SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): **April 27, 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 April 27, 2006, Isis Pharmaceuticals, Inc. ("Isis") announced initial data from the low-dose cohorts of a Phase 2 clinical trial of ISIS 301012 as a single-agent in patients with high cholesterol. A copy of the Press Release related to these results is attached hereto as Exhibit 99.1 and is incorporated herein by reference.

On April 28, 2006, Isis will web cast a conference call regarding these results. A copy of the slides Isis will present 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 April 27, 2006.
99.2	Slides to be Presented on the April 28, 2006 Conference Call.

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: April 27, 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 April 27, 2006.
99.2	Slides to be Presented on the April 28, 2006 Conference Call.

Exhibit 99.1

Contact: Navjot Rai
Corporate Communications
760-603-2331

ISIS PHARMACEUTICALS REPORTS POSITIVE PHASE 2 DATA: ISIS 301012 REDUCES CHOLESTEROL AND TRIGLYCERIDES IN PATIENTS WITH HIGH CHOLESTEROL

- *47% Reduction of ApoB-100*
- *42% Reduction of LDL*
- *46% Reduction of Triglycerides*

Isis to Hold Webcast Presentation and Conference Call on Friday, April 28 at 8:30 a.m. E.T.

Carlsbad, Calif. – April 27, 2006 – Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today initial data from the low-dose cohorts of a Phase 2 clinical trial of ISIS 301012 as a single-agent in patients with high cholesterol. ISIS 301012 produced rapid, dose-dependent and prolonged reductions of its target, apoB-100, with concomitant reductions in low density lipoprotein (LDL or "bad" cholesterol), very low density lipoprotein (VLDL), total cholesterol and triglyceride levels in patients with high cholesterol. At a dose of 200 mg/wk for three months, ISIS 301012 achieved a median percent reduction from baseline of 47% in apoB-100, 42% in LDL, 34% in total cholesterol and 46% in triglycerides at day 99. ISIS 301012 was well tolerated in this study. Results from the low-dose cohorts of this study were presented by Mark Wedel, MD, JD, Senior Vice President Development and Chief Medical Officer of Isis at the Arteriosclerosis, Thrombosis and Vascular Biology (ATVB) meeting in Denver, Colorado.

ISIS 301012, a second-generation antisense drug, inhibits apoB-100, a protein critical to the synthesis and transport of the "bad" cholesterol involved in heart disease – LDL and VLDL. Lowering cholesterol and triglyceride levels is a key component to the prevention and management of cardiovascular disease.

The objectives of this Phase 2 study were to evaluate the safety and efficacy of weekly doses of ISIS 301012 as a single-agent in patients with high cholesterol, who are not able to control their cholesterol with just diet and exercise. Data presented represent the three low-dose groups (50, 100 and 200 mg per week) in this study. The study is continuing to explore two higher doses (300 and 400 mg per week). In this double-blind, placebo-controlled (4:1 randomization in each dose group), dose-escalation study, 30 patients with elevated cholesterol levels have been dosed over a period of 3 months with a dose of 50, 100 or 200 mg/week of ISIS 301012. The two lowest dose groups received a loading dose over the first two weeks of the study. ISIS 301012 is being developed by Isis as part of its recently announced collaboration with Symphony GenIsis.

"These are very encouraging results. The level of LDL lowering with ISIS 301012 is comparable to the LDL lowering observed in recent trials studying statins and still only the lower end of the dosing spectrum of ISIS 301012 has been explored so far," said John Kastelein, MD, Chairman, Department of Vascular Medicine at the Academic Medical Center, Amsterdam. "We look forward to additional clinical results from studies with this exciting drug that is showing statin-like reductions via a non-statin mechanism."

"The results of this initial Phase 2 study show that all three doses of ISIS 301012 produced attractive lowering of lipids and triglycerides, and were well tolerated. We have demonstrated that 50 mg/week of ISIS 301012 effectively reduces LDL and that 200 mg/week results in statin-like LDL reductions. In addition, we have shown that ISIS 301012 reduces triglycerides significantly," Dr. Wedel added. "This is a key step forward in the development of ISIS 301012."

"The results from this trial add to the body of data demonstrating that ISIS 301012 is a novel and effective lipid lowering drug," Dr. Wedel said. "The predictability of drug concentrations and the effect of ISIS 301012 are particularly impressive and support plans for aggressively continuing development. We believe that ISIS 301012 has the potential to lower cholesterol as an add-on therapy in patients who can not reach their therapeutic target and as an alternative for patients who can not tolerate currently available therapies."

Key Highlights from Study:

- **Objectives**
  - To evaluate the safety and efficacy of weekly subcutaneous doses of ISIS 301012 in patients with high cholesterol not controlled with just diet and exercise
  - To evaluate the effects of dose and schedule on pharmacokinetics, safety and efficacy of ISIS 301012
- **Subject Characteristics**
  - Subjects enrolled in the study were previously untreated and the four treatment groups (placebo, 50 mg, 100 mg, and 200 mg) were well matched with regard to baseline parameters. Medians of the four treatment groups ranged from 246-271 mg/dL for total cholesterol and 154-173 mg/dL for LDL.
- **Efficacy**
  - Because patients in the 50 mg and 100 mg dose groups received a loading schedule, the effects of the three dose groups occurred on different days. The table below shows the effects for each dose group on Day 50 and Day 99. In the webcast, Isis will present detailed data on all days.

Median Percent Change From Baseline
(p values compare to placebo)

	200 mg		100 mg		50 mg	
	(Day 50)	(Day 99)	(Day 50)	(Day 99)	(Day 50)	(Day 99)

apoB-100	-36 (p=0.001)	-47 (p<0.001)	-29 (p<0.001)	-23 (p=0.005)	-32 (p=0.005)	-22 (p=0.14)
LDL	-30 (p<0.001)	-42 (p<0.001)	-17 (p<0.001)	-22 (p=0.05)	-22 (p=0.03)	-12 (p=0.57)
Total cholesterol	-25 (p<0.001)	-34 (p<0.001)	-15 (p=0.005)	-15 (p=0.29)	-18 (p=0.02)	-12 (p=0.66)
Triglycerides	-34 (p=0.08)	-46 (p=0.04)	-39 (p=0.28)	-22 (p=0.73)	-33 (p=0.57)	-7 (p=0.57)
Non-HDL	-34 (p=0.003)	-44 (p<0.001)	-19 (p=0.005)	-21 (p=0.07)	-20 (p=0.01)	-17 (p=0.51)

There were no statistically significant increases in HDL

- **Duration of response** (time to return to 90% of baseline LDL after last dose)
  - 50 mg/week 0.4 months
  - 100 mg/week 2.0 months
  - 200 mg/week 5.2 months (projected)

- **Safety**
  - No drug-related severe adverse events
  - One transient ALT elevation, 60 days post-dosing, 3.4 times upper limits of normal
  - Mild transient injection site reactions
  - No other laboratory or clinical abnormalities

ABOUT ISIS 301012
ISIS 301012, a second-generation antisense drug, inhibits apoB-100, a protein critical to the synthesis and transport of the “bad” cholesterol involved in heart disease — low density lipoprotein cholesterol (LDL) and very low density lipoprotein (VLDL). Lowering cholesterol and triglyceride levels is a key component in the prevention and management of cardiovascular disease.

Development plans for ISIS 301012 are to rapidly develop the drug for patients with familial hypercholesterolemia (FH), a genetic disorder that causes extremely high cholesterol levels and results in the early onset of heart disease. ISIS 301012 has the potential to provide an accelerated pathway to commercialization because of the unmet medical need in this desperate patient population. Additional trials are designed to address the larger commercial market represented by the traditional population of patients with high cholesterol, who are still not reaching their targeted cholesterol levels.

In September 2005, Isis initiated the Phase 2 development program of ISIS 301012. Phase 2 trials of ISIS 301012 are being conducted in patients with high cholesterol. Isis is continuing its Phase 2 single-agent trial using higher dosing (300 and 400 mg/wk) of ISIS 301012 in patients with high cholesterol. Isis is also conducting a Phase 2 trial of ISIS 301012 in combination with statin therapy in patients with high cholesterol. Isis is also conducting Phase 2 studies of ISIS 301012 in FH.

In Phase 1 trials, ISIS 301012 produced rapid, dose-dependent and prolonged reductions of its target, apoB-100, with concomitant reductions in LDL, VLDL, total cholesterol and triglycerides in normal subjects with elevated cholesterol. In a drug-drug interaction study, ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. Additionally, the drug has been well tolerated.

ABOUT CHOLESTEROL AND CARDIOVASCULAR DISEASE
According to the American Heart Association, an estimated 107 million American adults have total blood cholesterol values of 200 mg/dL and higher, and of these about 38 million American adults have levels of 240 or above. In adults, total cholesterol levels of 240 mg/dL or higher are considered “high risk”. Levels from 200 to 239 mg/dL are considered “borderline-high risk”. Low-density lipoprotein, or LDL, known as the “bad” cholesterol, can clog arteries, increasing the risk of heart attack and stroke.

According to the World Health Organization (WHO), heart disease and stroke kill 17 million people a year, which is almost one-third of all deaths globally. By 2020, the WHO projects that heart disease and stroke will become the leading cause of both death and disability worldwide, with the number of fatalities projected to increase to over 20 million a year and by 2030 to over 24 million a year.

Familial hypercholesterolemia is a dominantly inherited genetic condition that results in markedly elevated LDL (low-density lipoprotein) cholesterol levels beginning at birth, and resulting in heart attacks at an early age. Affected people have consistently high levels of low-density lipoprotein, which leads to premature atherosclerosis of the coronary arteries.

ABOUT ISIS’ SYMPHONY GENISIS COLLABORATION
In April 2006, Isis entered into a collaboration with Symphony Capital Partners, L.P. and a group of co-investors to form Symphony GenIsis, Inc., capitalized with $75 million, to fund the development of Isis’

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cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis’ metabolic disease program. Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. The financing will support Isis’ development of ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support Isis’ development of two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows Isis to continue to control and manage the development of ISIS 301012 and two other potentially valuable drugs through key development milestones.

WEBCAST PRESENTATION AND CONFERENCE CALL INFORMATION

Isis will conduct a live webcast presentation with slides and conference call to discuss this press release Friday, April 28 at 8:30 am Eastern time. To participate over the Internet go to http://www.videonewswire.com/event.asp?id=33534 or http://www.isispharm.com. A replay of the webcast will be available at these addresses for a limited time.

ABOUT ISIS PHARMACEUTICALS, INC.
Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 15 drugs in development. Isis' drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Isis' partners are focused in disease areas such as inflammatory, ocular, viral and neurodegenerative diseases, and cancer. In its Ibis division, Isis is developing and commercializing the Ibis biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding the development, therapeutic potential of ISIS 301012 to lower high cholesterol as well as the drug's safety profile. Any statement describing Isis' goals, expectations, 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. 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, 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, which is on file with the U.S. Securities and Exchange Commission (SEC) and available from the Company.

