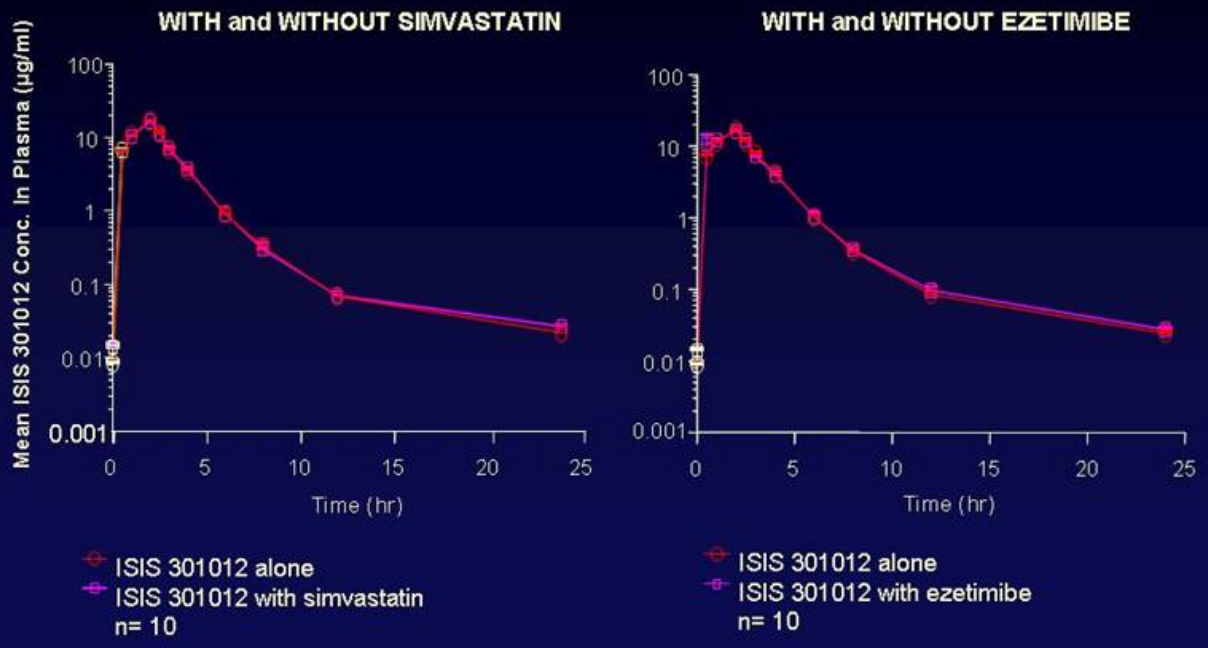
Day: 1 8 10 12 15

Ezetimibe: 10 mg

ISIS

ISIS 301012 – Drug-Drug Interaction Study

Lack of PK Interaction with Oral Lipid Lowering Drugs



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ISIS 301012
Pharmacokinetics Summary

- Elimination half-life: 31 days at 200 mg/week dose
- No clinically significant PK or metabolism interactions seen with simvastatin or ezetimibe supporting further work in combination

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ISIS 301012 Monotherapy
Study Design

- Randomized, placebo-controlled, double-blind, dose-escalation trial with 10 subjects per cohort (1:4)
- Study population: hypercholesterolemic subjects with LDL-C > 130 mg/dL on diet alone
- Dosing cohorts:
  - 50 mg/wk
  - 100 mg/wk
  - 200 mg/wk

  midpoint safety data review
  - 300 mg/wk
  - 400 mg/wk
- Dosing duration: 3 months
- Primary endpoint: % apoB reduction at Day 99

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ISIS 301012 Monotherapy

Patient Demographics & Baseline Lipid Values

Characteristic	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
n	8	8	8	8	8
age	53	50	40	48	55
M/F	6/2	7/1	7/1	7/1	8/0
ApoB	135 (110-154)	156 (106-184)	129 (100-185)	130 (93-150)	139 (109-160)
LDL-C	163 (127-181)	172 (132-218)	154 (132-266)	173 (135-210)	178 (119-232)
TC	246 (195-299)	271 (205-307)	249 (202-340)	252 (208-279)	248 (194-298)
Non-HDL-C	197 (156-238)	212 (158-250)	188 (152-276)	196 (150-225)	199 (153-239)
TG	177 (88-474)	161 (79-330)	125 (54-295)	129 (62-200)	182 (67-240)
VLDL-C	23 (12-57)	17 (10-57)	19 (7-34)	17 (8-34)	23 (5-40)
HDL-C	54 (39-61)	55 (45-63)	57 (50-65)	54 (49-60)	50 (40-59)

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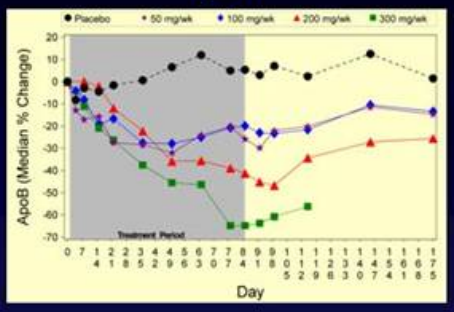
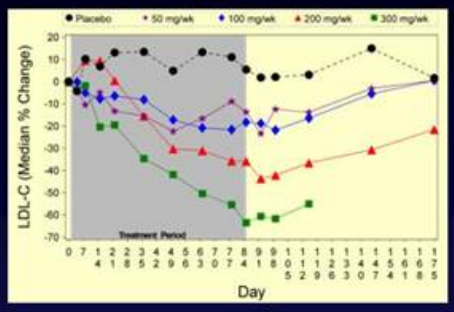
ISIS 301012 Monotherapy

Dose-Dependent ApoB & LDL-C Reduction

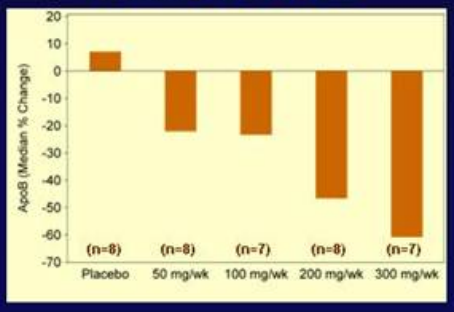
ApoB



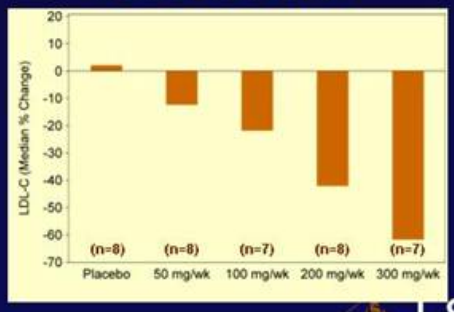
LDL-C



% Change at Day 99*



% Change at Day 99*



* 14 days post dosing

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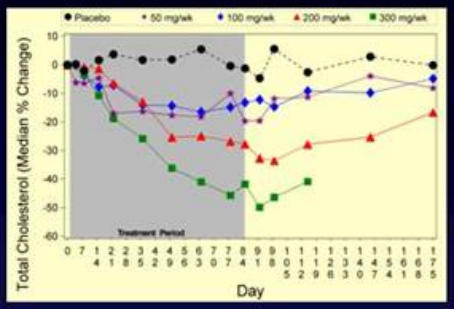
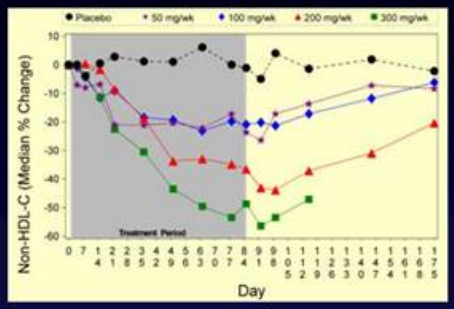
ISIS 301012 Monotherapy

Dose-Dependent Total-C & Non-HDL-C Reduction

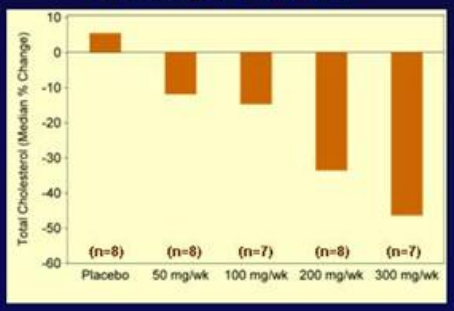
Total Cholesterol



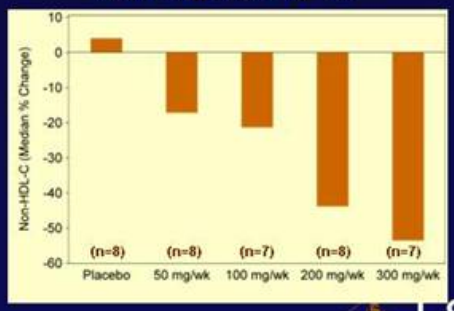
non-HDL-C



% Change at Day 99*



% Change at Day 99*



* 14 days post dosing

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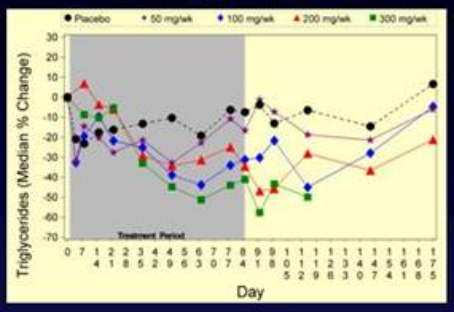
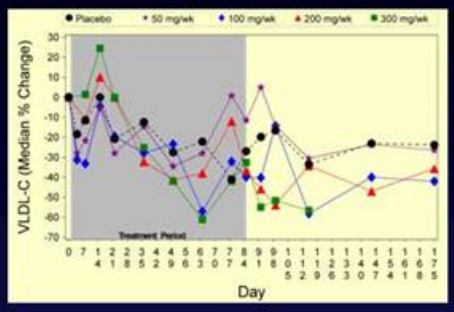
ISIS 301012 Monotherapy

Dose-Dependent TG & VLDL-C Reduction

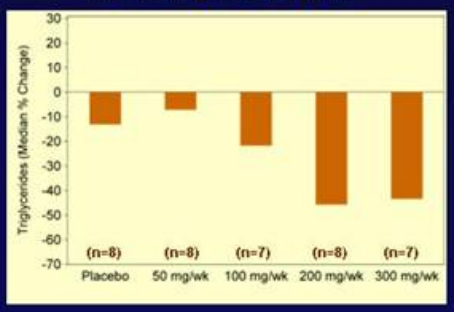
Triglyceride



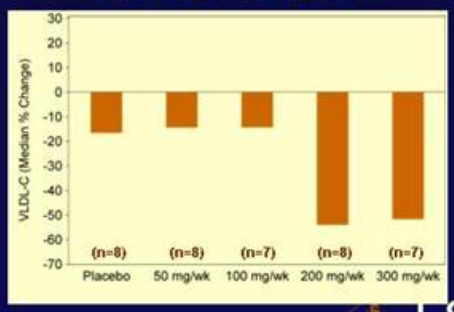
VLDL-C



% Change at Day 99*



% Change at Day 99*



* 14 days post dosing

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ISIS 301012 Monotherapy

Median % Change from Baseline, Day 99

	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
ApoB	7 %	-22 % P=0.07	-23 % P=0.001	-47% P=0.0002	-61 % P=0.0003
LDL-C	2 %	-12 % P=0.33	-22 % P=0.01	-42 % P=0.0002	-62 % P=0.0003
TC	6 %	-12 % P=0.33	-15 % P=0.09	-34 % P=0.0002	-46 % P=0.0003
Non-HDL-C	4 %	-17 % P=0.25	-21 % P=0.02	-44 % P=0.0002	-54 % P=0.0003
TG	-13 %	-7 % P=0.65	-22 % P=0.54	-46 % P=0.02	-43 % P=0.04
VLDL-C	-17 %	-14 % P=0.43	-14 % P= 0.93	-54 % P=0.006	-52 % P=0.04
HDL-C	2 %	9 % P=0.28	5 % P=0.40	-1 % P=0.72	-15 %* P=0.009

P value = versus placebo

*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 300 mg/wk cohort in this study using a common precipitation method showed an 11% increase in HDL-C.

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ISIS 301012 Monotherapy

ApoB/ApoA1 and TC/HDL Ratios

	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
apoB/apoA1					
Baseline	1.0 (0.8-1.1)	1.1 (0.6-1.4)	0.8 (0.7-1.3)	1.0 (0.7-1.3)	1.1 (1.0-1.7)
Day 99	1.0 (0.9-1.2)	0.8 (0.4-1.1)	0.6 (0.5-1.1)	0.5 (0.3-0.9)	0.6 (0.4-0.9)
% Δ	11 %	-22 % P=0.007	-26 % P=0.002	-46 % P=0.0002	-51 % P=0.0003

	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
TC/HDL-C					
Baseline	4.9 (3.7-5.0)	4.8 (3.6-5.7)	4.1 (3.7-5.6)	4.7 (3.6-5.3)	4.8 (4.5-6.3)
Day 99	4.5 (4.1-5.3)	4.1 (2.7-5.0)	3.4 (3.0-4.8)	3.1 (2.0-4.5)	3.0 (2.6-4.6)
% Δ	-4 %	-14 % P=0.10	-18 % P=0.006	-34 % P=0.0006	-35 % P=0.001

P value = versus placebo

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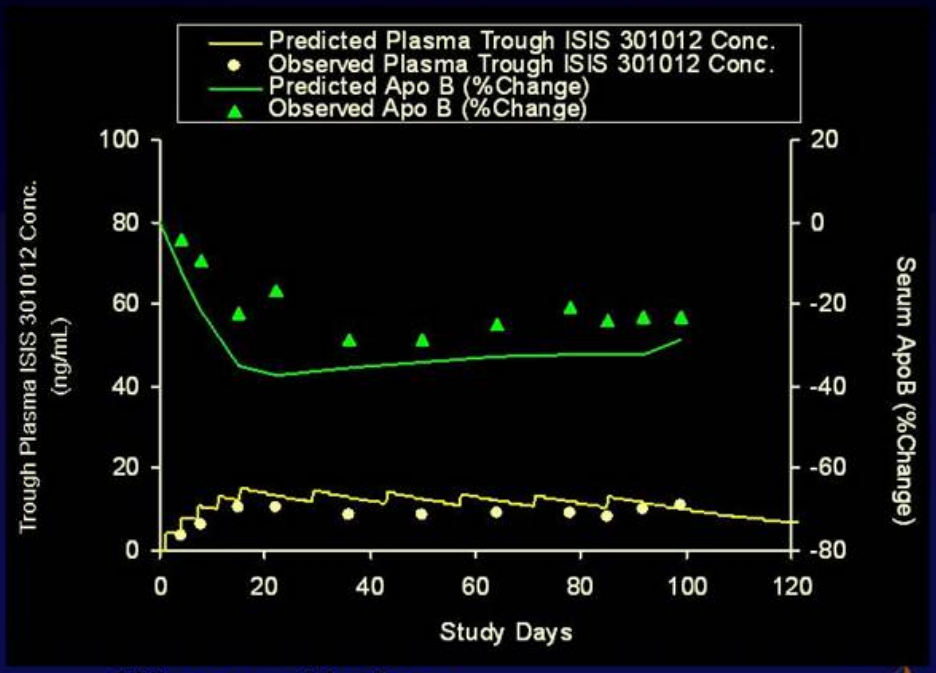
ISIS 301012 Monotherapy

PK/PD Model Predicts Trough Concentrations and Pharmacologic Response



100 mg weekly dose

ISIS

ISIS 301012 Monotherapy

Safety Observations

Serious Adverse Events:

- one 'unrelated' SAE (encephalitis)

Adverse Events (> 10%):

- painless, transient erythema at site of injection

	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
Inject. site erythema	0	7	8	8	pending
Headache	5	4	5	3	pending
Nasopharyngitis	4	2	2	4	pending

Laboratory Findings:

- one subject with confirmed ALT > 3x ULN elevation, which resolved

	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
1-2X ULN	1	3	1	2	3
2-3X ULN	0	2	1	1	4
>3X ULN	0	0	0	1	0

ISIS

ISIS 301012 added to Statins

Study Design

- Randomized, placebo-controlled, double-blind, dose-escalation trial with 10 subjects per cohort (1:4)
- Study population: hypercholesterolemic subjects with LDL-C > 100 mg/dL on stable dose of ≤ 40 mg simvastatin or atorvastatin for ≥ 3 months
- Dosing cohorts:
  - 30 mg/wk
  - 100 mg/wk
  - 200 mg/wk
  - 300 mg/wk
  - 400 mg/wk
- **Dosing duration: 5 weeks**
- Primary endpoint: % apoB reduction at Day 59

• additional cohorts at 200 & 300 mg/wk have been added with an extended dosing duration of 3 months