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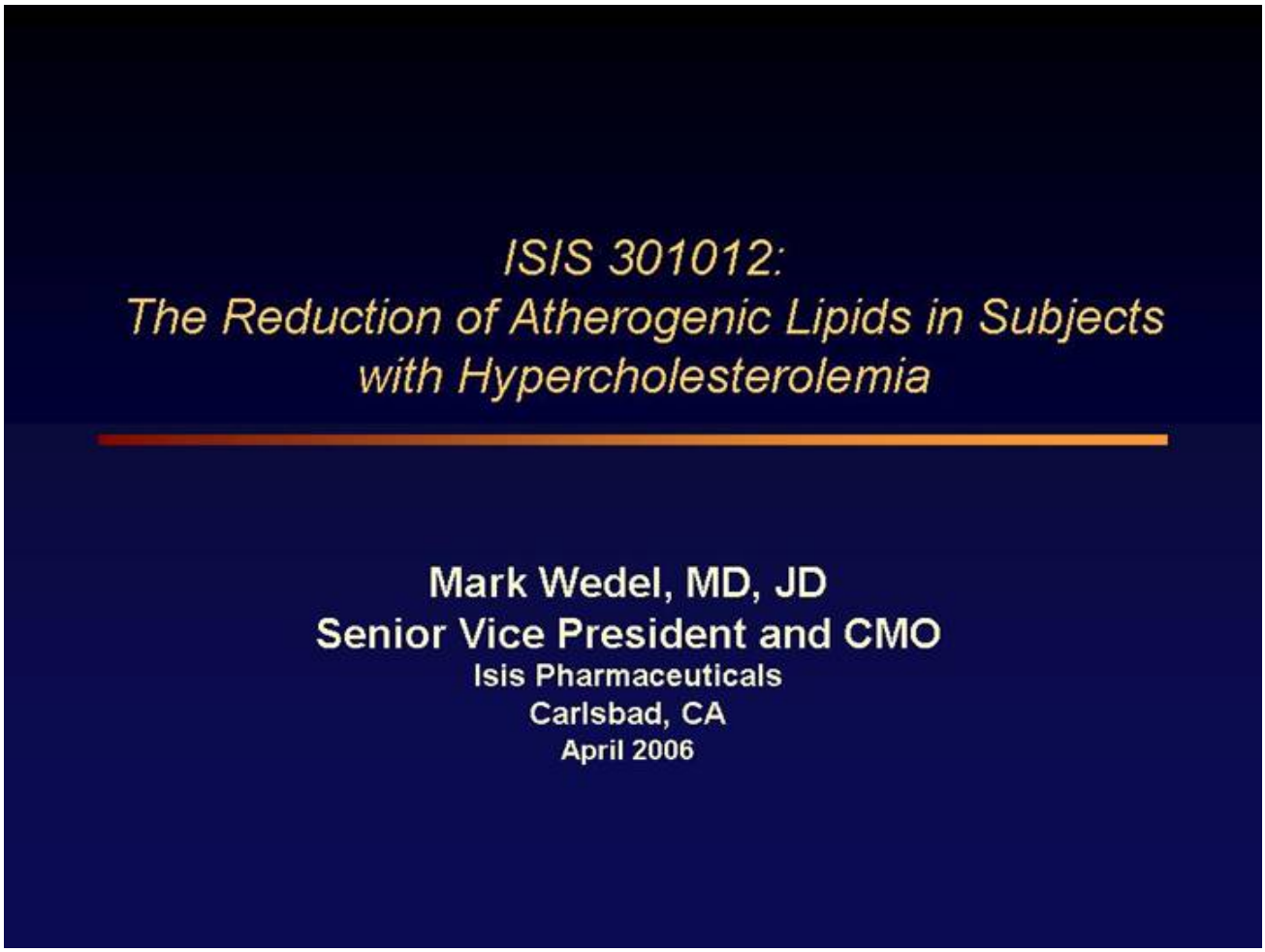

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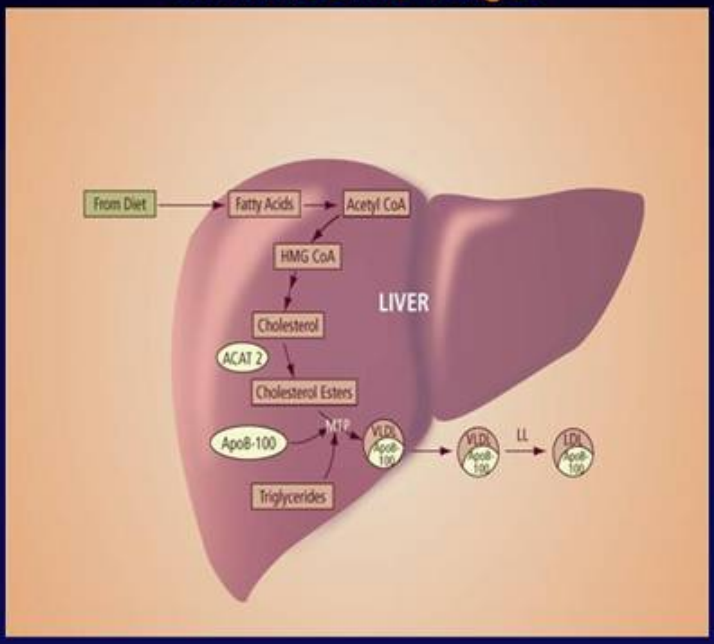
ISIS 301012

A Second Generation Antisense Drug Inhibiting apoB-100

Meets Criteria for an Antisense Target



- Expressed in the liver
- Essential for the synthesis and transport of VLDL and LDL
- Crucial role in lipid management
- Unapproachable with small molecules
- An apoB-100 inhibitor should have a unique lipid lowering profile

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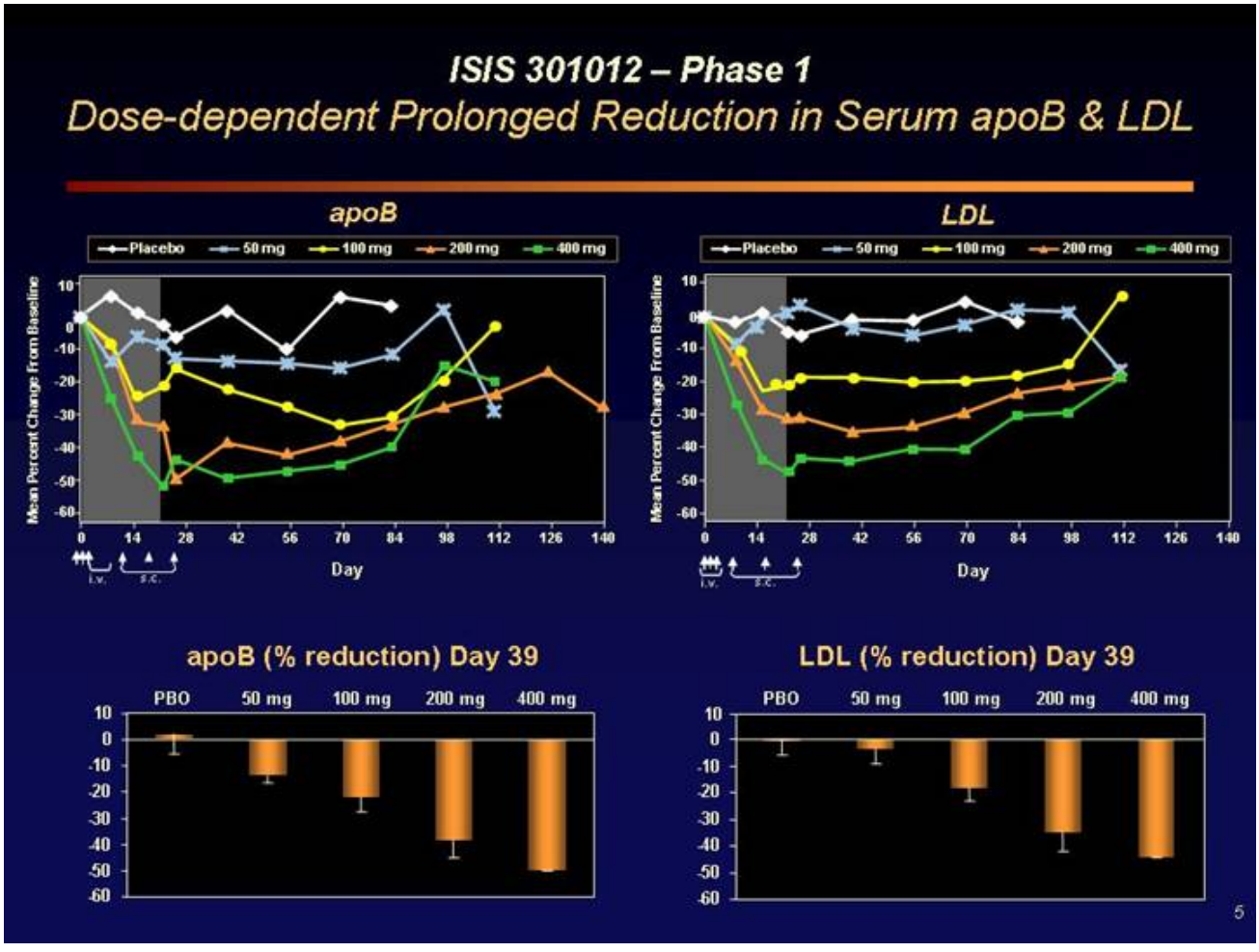