ISIS

ISIS 301012 added to Statins

Patient Demographics & Baseline Lipid Values

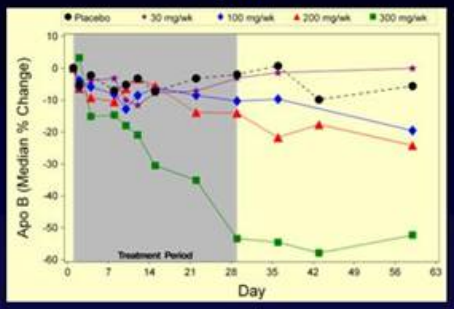
Characteristic	Placebo	30 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
n	9	8	8	8	8
age	62	59	59	58	57
M/F	6/3	6/2	4/4	6/2	4/4
ApoB	114 (84-137)	95 (86-116)	106 (69-147)	112 (78-141)	133 (122-159)
LDL-C	137 (110-175)	107 (95-154)	134 (84-189)	131 (107-162)	168 (143-216)
TC	210 (169-250)	173 (162-234)	193 (149-250)	212 (170-265)	257 (199-293)
Non-HDL-C	154 (118-191)	125 (110-162)	142 (98-203)	138 (113-221)	184 (150-232)
TG	151 (93-249)	118 (76-188)	117 (85-237)	105 (65-301)	152 (128-210)
VLDL-C	13 (6-29)	13 (5-23)	9 (4-29)	7 (5-58)	16 (5-31)
HDL-C	56 (43-101)	53 (45-72)	50 (38-63)	65 (34-100)	67 (36-87)

ISIS

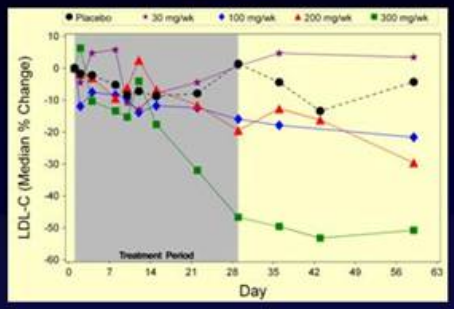
ISIS 301012 added to Statins

Dose-Dependent ApoB & LDL-C Reduction

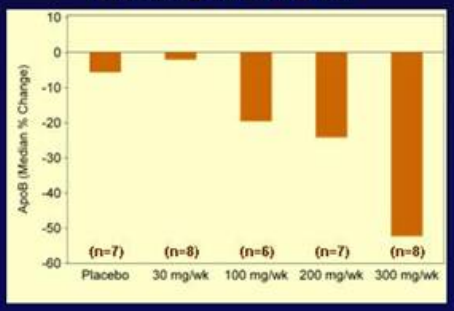
ApoB



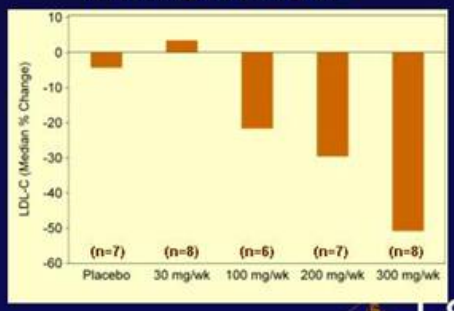
LDL-C



% Change at Day 59*



% Change at Day 59*



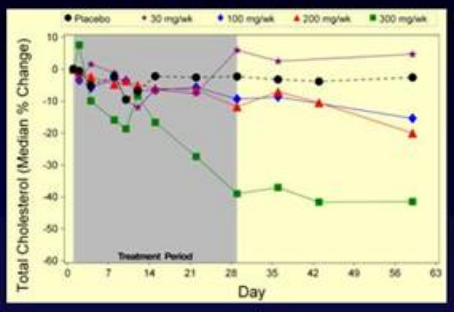
* 30 days post dosing

ISIS

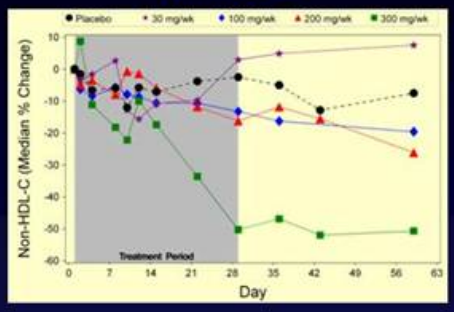
ISIS 301012 added to Statins

Dose-Dependent Total-C & Non-HDL-C Reduction

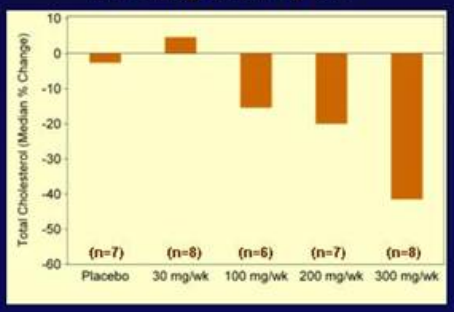
Total Cholesterol



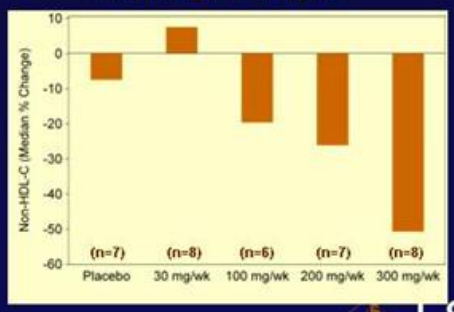
Non-HDL-C



% Change at Day 59*



% Change at Day 59*



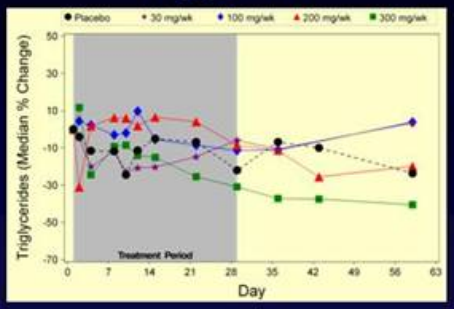
* 30 days post dosing

ISIS

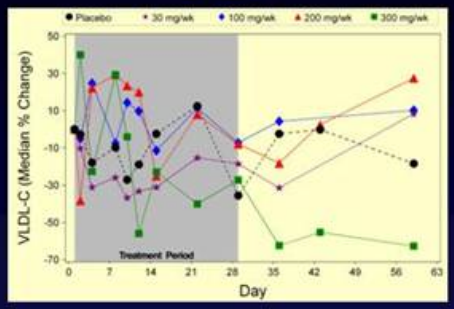
ISIS 301012 added to Statins

Dose-Dependent TG & VLDL-C Reduction

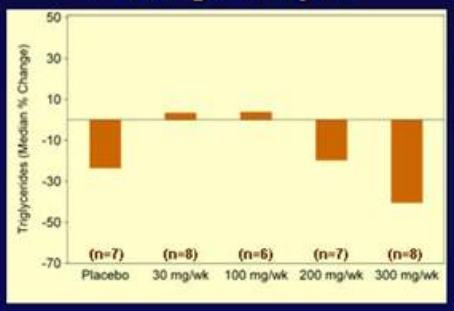
Triglyceride



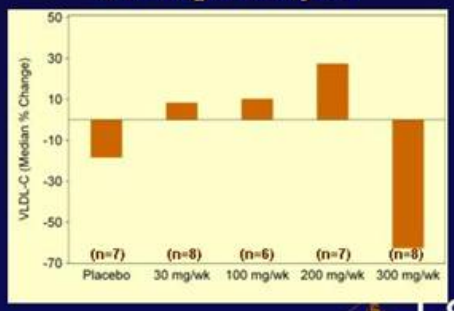
VLDL-C



% Change at Day 59*



% Change at Day 59*



* 30 days post dosing

ISIS

ISIS 301012 added to Statins

Median % Change from Baseline, Day 59

	Placebo	30 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
ApoB	-6 %	0 % P=0.54	-20 % P=0.18	-24 % P=0.05	-52 % P=0.0006
LDL-C	-4 %	4 % P=0.23	-22 % P=0.05	-30 % P=0.002	-51 % P=0.0005
TC	-3 %	5 % P=0.61	-15 % P=0.02	-20 % P=0.03	-42 % P=0.0006
Non-HDL-C	-8 %	8 % P=0.23	-20 % P=0.10	-26 % P=0.07	-51 % P=.0003
TG	-24 %	4 % P=0.12	4 % P=0.14	-20 % P=0.90	-41 % P=0.15
VLDL-C	-18 %	8 % P=0.23	10 % P=0.10	28 % P=0.46	-63 % P=0.19
HDL-C	12 %	1 % P=0.09	-4 % P=0.05	-2 % P=0.04	5 % P=0.24