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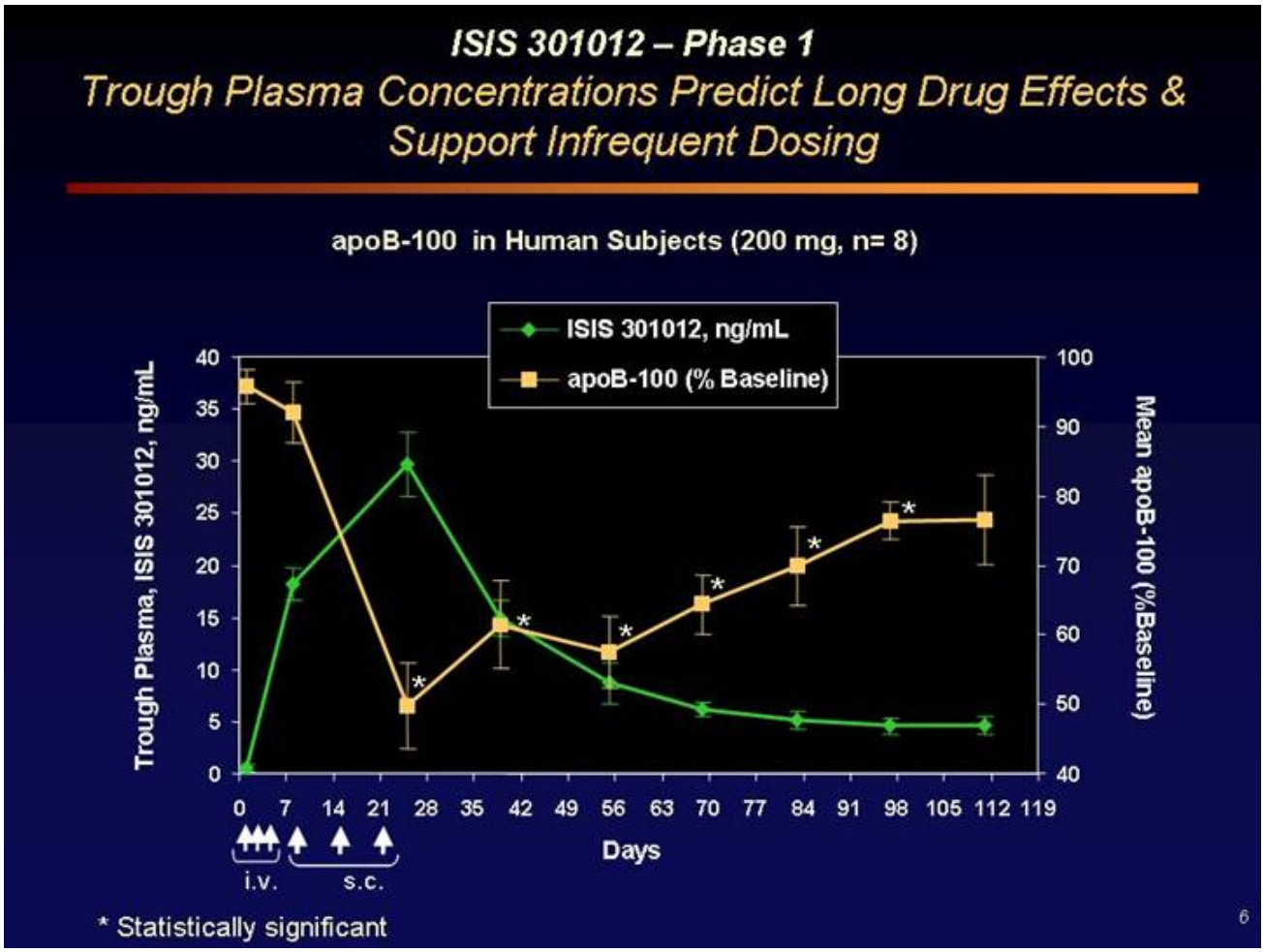

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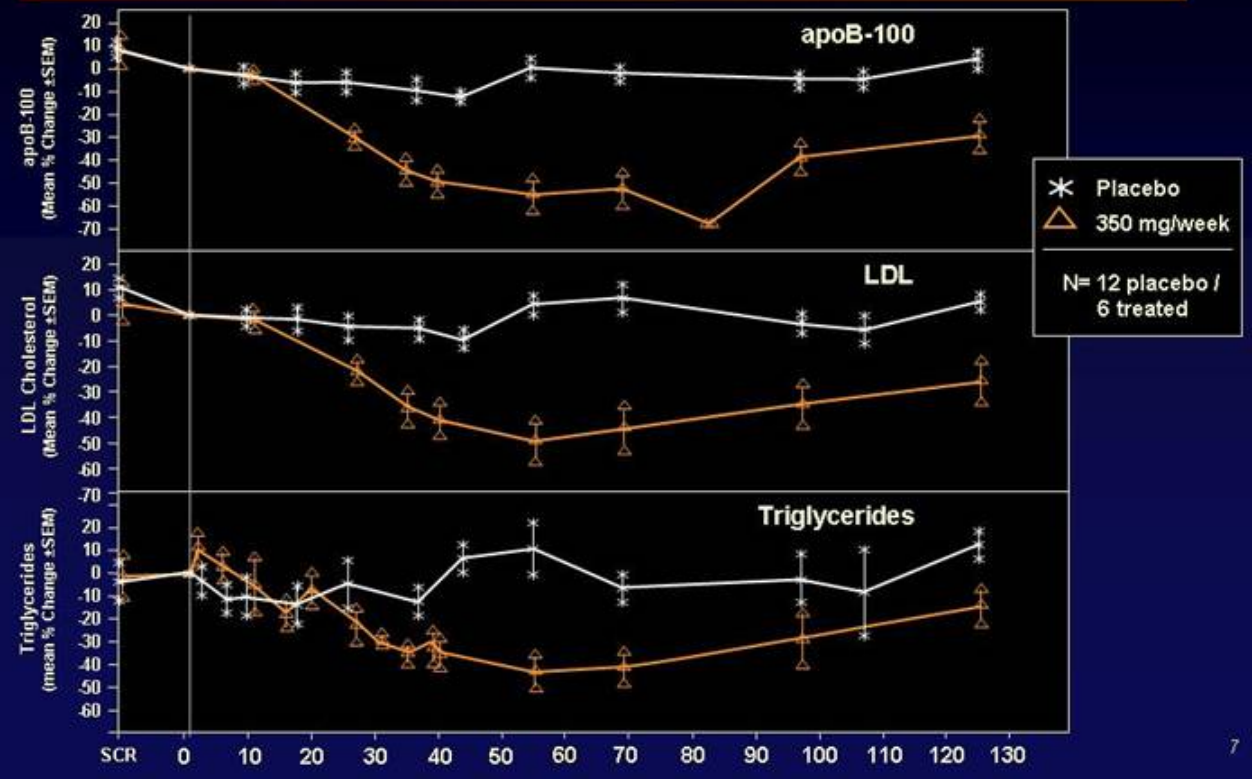
ISIS 301012 – Phase 1

ISIS 301012 (350 mg/wk for 1 month) Lowers All Atherogenic Lipids Including Triglycerides



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ISIS 301012 – Phase 2a

Study Objectives

- Safety & tolerability
- Efficacy
  - Statistical significance
  - Dose dependence
    - apoB
    - LDL
    - Other atherogenic lipids
- PK/PD correlation

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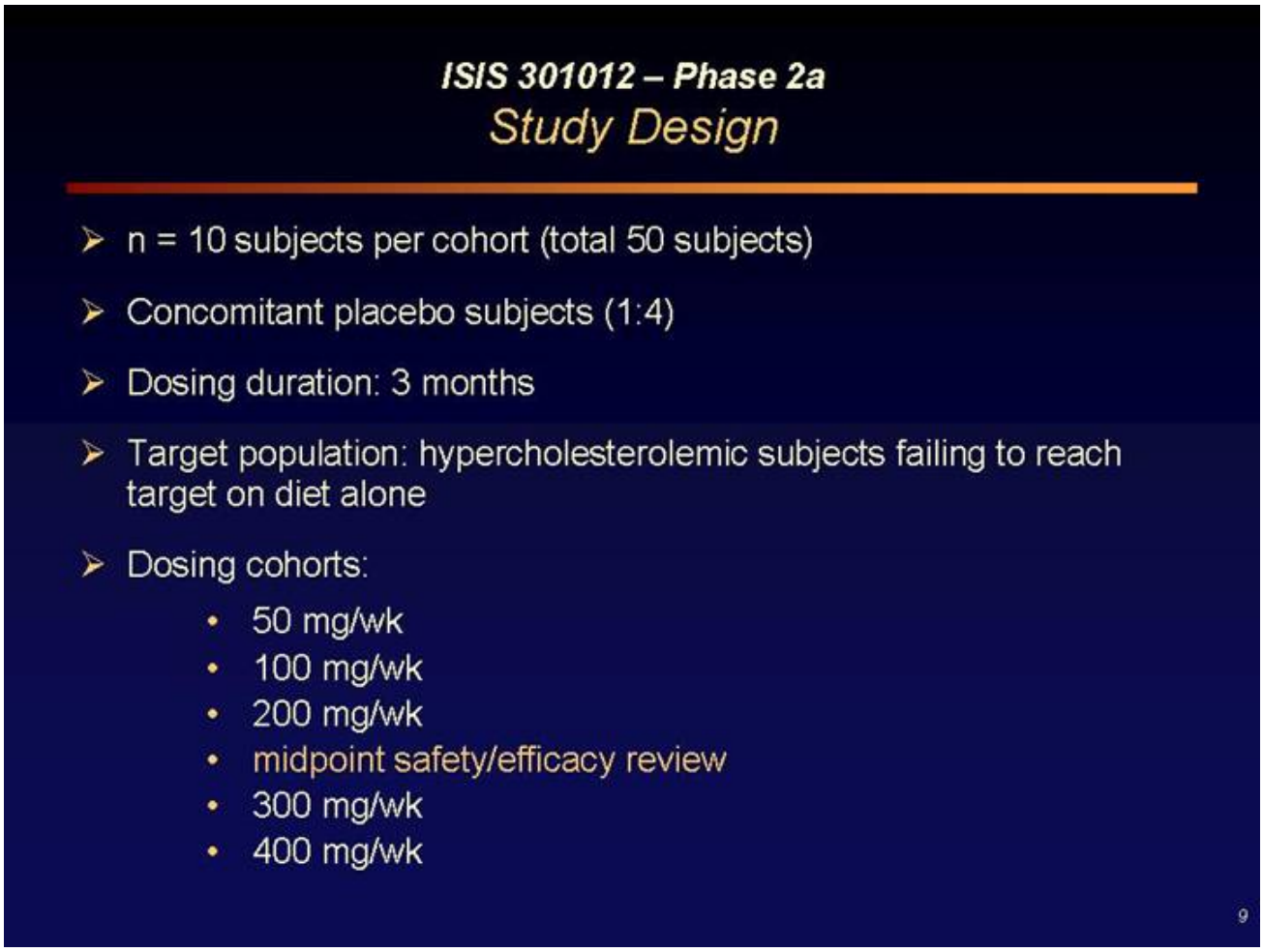

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ISIS 301012 – Phase 2a
Dosing Cohorts Completed

Weekly Dose Equivalent	Dose	Loading Dose*
50	100 every other week	Yes
100	200 every other week	Yes
200	200 every week	No

* 200 mg subcutaneous on days 1, 4, 8 & 11

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ISIS 301012 – Phase 2a
Demographics

	PBO	50 mg/wk	100 mg/wk	200 mg/wk
n	6	8	8	8
age	55	50	40	48
M/F	4/2	7/1	7/1	7/1
ApoB	135	156	131	130
LDL	160 (127-181)	172 (132-218)	154 (132-266)	173 (135-210)
Total Cholesterol	246	271	253	252
HDL	52	55	57	54
TG	177 (88-298)	161 (79-330)	125 (54-295)	129 (62-200)
VLDL	23 (12-45)	17 (10-57)	20 (7-34)	17 (8-34)