P value = versus placebo

ISIS

ISIS 301012 added to Statins
ApoB/ApoA1 and TC/HDL Ratios

	Placebo	30 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
apoB/apoA1					
Baseline	0.7 (0.4-0.9)	0.6 (0.5-0.7)	0.7 (0.5-1.1)	0.6 (0.4-1.0)	0.8 (0.6-1.0)
Day 59	0.7 (0.5-20.7)	0.6 (0.5-0.7)	0.6 (0.4-0.7)	0.4 (0.2-0.9)	0.4 (0.2-0.7)
% Δ	-1 %	0 % P=0.78	-15 % P=0.10	-30 % P=0.02	-55 % P=0.0003

	Placebo	30 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
TC/HDL-C					
Baseline	3.8 (2.2-4.9)	3.4 (2.9-3.7)	3.8 (2.8-5.5)	2.9 (2.1-6.1)	4.0 (3.1-5.6)
Day 59	3.3 (2.8-5.3)	3.4 (3.1-3.9)	3.4 (2.5-4.0)	2.4 (1.7-7.5)	2.6 (1.6-3.2)
% Δ	-13 %	0 % P=0.04	-15 % P=1.00	-14 % P=0.62	-41 % P=0.0003

P value = versus placebo

ISIS

ISIS 301012 added to Statins
Safety Observations

Serious Adverse Events:

- none

Adverse Events:

- painless, transient erythema at site of injection

	Placebo	30 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
Injection site erythema	0	6	8	5	7
Headache	4	2	2	4	1
Nasopharyngitis	1	1	3	0	2

Laboratory Findings:

- one subject with confirmed ALT > 3x ULN

	Placebo	30 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
1-2X ULN	2	1	0	2	4
2-3X ULN	0	0	0	2	1
>3X ULN	0	0	0	0	1

ISIS

ISIS 301012
Phase 2 Conclusions

- ISIS 301012
  - results in a potent, dose-dependent, linear reduction in atherogenic lipids and lipoproteins in hypercholesterolemic subjects
  - demonstrates prolonged effects consistent with a greater than 30 day elimination half-life
  - is comparable in effect when used as monotherapy or when added to ongoing, stable statin therapy
  - is well tolerated alone or with statins & appears to have an acceptable safety profile
  - can be dosed infrequently

ISIS

ISIS 301012
Clinical Development Strategy

- We intend for ISIS 301012 to be:
  - The drug of choice for patients at risk who are unable to achieve target levels when added to statins & ezetimibe
    - initially in patients with Familial Hypercholesterolemia (FH)
    - ultimately in patients with polygenic hypercholesterolemia
  - An alternative to statins for those who are intolerant of statins
  - An alternative to statins period

ISIS

ISIS 301012 Development Path
Near and Longer Term Opportunities

- Parallel approach
  - Clinical studies in severe populations
    - Homozygous familial hypercholesterolemia (HoFH)
    - Heterozygous familial hypercholesterolemia (HeFH)
  - Parallel clinical studies addressing the large cholesterol market
    - Polygenic hypercholesterolemia
- Pursue development as combination therapy

ISIS

ISIS 301012 – Market Opportunity
HoFH and HeFH: Unmet Need, Accelerated Path to Market

- Homozygous Familial Hypercholesterolemia (HoFH)
  - Most severe and therapy-resistant form of high cholesterol (LDL levels > 500mg/dL)
  - HoFH patients do not achieve target levels of LDL with existing treatments
  - Prevalence of 1 per 1,000,000
- Heterozygous Familial Hypercholesterolemia (HeFH)
  - Premature cardiovascular disease (LDL levels 200 - 400mg/dL)
  - Prevalence of 1 per 500
- Development path is relatively rapid
  - Unmet need with clear cut efficacy measures
  - Orphan designation for HoFH achieved
  - NDA in the 2008/2009 timeframe possible
- Represents an important step forward in the path to commercial success for the larger high cholesterol population

ISIS

ISIS 301012 – Market Opportunity
In Combination with Statins and in Statin-Intolerant Patients

- As an Add-On to Statins: a more $3 billion U.S. market
  - >16 million High-Risk patients (CHD or equivalent) are not meeting target LDL-C
  - >5 million Moderately High-Risk U.S. patients in category (≥2 risk factors) are not meeting target LDL-C
  - Conservative estimates of 15% penetration equal more >3 million patients in the U.S. treated with ISIS 301012
- In Statin-Intolerant Patients
  - 5% – 10% of people prescribed statins don't take them because of "side effects"
- Markets outside the U.S. and prospective use by patient populations beyond the High Risk, Moderately High Risk, and statin-intolerant patients increase the opportunity
- Profile enhancements could significantly increase sales of ISIS 301012

ISIS

ISIS 301012
Anticipated Initial Product Efficacy and Safety Profile

- **Product Efficacy Profile**
  - Achieves statin-like reductions in cholesterol via a non-statin mechanism
  - Enables more patients to safely achieve target lipid levels when combined with statins and ezetimibe
  - May be dosed at convenient intervals of weekly and monthly
  - Reduces triglycerides to similar extent as LDL reduction
- **Safety Profile**
  - Is well tolerated
  - Good liver safety profile
  - No drug-drug interactions
  - No CNS toxicity
  - No muscle toxicity
  - No excretion of fat in stool

ISIS

ISIS 301012
Next Steps

Polygenic Hypercholesterolemia

- **Monotherapy**
  - Report results of 400 mg/week dose for three months
- **Combination with Statins**
  - Report results of 400 mg/week dose for 5 weeks
  - Report results 200 and 300 mg/week doses for three months
- **Define induction and maintenance doses in longer term trials**

Familial Hypercholesterolemia

- Report results of HoFH dose-escalation study
- Report results of HeFH dose-escalation study
- Initiate registration studies for HoFH and HeFH

ISIS

ISIS 301012
Cardiovascular Advisory Board

- John Kastelein, MD, PhD, Amsterdam
- Thomas Michel, MD, PhD, Boston
- Steve Nissen, MD, Cleveland
- Dan Rader, MD, Philadelphia
- Paul Ridker, MD, Boston
- Evan Stein, MD, PhD, Cincinnati
- Erik Stroes, MD, PhD, Amsterdam
- Steve Young, MD, Los Angeles
- Willis Maddrey, MD, Dallas
- Bruce Bacon, MD, St. Louis

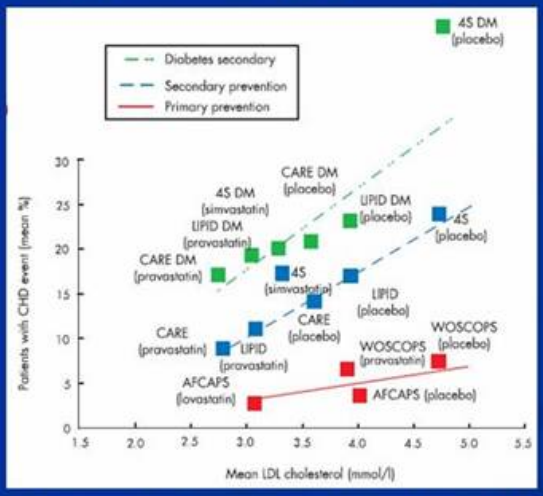
ISIS

Clinician's Perspective

John J.P. Kastelein, MD, PhD
Chairman, Department of Vascular Medicine
Academic Medical Center
Amsterdam, The Netherlands

LDL-C Concentrations and CHD Risk

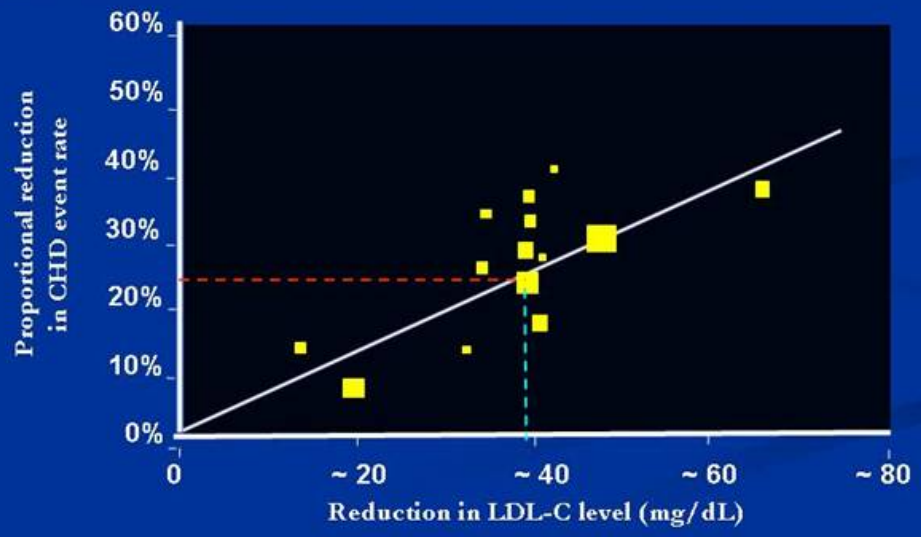
- Linear relationships exist between LDL-C and CHD outcomes in primary prevention, secondary prevention and diabetes secondary prevention populations