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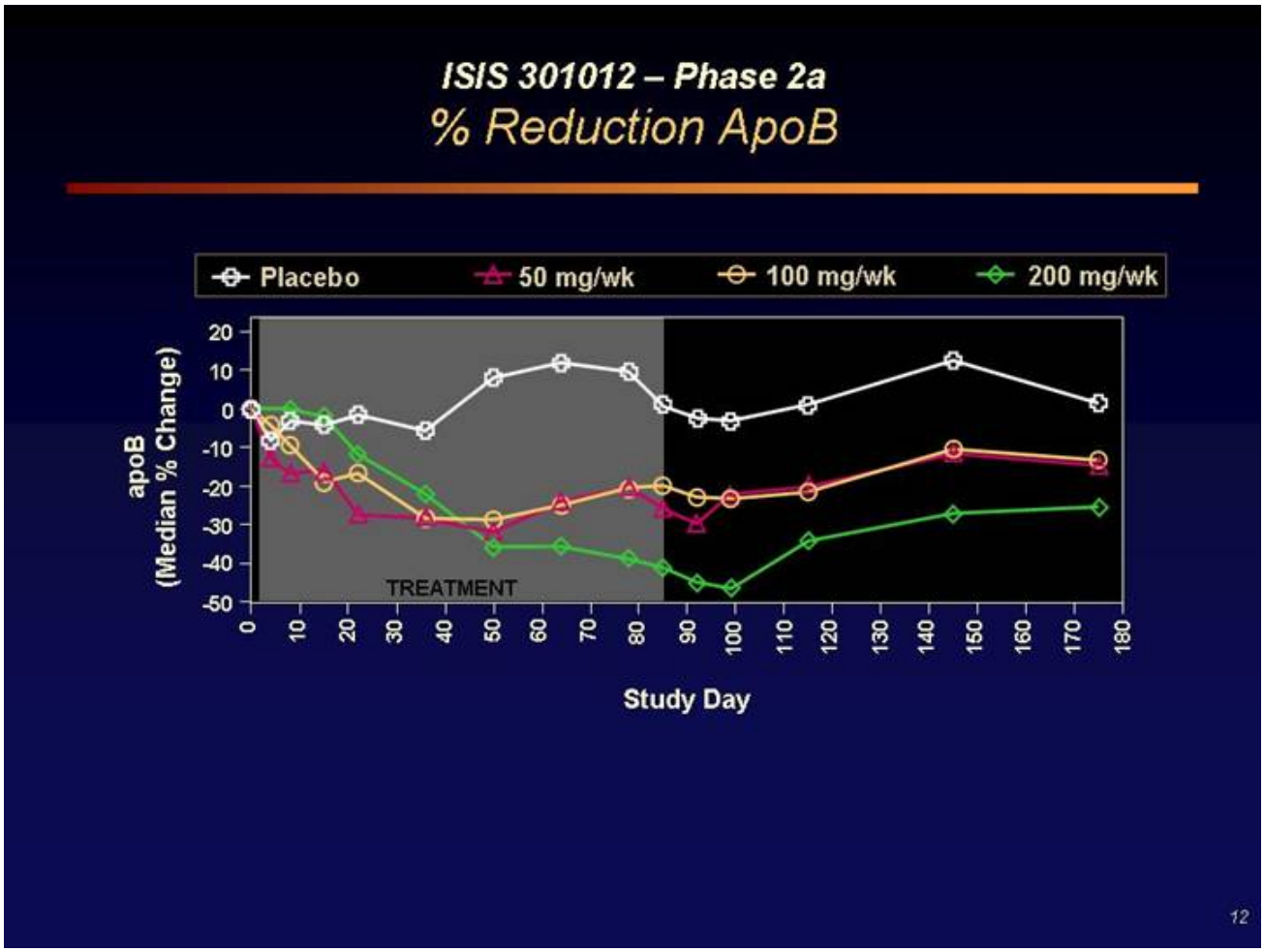

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ISIS 301012 – Phase 2a
Statistical Evaluation for ApoB*

		PBO	50 mg/wk	100 mg/wk	200 mg/wk
Dosing Period	day 36	-6%	**-28%** p=0.001	**-29%** p<0.001	**-22%** p=0.04
	day 50	8%	**-32%** p=0.005	**-29%** p<0.001	**-36%** p=0.001
	day 85	1%	**-26%** p=0.03	**-20%** p=0.001	**-41%** p<0.001
	day 99	-3%	-22% p=0.14	**-23%** p=0.005	**-47%** p<0.001
	day 115	1%	**-20%** p=0.03	**-22%** p=0.008	**-34%** p<0.001
	day 145	13%	**-11%** p=0.03	**-11%** p=0.003	**-27%** p<0.001
	day 175	2%	**-15%** p=0.04	**-13%** p=0.05	**-26%** p=0.003

*median; p value versus placebo

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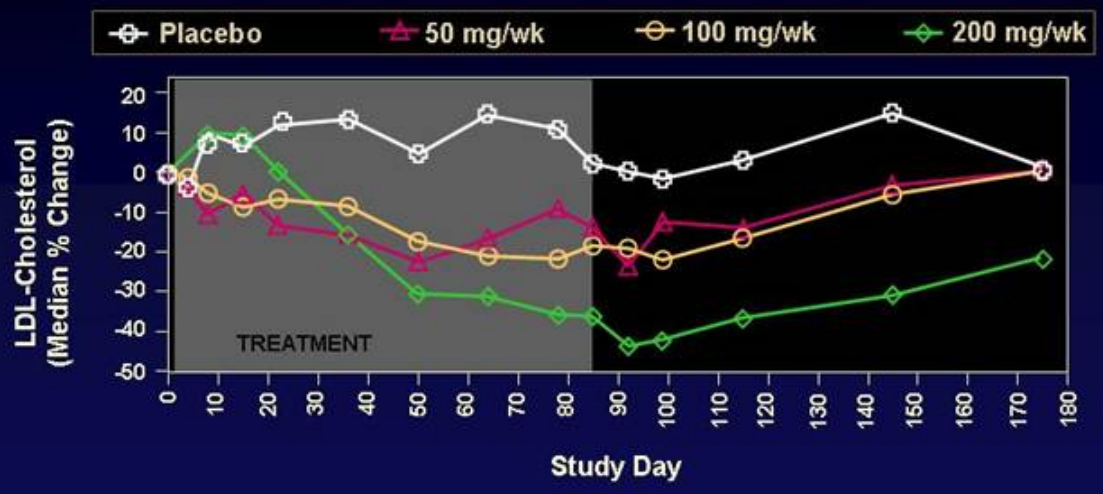
ISIS 301012 – Phase 2a
LDL % Reduction



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ISIS 301012 – Phase 2a

Statistical Evaluation for LDL*

Dosing Period

	PBO	50 mg/wk	100 mg/wk	200 mg/wk
day 36	14%	**-15%** p=0.001	**-8%** p=0.003	**-16%** p=0.001
day 50	5%	**-22%** p=0.03	**-17%** p<0.001	**-30%** p<0.001
day 85	3%	-14% p=0.11	**-18%** p=0.008	**-36%** p<0.001
day 99	-2%	-12% p=0.57	**-22%** p=0.05	**-42%** p<0.001
day 115	3%	**-14%** p=0.02	**-17%** p=0.05	**-37%** p<0.001
day 145	15%	**-3%** p=0.008	**-6%** p=0.03	**-31%** p<0.001
day 175	2%	1% p=0.49	1% p=0.57	**-22%** p<0.001

*median ; p value versus placebo

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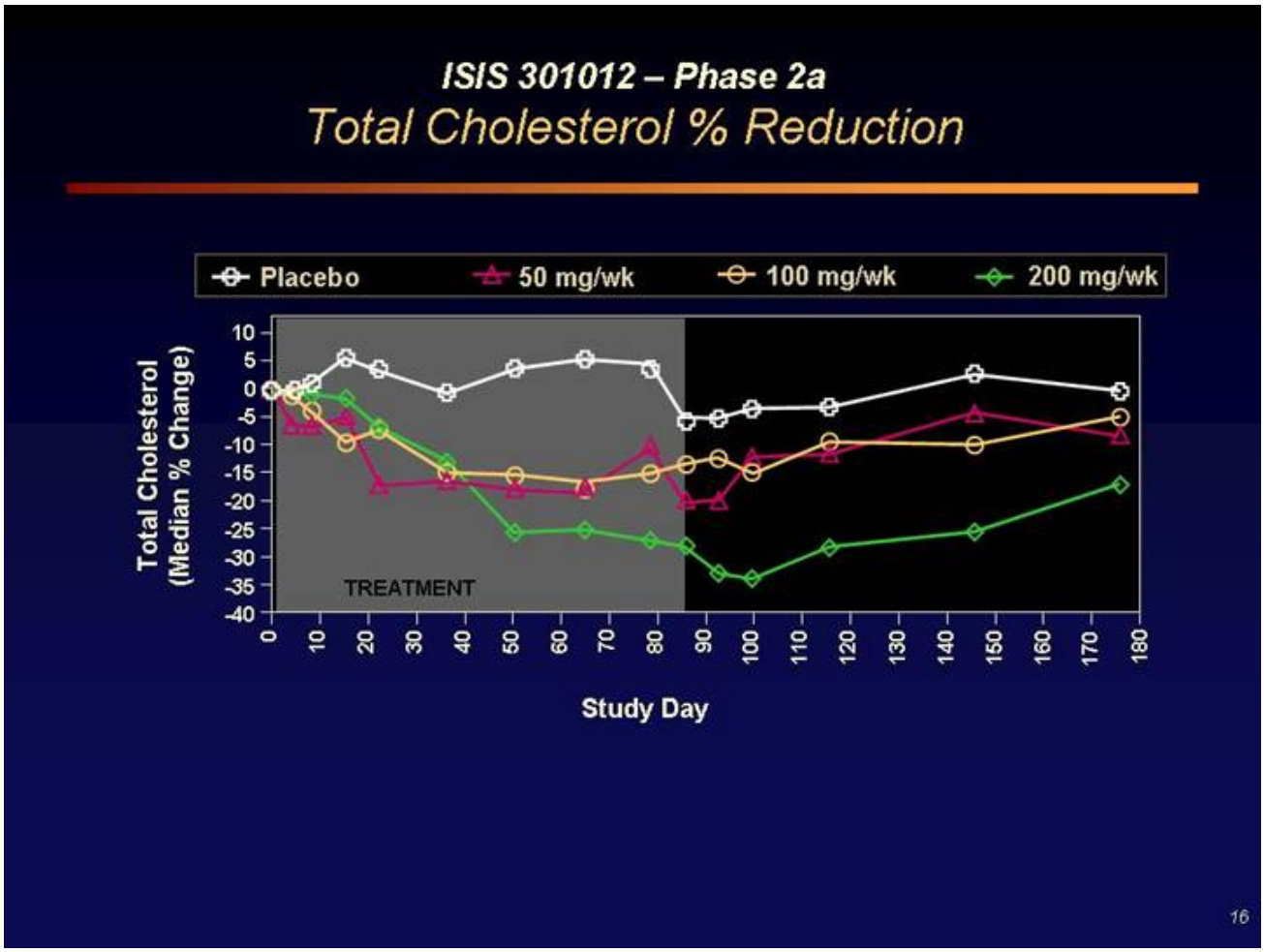