* Relationship between LDL-cholesterol & CHD risk (*Heart* 90:336, 2004)

Effects of LDL-C Reduction on CHD Outcomes

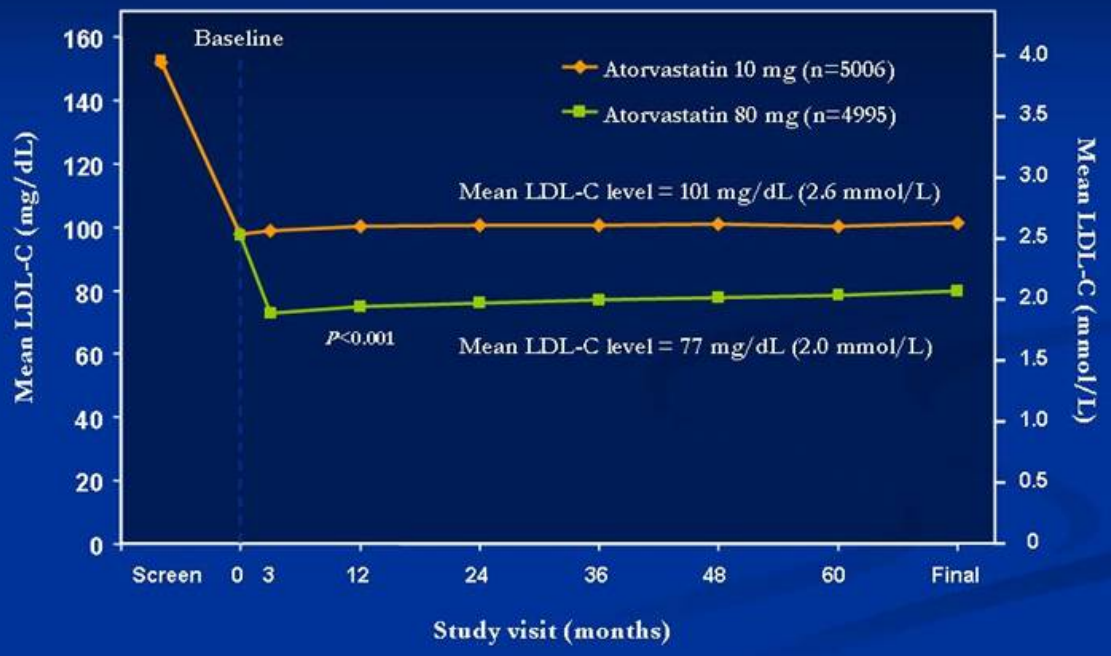
- Every 2 mg/dL reduction in LDL-C results in 1% reduction in CHD event rate
- Benefits of LDL-C lowering have been demonstrated in higher risk patients including diabetics as well as patients with relatively low LDL-C levels



Lower LDL-C is Better When It Comes to Preventing Cardiovascular Disease

- **NIH Post CABG:** 4.5 year treatment of lovastatin 2.5 mg vs 80 mg → significant difference in coronary stenosis and CAD events
- **ASAP:** 2-year treatment of FH patients with atorvastatin 80 mg vs simvastatin 40 mg → significant difference in IMT
- **REVERSAL:** 18-month treatment of CHD patients with atorvastatin 80 mg vs pravastatin 40 mg → significant difference in total atheroma volume
- **PROVE-IT:** 2-year treatment of ACS patients with atorvastatin 80 mg vs pravastatin 40 mg → significant difference in CV events
- **TNT:** long-term treatment of CHD patients with atorvastatin 80 mg vs atorvastatin 10 mg → significant difference in CV events
- **IDEAL:** long term treatment of CHD patients with atorvastatin 80 mg vs simvastatin 20/40 mg → significant difference in CV events
- **ASTEROID:** 24-month treatment of CHD patients with rosuvastatin 40 mg → significant regression in total atheroma

TNT- Changes in LDL-C by Treatment Group



LaRosa et al. *NEngJMed* 2005;352

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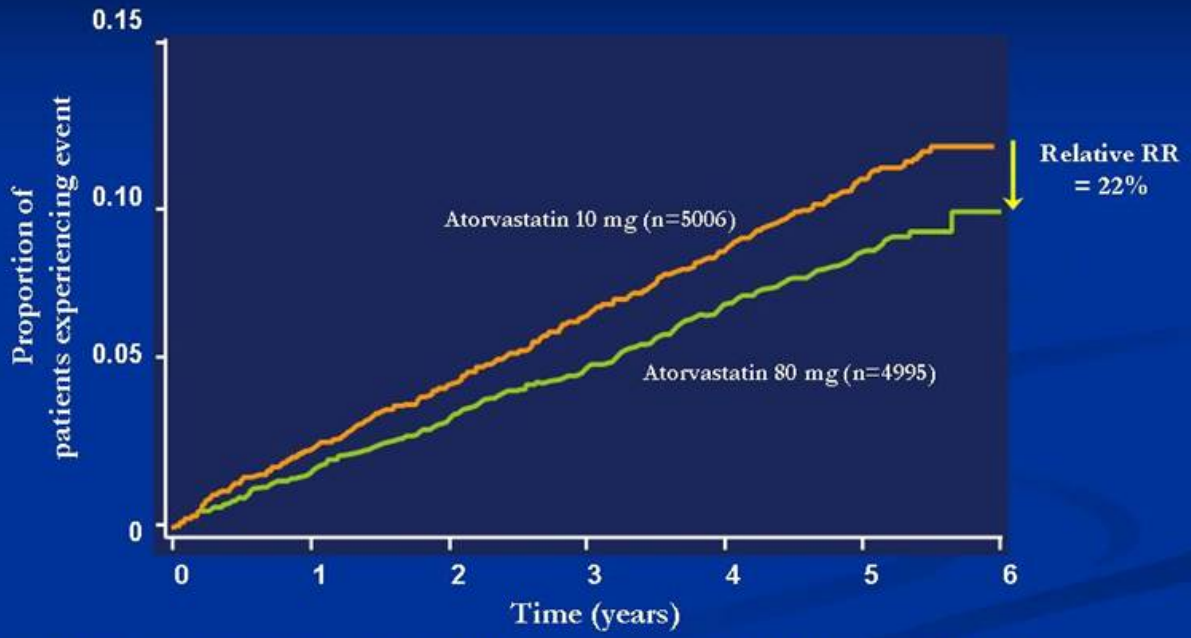
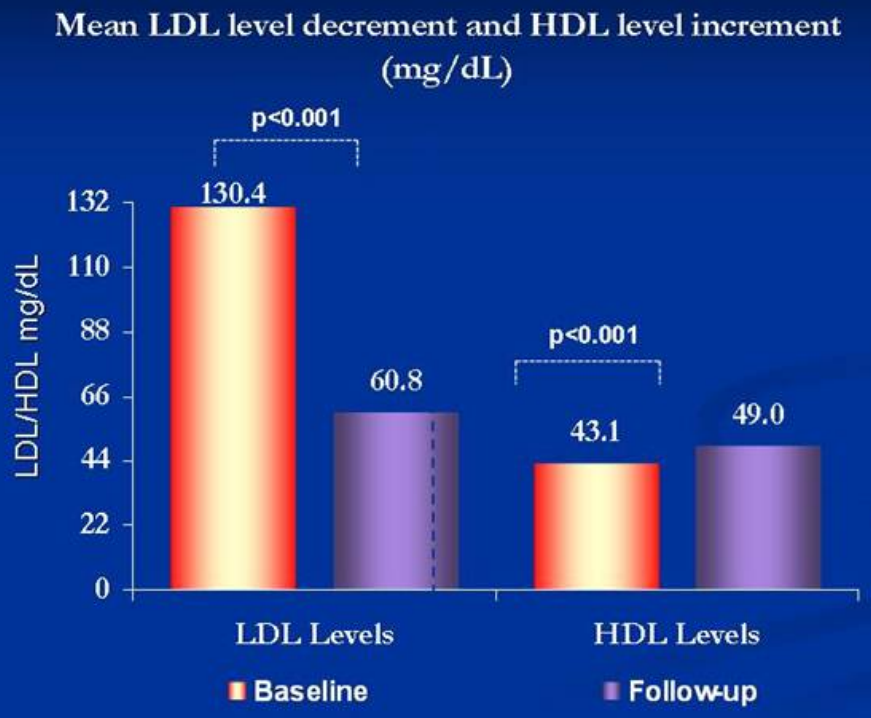
TNT - Primary Efficacy Outcome Measure: Time to First Major Cardiovascular Event*