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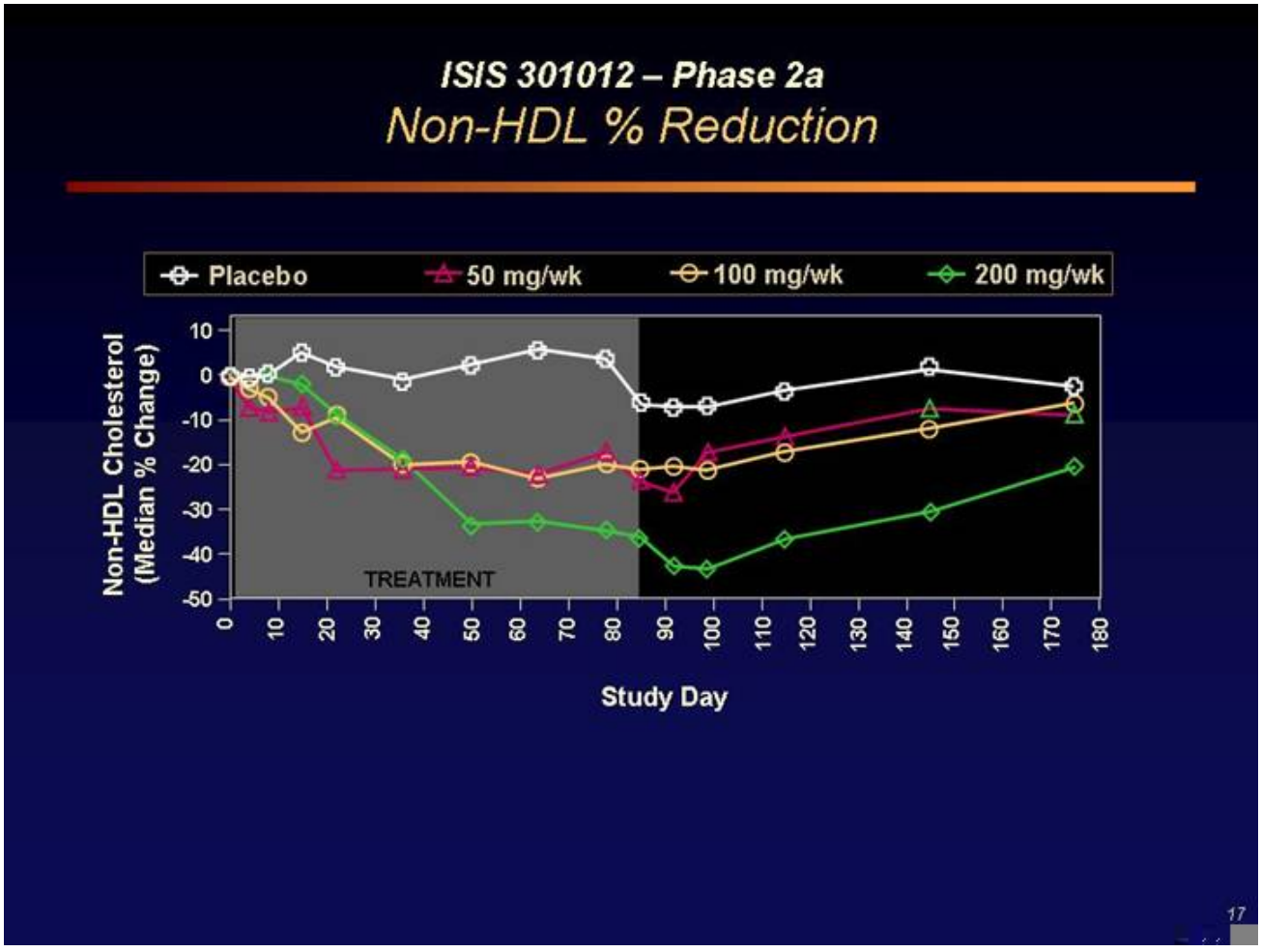

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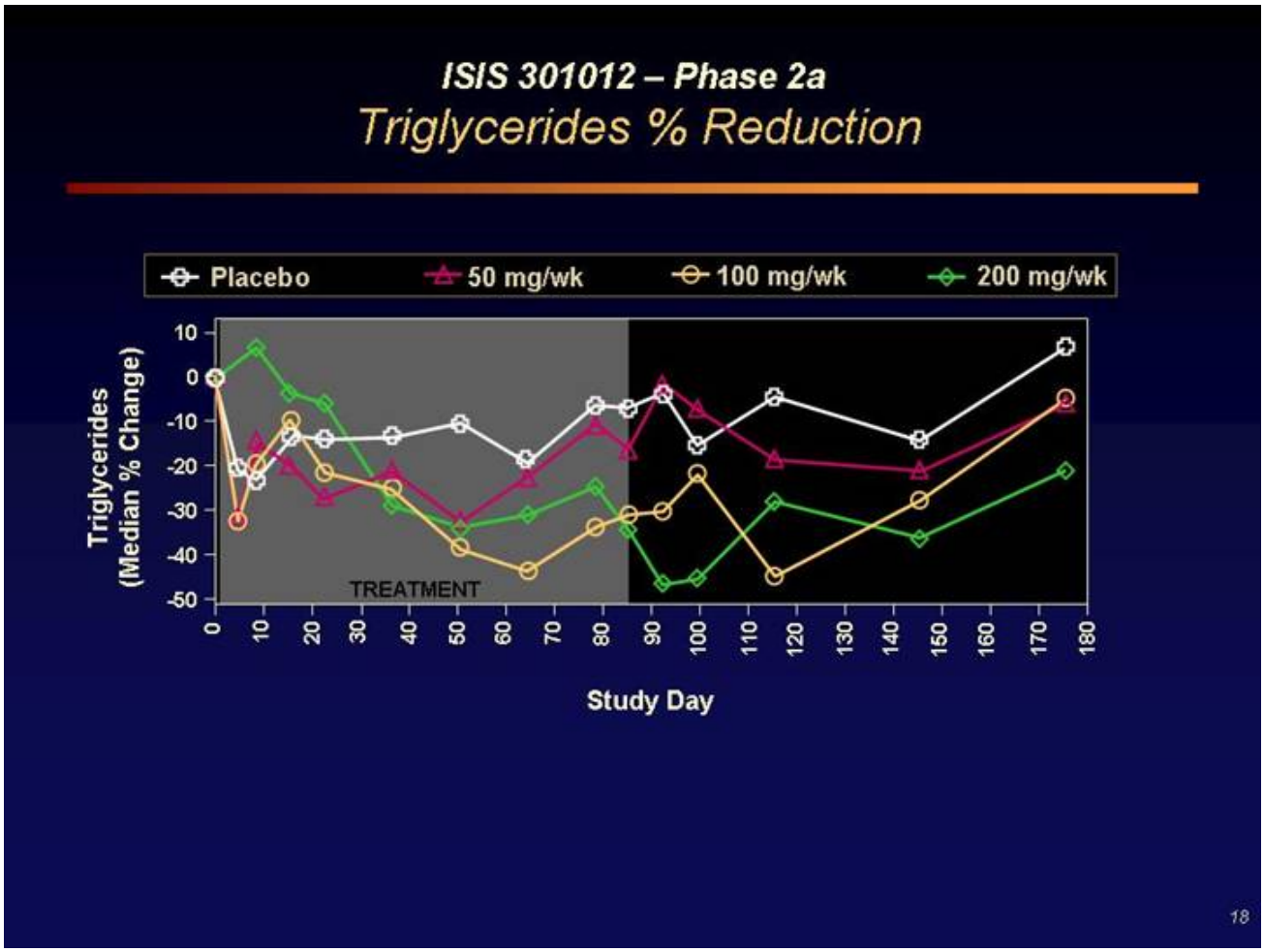

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ISIS 301012 – Phase 2a

Duration of Effect on LDL*

Post Dosing	
50 mg/week	0.4 months
100 mg/week	2.0 months
200 mg/week	5.2 months (projected)

*Return to 90% of baseline

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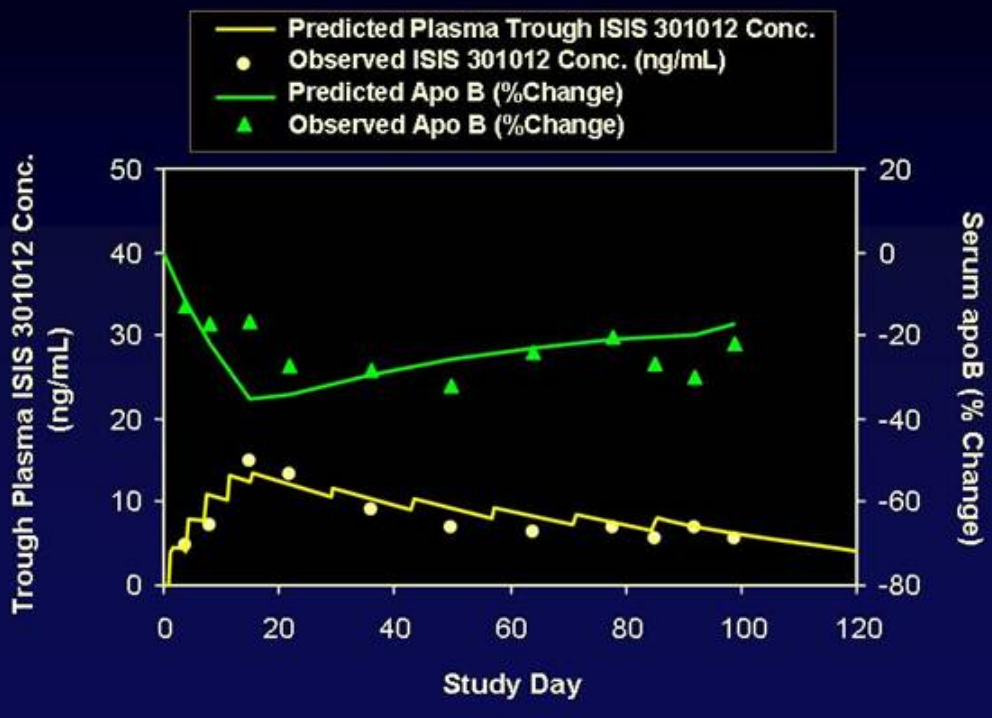
ISIS 301012 – Phase 2a

PK/PD Model Predicts Trough Concentrations and Pharmacologic Response (50 mg weekly)