*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

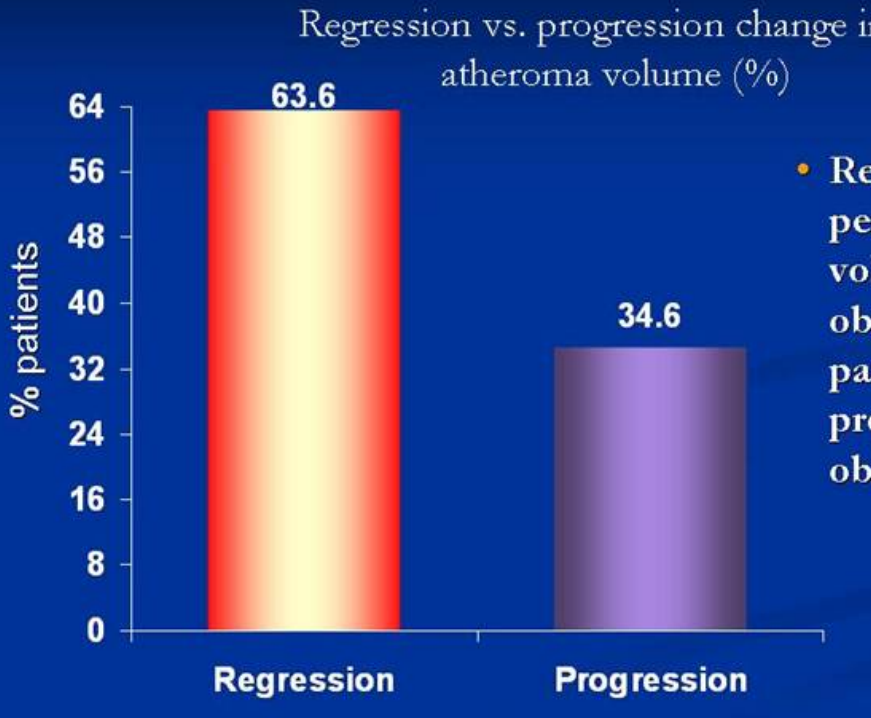
LaRosa et al. *N Engl J Med* 2005;352

ASTEROID Trial: Principal Findings



- LDL levels were reduced from 130.4 mg/dL at baseline to a mean of 60.8 mg/dL at 2 year follow-up ($p<0.001$), with 75% of patients achieving an LDL <70 mg/dL
- HDL levels were increased from 43.1 mg/dL at baseline to a mean of 49.0 mg/dL at follow-up ($p<0.001$)

ASTEROID Trial: Primary Endpoint



- Regression in percent atheroma volume was observed in 63.6% of patients, whereas progression was observed in 34.6%

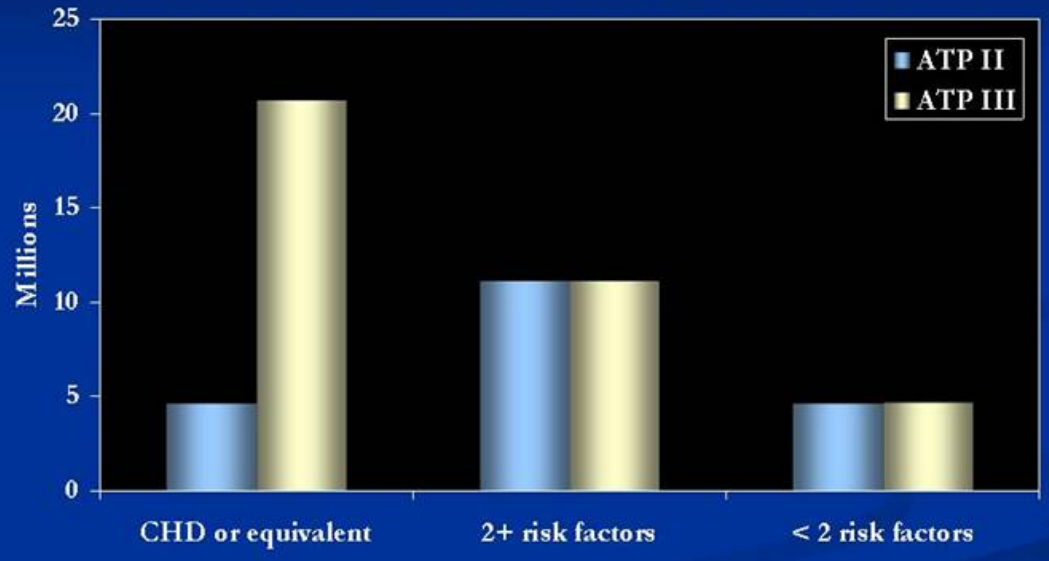
Evolution of Lipid Management Guidelines:

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP)

ATP I (1988)	ATP II (1993)	ATP III (2001)
Diet, low-dose non-statin monotherapy	Moderate to high-dose statin therapy	High-dose statin, combination therapy

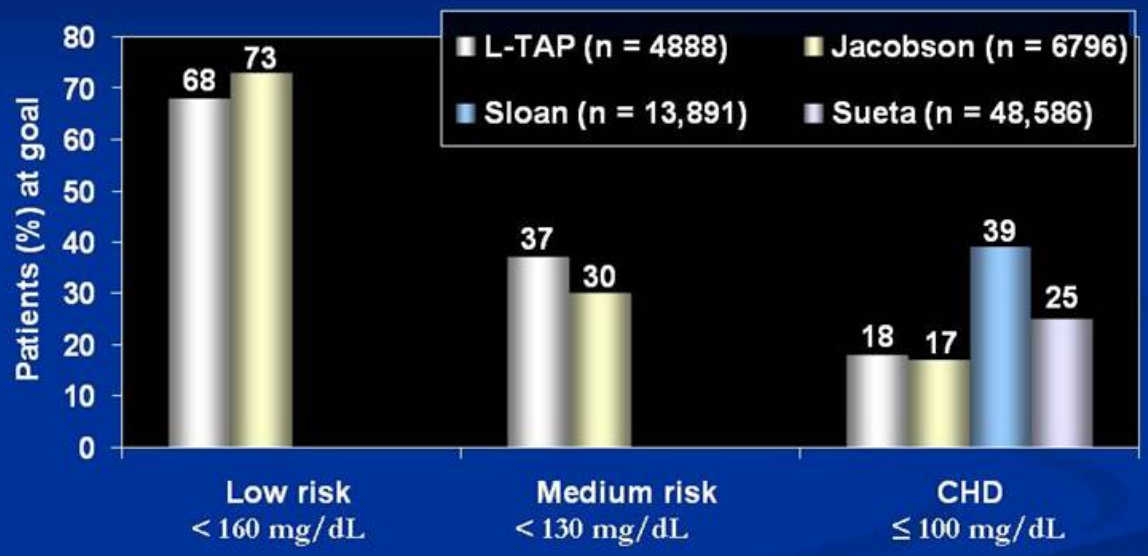
Increasing aggressiveness of cholesterol-lowering therapy

ATP III: Greatest Increase in Individuals Requiring Drug Therapy in Category of CHD or CHD-Risk Equivalent



Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

Most Patients Fail to Achieve Even ATPII LDL-C Goals with Lipid-Lowering Therapy



Pearson TA et al. *Arch Intern Med.* 2000;160:459-467
Jacobson TA et al. *Arch Intern Med.* 2000;160:1361-1369

Sloan KL et al. *Am J Cardiol.* 2001;88:1143-1146;
Sueta CA et al. *Am J Cardiol.* 1999;83:1303-1307