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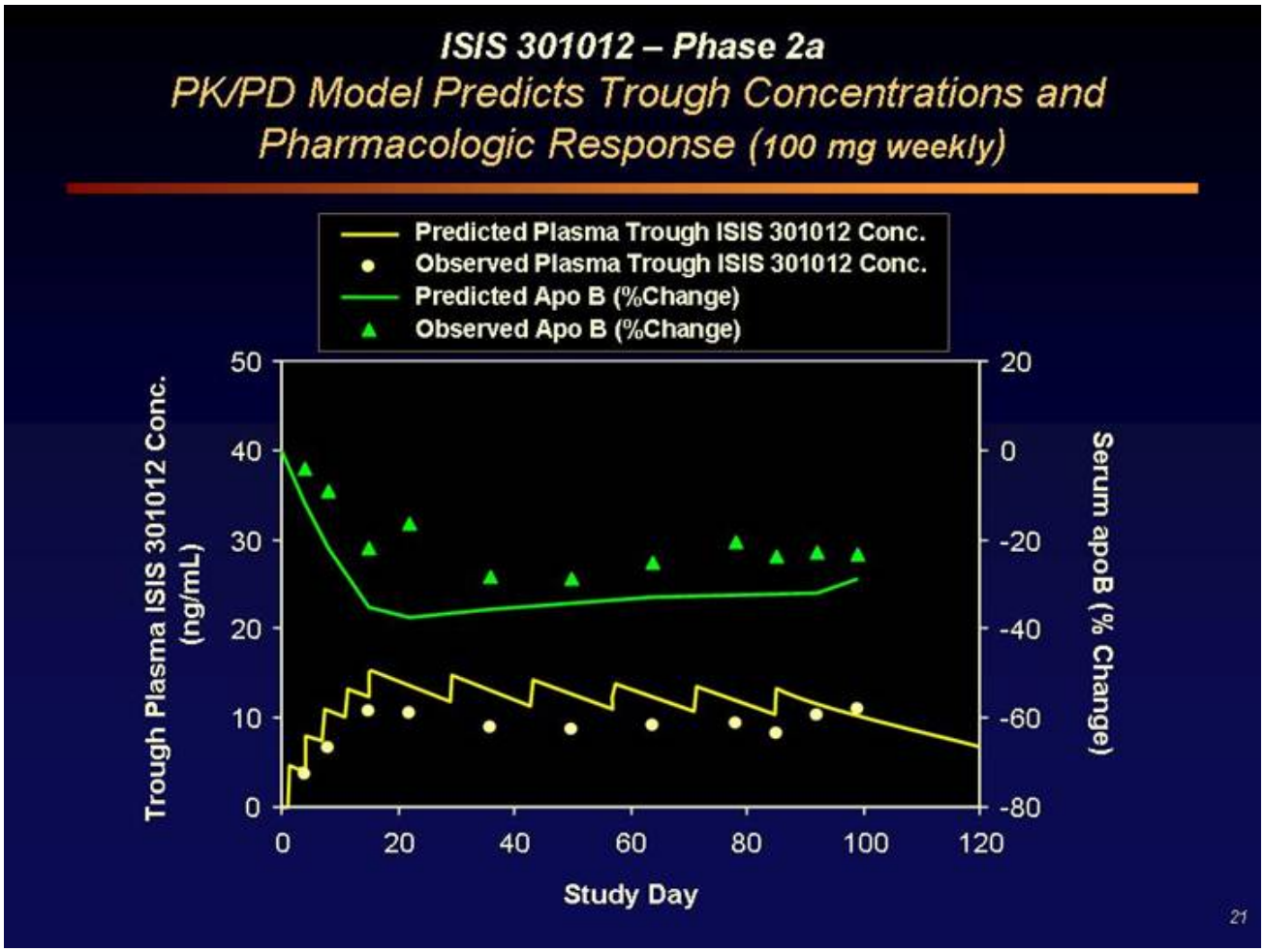

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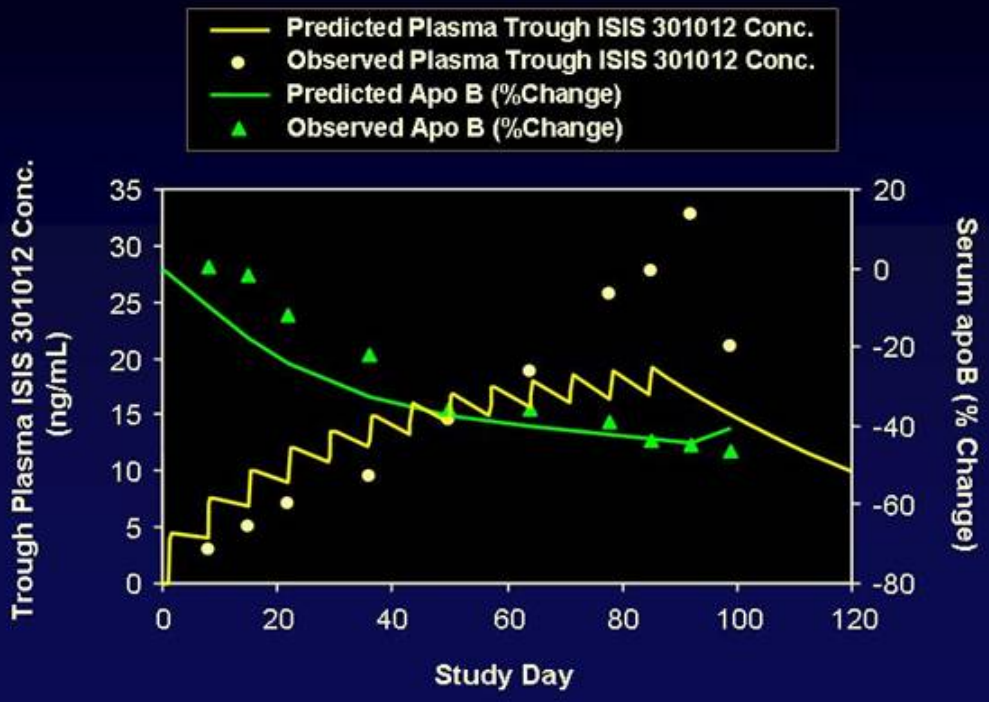
ISIS 301012 – Phase 2a

PK/PD Model Predicts Trough Concentrations and Pharmacologic Response (200 mg weekly)



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ISIS 301012 – Phase 2a

Safety

Serious Adverse Events:

- One unrelated SAE (encephalitis)

Adverse Events:

- Injection site reactions: Mild transient painless erythema
  - No impact on compliance
- One subject with transient ALT rise (3.4x ULN) 60 days post last dose
  - No dose response relationship for LFT elevations of any level
- No other laboratory or clinical abnormalities observed

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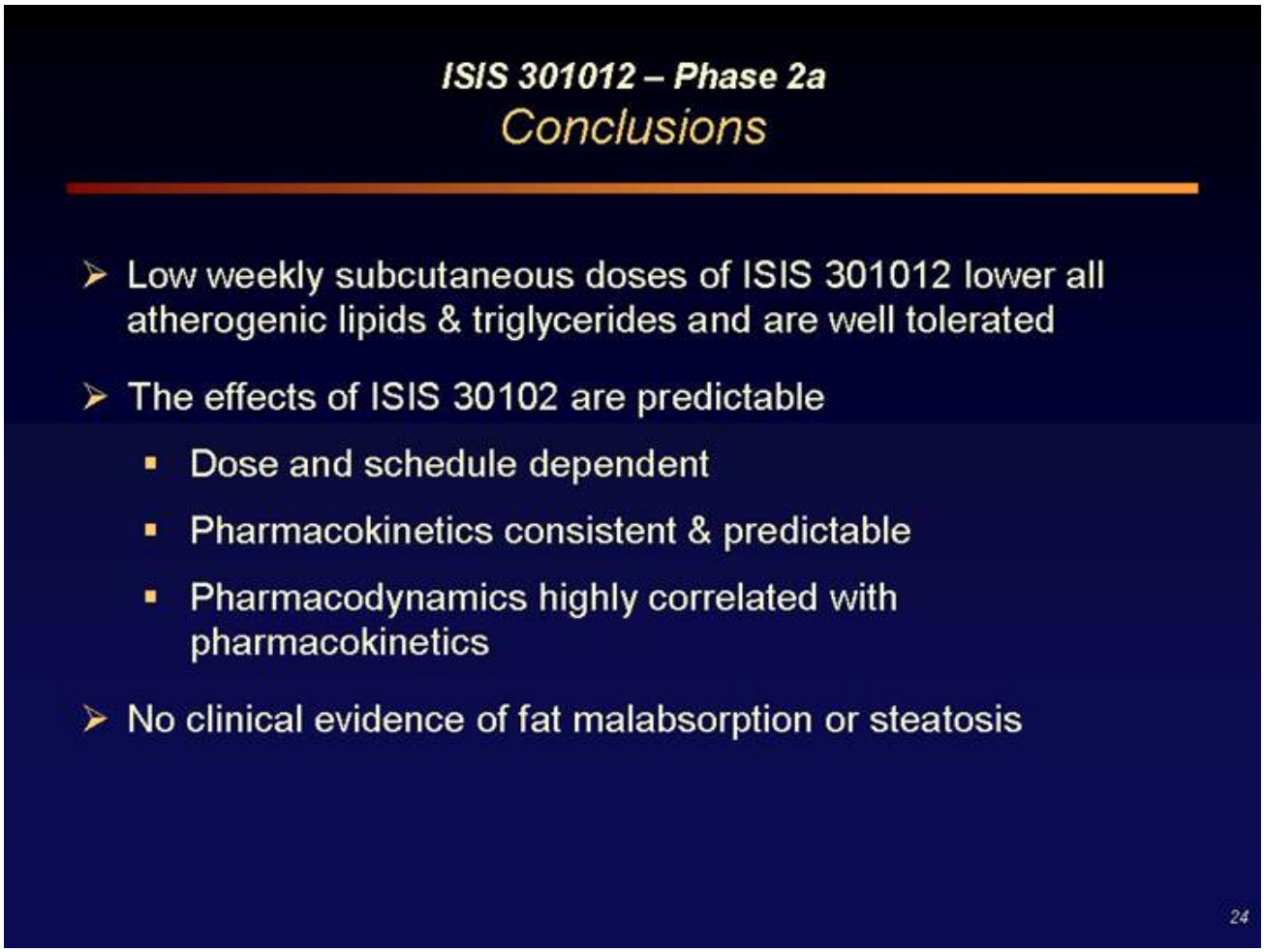

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ISIS 301012
Next Steps

- Evaluate effects of 300 and 400mg per week for three months in patients with high cholesterol
- Evaluate effects of ISIS 301012 in combination with statins
  - Initially for 5 weeks
  - Then 6 months
- Evaluate the effects of ISIS 301012 in patients with Familial Hypercholesterolemia (FH)
- Define induction and maintenance doses of ISIS 301012 in longer term trials
- Continue to define profile
- Initiation of surrogate outcome studies