Unmet Medical Need

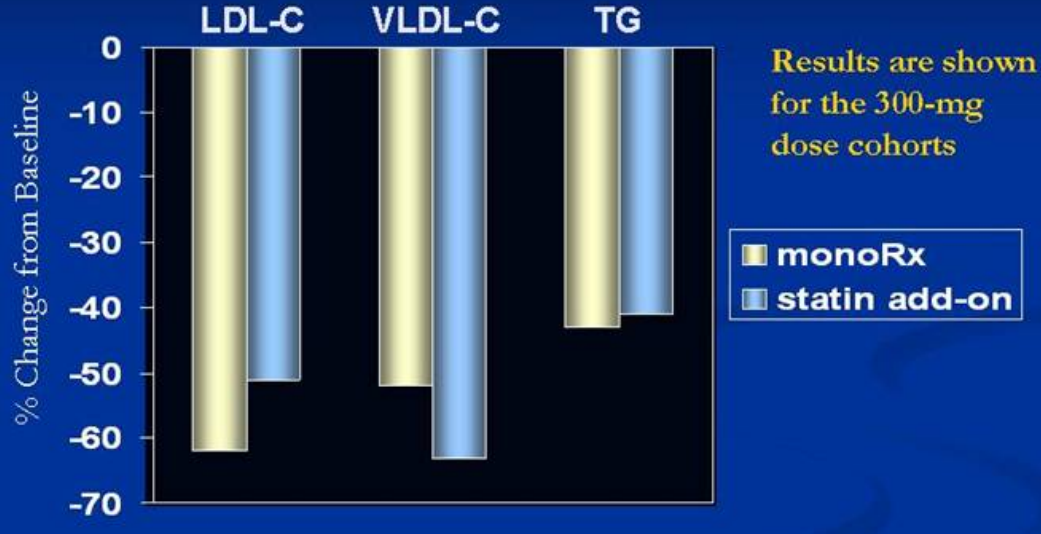
- **A drug or combination lipid-lowering therapy with the following profile:**
  - LDL-C reductions ≥ those achieved with statins
  - lipid-lowering effects additive to those of statins
  - lowers all major atherogenic lipoproteins and TGs
  - beneficially impacts key risk ratios (e.g., apo B/apo AI)
  - linear dose response (doubling dose = doubling response)
  - limited potential for drug-drug interactions
  - an acceptable safety profile
  - properties that promote better patient compliance

ISIS 301012 Produces Apo B and LDL-C Reductions Greater Than Those Achieved With the Most Potent Statins

Drug	Dose	% apo B reduction	% LDL-C reduction	Ref.
ISIS 301012	200 mg qw	24 - 47	30 - 42	CS-3, CS-4
	300 mg qw	52 - 61	51 - 62	CS-3, CS-4
Rosuvastatin	10 mg qd	33 - 40	42 - 46	1,2,6,7
	20 mg qd	42 - 43	47 - 48	5,7
Atorvastatin	20 mg qd	33 - 35	43 - 50	5,7
	40 mg qd	38 - 41	50 - 52	5,7

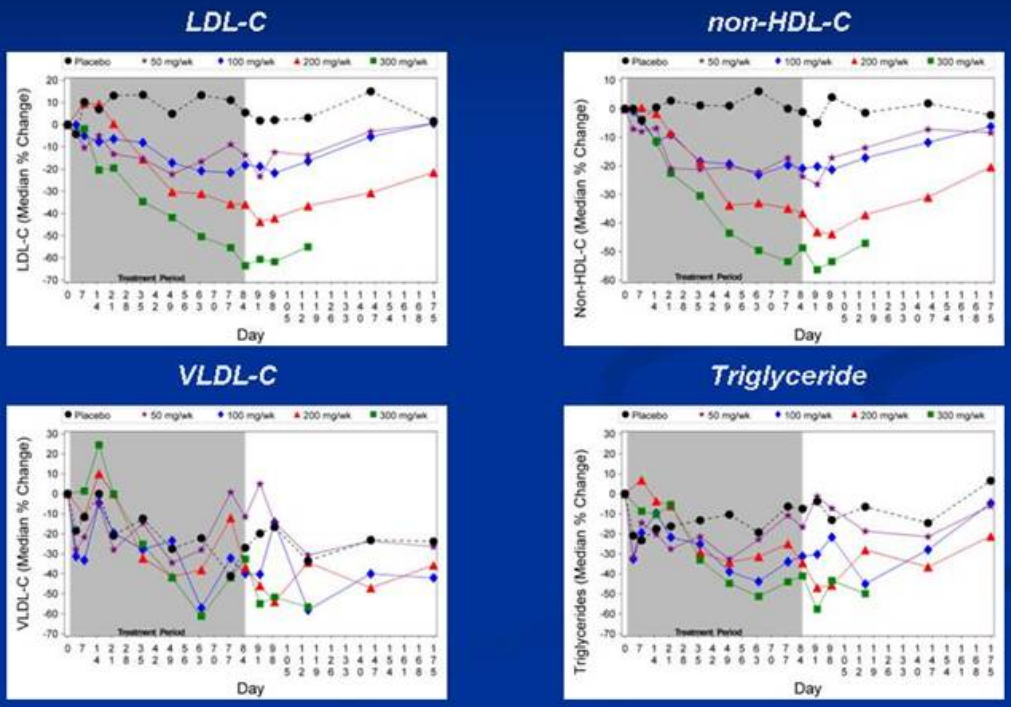
[1] Brown, Am Heart J 2002
[2] Davidson, Am J Card 2002
[3] Jones, Am J Card 1998
[4] Jones, Am J Card 2003
[5] Jones, Curr Ther 2004
[6] Olsson, Am Heart J 2002
[7] Schneck, Am J Card 2003
[8] Strandberg, Curr Ther 2004

ISIS 301012 Produces LDL-C, VLDL-C, and TG Reductions That Are Additive to Those of Statins



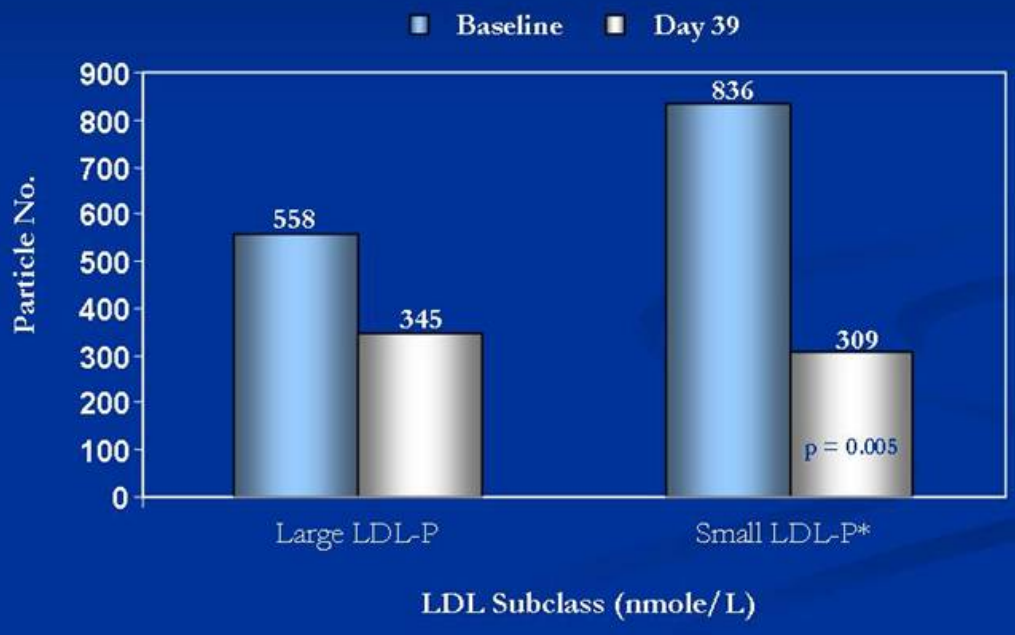
These additive effects are at least 2-fold greater than those reported for any other marketed statin add-on therapies

ISIS 301012 Lowers all Major Atherogenic Lipoprotein Classes and Triglycerides



ISIS 301012 Preferentially Reduces Small Dense LDL

Phase 1: 200 mg & 400 mg cohorts combined



ISIS 301012 Beneficially Impacts Key Risk Ratios: ApoB/ApoA1 and TC/HDL Ratios

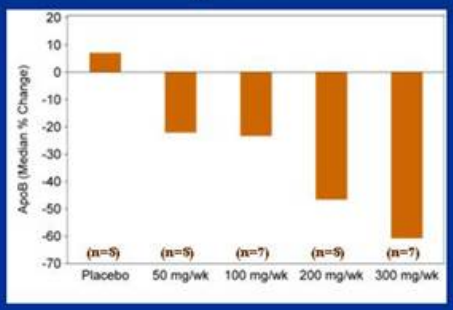
	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
apoB/apoA1					
Baseline	1.0 (0.8-1.1)	1.1 (0.6-1.4)	0.8 (0.7-1.3)	1.0 (0.7-1.3)	1.1 (1.0-1.7)
Day 99	1.0 (0.9-1.2)	0.8 (0.4-1.1)	0.6 (0.5-1.1)	0.5 (0.3-0.9)	0.6 (0.4-0.9)
% D	11 %	-22 % P=0.007	-26 % P=0.002	-46 % P=0.0002	-51 % P=0.0003