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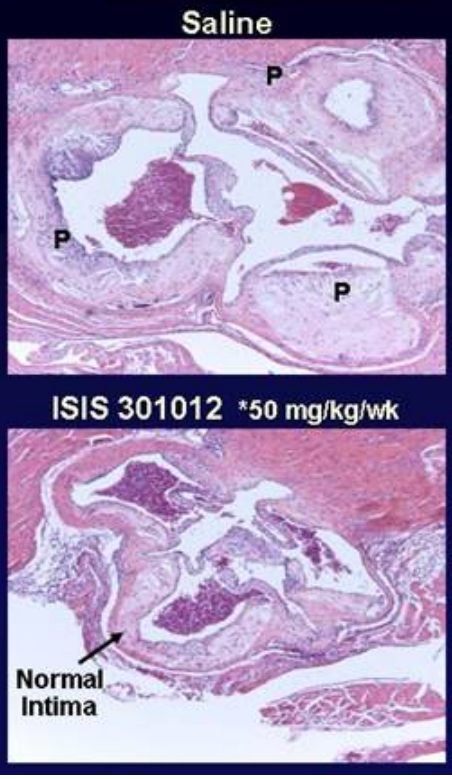
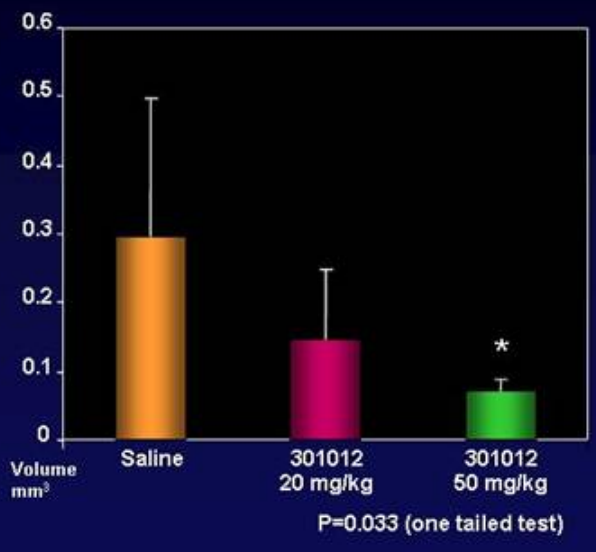
ISIS 301012
Treatment with ISIS 301012 for 14 Weeks Significantly Reduces Aortic Sinus Plaque Burden in Transgenic Mice





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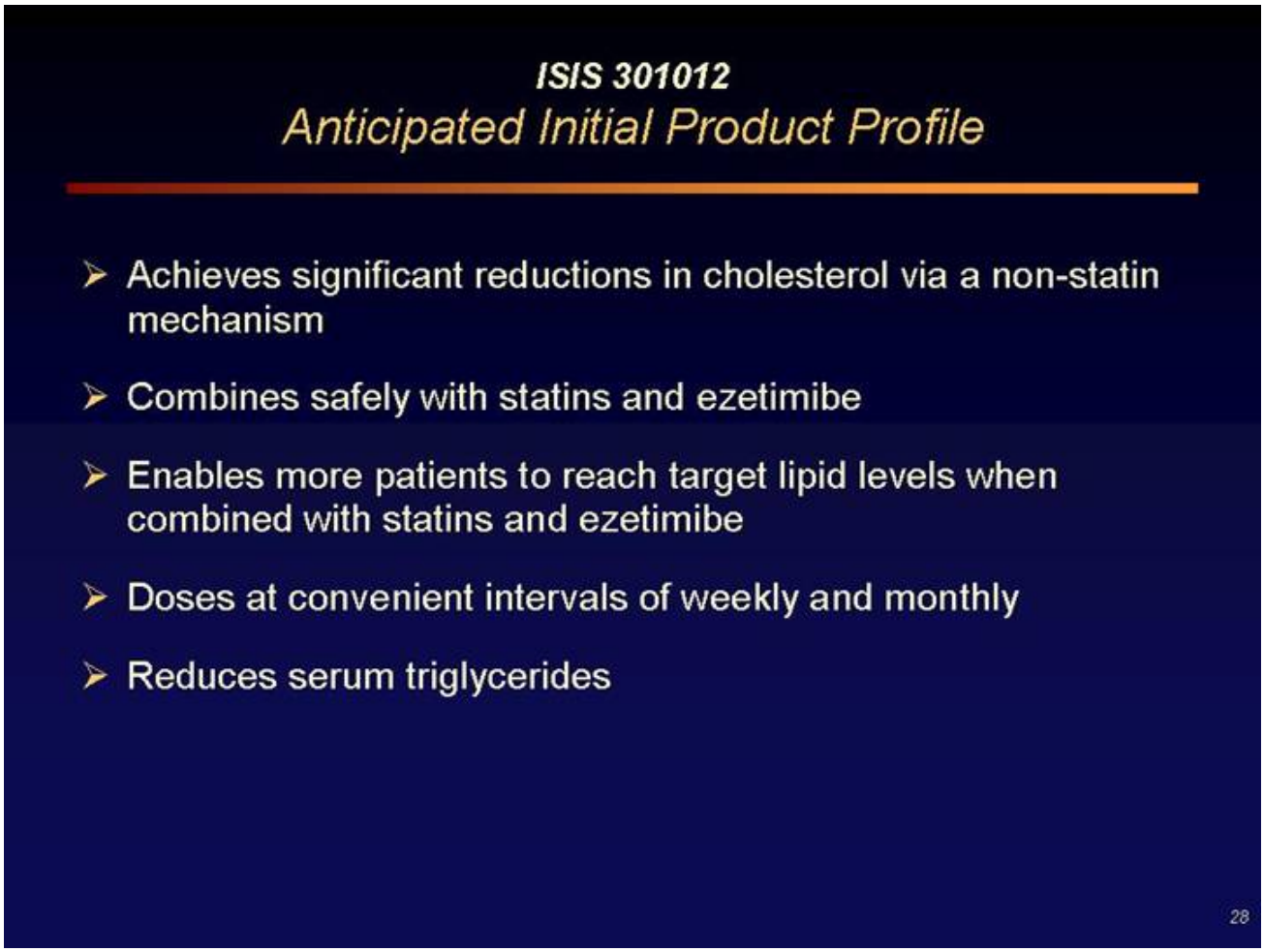

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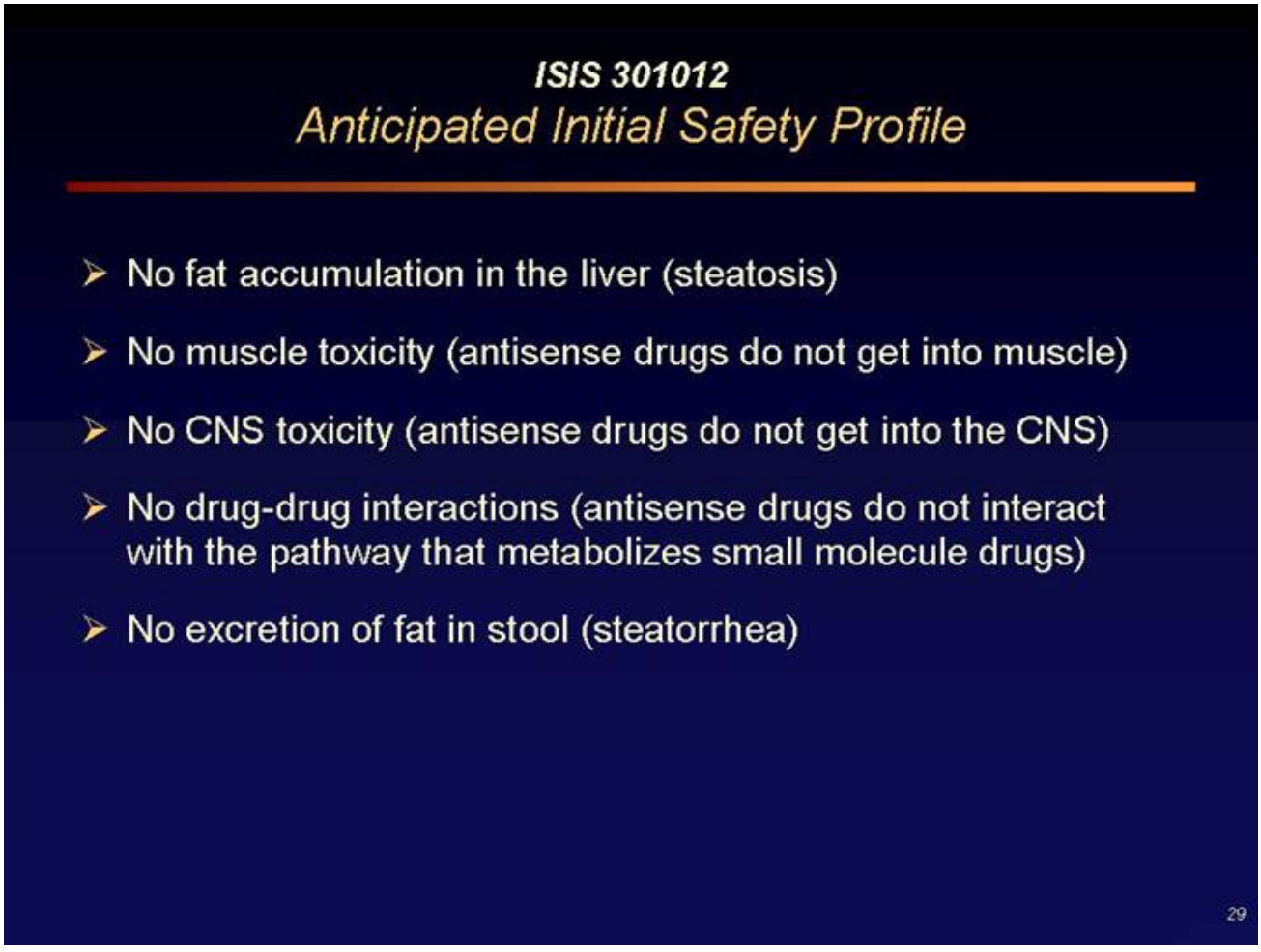

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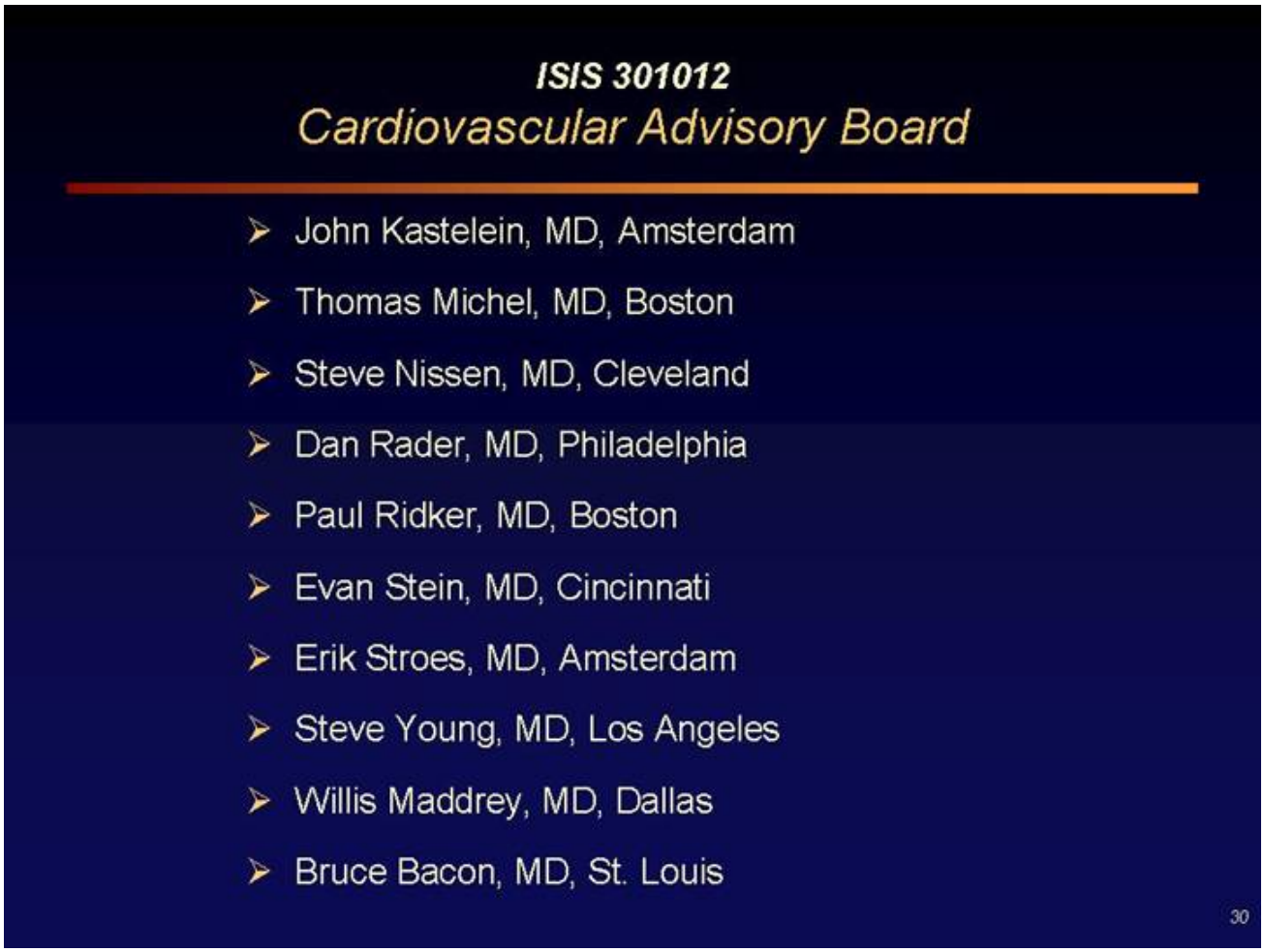

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[LOGO]

Developing RNA Drugs and Technologies to Improve the Lives and Health of Patients

April 2006

ISIS 301012:
The Reduction of Atherogenic Lipids in Subjects with Hypercholesterolemia

Mark Wedel, MD, JD
Senior Vice President and CMO
Isis Pharmaceuticals
Carlsbad, CA
April 2006

ISIS 301012
A Second Generation Antisense Drug Inhibiting apoB-100

Meets Criteria for
an Antisense Target

[GRAPHIC]

- **Expressed in the liver**
- **Essential for the synthesis and transport of VLDL and LDL**
- **Crucial role in lipid management**
- **Unapproachable with small molecules**
- **An apoB-100 inhibitor should have a unique lipid lowering profile**

ISIS 301012: Phase 1 Results

ISIS 301012 – Phase 1
Dose-dependent Prolonged Reduction in Serum apoB & LDL

apoB

[CHART]

apoB (% reduction) Day 39

[CHART]

LDL

[CHART]

LDL (% reduction) Day 39

[CHART]

ISIS 301012 – Phase 1
Trough Plasma Concentrations Predict Long Drug Effects & Support Infrequent Dosing

apoB-100 in Human Subjects (200 mg, n= 8)

[CHART]

* Statistically significant

ISIS 301012 – Phase 1
ISIS 301012 (350 mg/wk for 1 month)
Lowers All Atherogenic Lipids Including Triglycerides

[CHART]

ISIS 301012 – Phase 2a
Study Objectives

- Safety & tolerability
- Efficacy
  - Statistical significance
  - Dose dependence
    - apoB

- LDL
- Other atherogenic lipids

- PK/PD correlation

ISIS 301012 – Phase 2a
Study Design

- n = 10 subjects per cohort (total 50 subjects)
- Concomitant placebo subjects (1:4)
- Dosing duration: 3 months
- Target population: hypercholesterolemic subjects failing to reach target on diet alone
- Dosing cohorts:
  - 50 mg/wk
  - 100 mg/wk
  - 200 mg/wk
  - midpoint safety/efficacy review
  - 300 mg/wk
  - 400 mg/wk

ISIS 301012 – Phase 2a
Dosing Cohorts Completed

Weekly Dose Equivalent	Dose	Loading Dose*
50	100 every other week	Yes
100	200 every other week	Yes
200	200 every week	No

*** 200 mg subcutaneous on days 1, 4, 8 & 11**

ISIS 301012 – Phase 2a
Demographics

	PBO	50 mg/wk	100 mg/wk	200 mg/wk
n	6	8	8	8
age	55	50	40	48
M/F	4/2	7/1	7/1	7/1
ApoB	135	156	131	130
LDL	160	172	154	173
	(127-181)	(132-218)	(132-266)	(135-210)
Total Cholesterol	246	271	253	252
HDL	52	55	57	54
TG	177	161	125	129
	(88-298)	(79-330)	(54-295)	(62-200)
VLDL	23	17	20	17
	(12-45)	(10-57)	(7-34)	(8-34)

ISIS 301012 – Phase 2a
% Reduction ApoB

[CHART]

ISIS 301012 – Phase 2a
*Statistical Evaluation for ApoB**

Dosing Period	PBO	50 mg/wk	100 mg/wk	200 mg/wk
day 36	-6%	**-28%** p=0.001	**-29%** p<0.001	**-22%** p=0.04
day 50	8%	**-32%** p=0.005	**-29%** p<0.001	**-36%** p=0.001
day 85	1%	**-26%** p=0.03	**-20%** p=0.001	**-41%** p<0.001
day 99	-3%	-22% p=0.14	**-23%** p=0.005	**-47%** p<0.001
day 115	1%	**-20%** p=0.03	**-22%** p=0.008	**-34%** p<0.001
day 145	13%	**-11%** p=0.03	**-11%** p=0.003	**-27%** p<0.001
day 175	2%	**-15%** p=0.04	**-13%** p=0.05	**-26%** p=0.003

***median; p value versus placebo**

ISIS 301012 – Phase 2a
LDL % Reduction

[CHART]

ISIS 301012 – Phase 2a
*Statistical Evaluation for LDL**

Dosing Period	PBO	50 mg/wk	100 mg/wk	200 mg/wk
day 36	14%	**-15%** p=0.001	**-8%** p=0.003	**-16%** p=0.001
day 50	5%	**-22%** p=0.03	**-17%** p<0.001	**-30%** p<0.001
day 85	3%	-14% p=0.11	**-18%** p=0.008	**-36%** p<0.001
day 99	-2%	-12% p=0.57	**-22%** p=0.05	**-42%** p<0.001
day 115	3%	**-14%** p=0.02	**-17%** p=0.05	**-37%** p<0.001
day 145	15%	**-3%** p=0.008	**-6%** p=0.03	**-31%** p<0.001
day 175	2%	1% p=0.49	1% p=0.57	**-22%** p<0.001

***median ; p value versus placebo**

ISIS 301012 – Phase 2a
Total Cholesterol % Reduction

[CHART]

ISIS 301012 – Phase 2a
Non-HDL % Reduction

[CHART]

ISIS 301012 – Phase 2a
Triglycerides % Reduction

[CHART]

ISIS 301012 – Phase 2a
*Duration of Effect on LDL**

	Post Dosing
50 mg/week	**0.4 months**
100 mg/week	**2.0 months**
200 mg/week	**5.2 months (projected)**

***Return to 90% of baseline**

ISIS 301012 – Phase 2a
*PK/PD Model Predicts Trough Concentrations and Pharmacologic Response (**50 mg weekly**)*

[CHART]

ISIS 301012 – Phase 2a
*PK/PD Model Predicts Trough Concentrations and Pharmacologic Response (**100 mg weekly**)*

[CHART]

ISIS 301012 – Phase 2a
*PK/PD Model Predicts Trough Concentrations and Pharmacologic Response (**200 mg weekly**)*

[CHART]

ISIS 301012 – Phase 2a
Safety

Serious Adverse Events:

- One unrelated SAE (encephalitis)

Adverse Events:

- Injection site reactions: Mild transient painless erythema
    - No impact on compliance
- One subject with transient ALT rise (3.4x ULN) 60 days post last dose
    - No dose response relationship for LFT elevations of any level
- No other laboratory or clinical abnormalities observed

ISIS 301012 – Phase 2a
Conclusions

- Low weekly subcutaneous doses of ISIS 301012 lower all atherogenic lipids & triglycerides and are well tolerated
- The effects of ISIS 30102 are predictable
  - Dose and schedule dependent
  - Pharmacokinetics consistent & predictable
  - Pharmacodynamics highly correlated with pharmacokinetics
- No clinical evidence of fat malabsorption or steatosis

ISIS 301012
Next Steps

- Evaluate effects of 300 and 400mg per week for three months in patients with high cholesterol
- Evaluate effects of ISIS 301012 in combination with statins
  - Initially for 5 weeks
  - Then 6 months
- Evaluate the effects of ISIS 301012 in patients with Familial Hypercholesterolemia (FH)
- Define induction and maintenance doses of ISIS 301012 in longer term trials
- Continue to define profile
- Initiation of surrogate outcome studies

ISIS 301012
Treatment with ISIS 301012 for 14 Weeks Significantly Reduces Aortic Sinus Plaque Burden in Transgenic Mice

Saline
[GRAPHIC]

[CHART]

ISIS 301012 *50 mg/kg/wk
[GRAPHIC]

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 on statins & ezetimibe
    - Initially in patients with FH
    - Ultimately in polygenic hypercholesterolemia
  - An alternative to statins for those who are intolerant of statins

- An alternative to statins, period

ISIS 301012
Anticipated Initial Product Profile

- Achieves significant reductions in cholesterol via a non-statin mechanism
- Combines safely with statins and ezetimibe
- Enables more patients to reach target lipid levels when combined with statins and ezetimibe
- Doses at convenient intervals of weekly and monthly
- Reduces serum triglycerides

ISIS 301012
Anticipated Initial Safety Profile

- No fat accumulation in the liver (steatosis)
- No muscle toxicity (antisense drugs do not get into muscle)
- No CNS toxicity (antisense drugs do not get into the CNS)
- No drug-drug interactions (antisense drugs do not interact with the pathway that metabolizes small molecule drugs)
- No excretion of fat in stool (steatorrhea)

ISIS 301012
Cardiovascular Advisory Board

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