	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk
TC/HDL-C					
Baseline	4.9 (3.7-5.0)	4.8 (3.6-5.7)	4.1 (3.7-5.6)	4.7 (3.6-5.3)	4.8 (4.5-6.3)
Day 99	4.5 (4.1-5.3)	4.1 (2.7-5.0)	3.4 (3.0-4.8)	3.1 (2.0-4.5)	3.0 (2.6-4.6)
% D	-4 %	-14 % P=0.10	-18 % P=0.006	-34 % P=0.0006	-35 % P=0.001

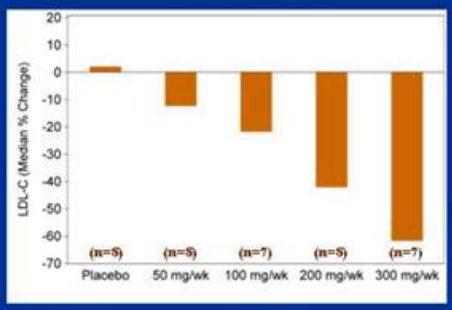
P value = versus placebo

ISIS 301012 produces a linear dose response (dose doubling = doubling of response)

Apo B



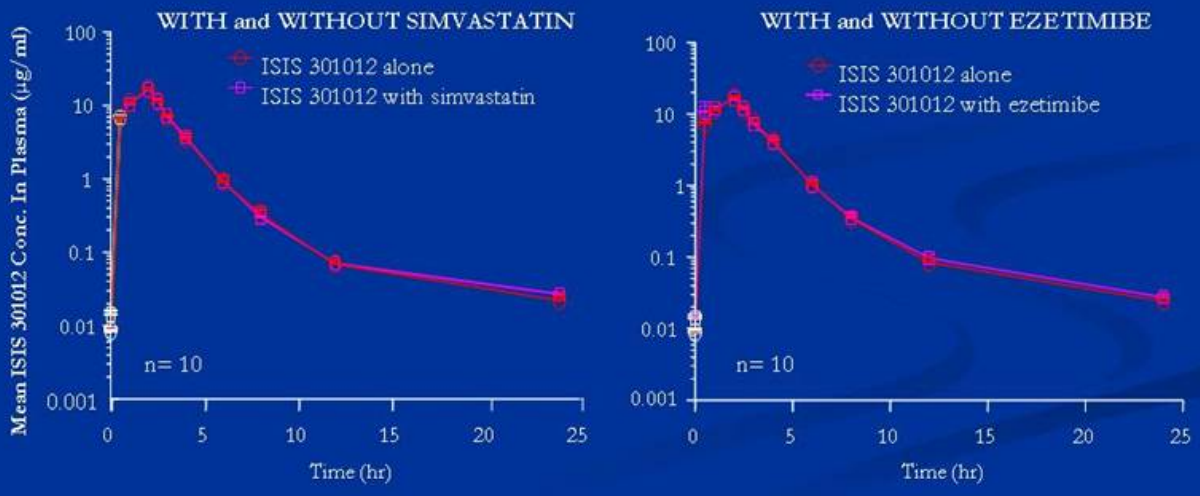
LDL-C



Results show % change at day 99 in phase 2 monotherapy study

ISIS 301012 Has Limited Potential for Drug-Drug Interactions

No clinically significant PK or metabolism interactions observed with simvastatin or ezetimibe



Summary:
ISIS 301012 Exhibits a Compelling Profile That Satisfies Key Unmet Medical Needs

- Prolonged reductions of key lipid parameters including apoB, LDL-C, TG, VLDL-C and non-HDL-C
  - Reductions in these parameters meet or exceed *and are additive to* those achieved with statins
- Beneficial impact on key risk ratios including apoB/apoA-I
- Preferential reduction in more atherogenic lipoprotein subspecies including small, dense LDL particles
- Has been used safely to date at the highest and most efficacious doses tested in target patient populations
- Less frequent dosing and subcutaneous administration may increase ease of use for some patients

Clinical Utility and Target Patient Populations for ISIS 301012

How Would I Use ISIS 301012 in Practice?

- Patients not meeting LDL-C goal on maximally tolerated therapy
  - FH patients
  - High-risk patients (e.g., CHD-equivalent) patients with low LDL-C targets
  - Statin hyporesponders
- Patients intolerant of statins and/or other statin add-on therapies
- Patients requiring broader lipid management
  - Patients with elevated triglycerides

ISIS® PHARMACEUTICALS

Stanley T. Crooke, MD, PhD

Concluding Remarks

2006: What a Great Year
ISIS 301012

Studies in patients with polygenic high cholesterol

- **Report single agent Phase 2 data**
  - √ Demonstrate safety and activity as a single agent after 3 months of treatment (2Q06)
  - √ Define dose and schedule for longer term studies (2Q06)
  - √ **Report data from higher dose in patients after 3 months of treatment (4Q06/1Q07)**
- **Report Phase 2 combination study data (4Q06)**
  - √ **Demonstrate safety and activity in combination with statins after 5 weeks of treatment**
  - √ Expand study to include higher doses and longer treatment duration
  - √ **Define dose and schedule as a combination agent**
- **Report Phase 1 drug-drug interaction studies (1H06)**
  - √ No clinically significant interactions with simvastatin or ezetimibe (2Q06)
- **Initiate longer term Phase 2 trials (2007)**
- **Continue to define drug profile advantages**
  - √ Reduces triglycerides (2Q06)
  - √ Reduces plaques in animals (2Q06)
  - √ Limited potential for drug-drug interactions (2Q06)

Studies in patients with familial hypercholesterolemia (FH)

- **Advance registration pathway for commercialization in 2008/2009**
  - □ Demonstrate preliminary activity and safety in FH (4Q06/1Q07)
  - □ Define dose to support registration studies (4Q06/1Q07)
  - √ Achieve Orphan Drug Status

ISIS PHARMACEUTICALS

2006: What a Great Year
ISIS 113715 and New Diabetes Drugs

ISIS 113715

- **Report single agent Phase 2 data in Type 2 diabetes patients**
  - √ Report results on safety and activity after 6 weeks treatment
  - √ Report initial results demonstrating safety and activity after 12 weeks treatment
- √ **Initiate mechanistic study in patients with Type 2 diabetes**
- √ **Initiate combination trials with other antidiabetic agents (2Q06)**

ISIS 325568 - Glucagon receptor drug (GCGR)

- √ **Initiate IND enabling toxicology studies (2H06)**

Glucocorticoid receptor drug (GCCR)

- **Initiate IND enabling toxicology studies (2007)**

ISIS PHARMACEUTICALS

2006: What a Great Year
Partner Pipeline

Partner Development Pipelines

- **OncoGenex: OGX-011 (Targeting Clusterin, for treatment of cancer)**
  - √ Advance 5 Phase 2 trials (3 in prostate, 1 in NSCLC, 1 in breast)
  - √ Report Phase 1 data on NSCLC
- **OncoGenex: OGX-427(Targeting Heat Shock Protein 27 in cancer)**
  - □ Initiate Phase 1 trials in 2007
- **Lilly: LY2181308 (Targeting Survivin for the treatment of cancer)**
  - □ Initiate Phase 2 clinical trials (4Q06)
- **Lilly: LY2275796 (Targeting eIF-4E for the treatment of cancer)**
  - □ Progress Phase 1 clinical trials in patients with cancer
- **Antisense Therapeutics Limited: ATL-1102 (Targeting VLA4)**
  - √ Progress Phase 2 studies in patients with multiple sclerosis
- **iCo Therapeutics: iCo 007 (Targeting c-Raf kinase in ocular disease)**
  - □ File IND (4Q06)

ISIS PHARMACEUTICALS

2006: What a Great Year
Ibis

- **Continue growth in revenue**
  - √ Orders for first assay kits received
  - √ Assay service business established and contract for 10,000 samples received
- **Deliver additional Ibis T5000 Biosensor Systems**
  - √ NHRC (Naval Health Research Center) system delivered
  - √ CDC (Centers for Disease Control) system delivered
- **Complete an instrument strategic alliance**
  - √ Bruker Daltonics alliance announced
  - √ European commercial launch of the Ibis T5000
- **Receive purchase order for first commercial instrument sale**
  - √ Order for two Ibis T5000 Biosensor Systems received
- **Continue development of application-specific assay kits**
- **Build internal commercial and manufacturing organizations**
  - √ Hired VP Sales and Marketing
  - √ Hired Executive Director, Manufacturing and Operations

ISIS PHARMACEUTICALS

This presentation includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial outlook for Isis' Ibis Biosciences division, and the commercial potential of the Company's technologies and products in development. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals or projections. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2005, and its quarterly report on Form 10-Q for the quarter ended September 30, 2006, which are on file with the SEC. Copies of these and other documents are available from the Company.