

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): **March 25, 2007**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125

(Commission File No.)

33-0336973

(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:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- 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 March 25 and March 26, 2007, Isis Pharmaceuticals, Inc. ("Isis") announced new Phase 2 clinical data from ISIS 301012 studies. A copy of the Press Releases related to these data is attached hereto as Exhibit 99.1 and Exhibit 99.2 and is incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated March 25, 2007.

99.2 Press Release dated March 26, 2007.

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: March 23, 2007

By: /s/ B. Lynne Parshall

B. LYNNE PARSHALL

Executive Vice President,

Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1 Press Release dated March 25, 2007.

99.2 Press Release dated March 26, 2007.



NEW DATA PRESENTED AT ACC SHOW ISIS 301012 MONOTHERAPY REDUCES apoB TO UNDETECTABLE LEVELS AND REDUCES LDL-C 70%

- *ISIS 301012 lowered apoB-100 to at or below the lower limit of normal in 8 of 8 patients and to the limit of detectability in 4 of 8 patients dosed at 400 mg/week*
- *ISIS 301012 lowered LDL-C 70%, with similar effects on other atherogenic lipids*
- *6 of 8 patients achieved LDL-C levels of less than 70 mg/dL; all 8 patients achieved LDL-C levels below 100 mg/dL*
- *ISIS 301012 was well tolerated through 400 mg/week, a dose that produced maximal measurable activity*

NEW ORLEANS, LA, and CARLSBAD, CA, March 25, 2007 09:00 CT - Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced new results from its monotherapy Phase 2 clinical trial of ISIS 301012 presented at the American College of Cardiology Annual Scientific Session (ACC) in New Orleans. In the dose cohort presented today, patients with high cholesterol were treated for ten weeks with 400 mg/week of ISIS 301012. Data for dose cohorts through 300 mg/week in which patients were treated for three months were previously reported. In this study, increasing the dose of ISIS 301012 to 400 mg/week was well tolerated and further reduced atherogenic lipids, with median improvements in LDL-cholesterol (LDL-C), non-HDL-cholesterol (non-HDL-C), total cholesterol (TC) and triglycerides (TG) of 70%, 65%, 56% and 53%, respectively. Collectively, data from this study demonstrate that the anticipated doses 100 — 300 mg/week should have broad lipid-lowering activity and be well tolerated.

Notably, by ten weeks into the protocol-specified thirteen-week dosing period, all eight treated patients in the cohort had levels of apoB-100 that were at or below the lower limit of normal (<60 mg/dL), and four of the eight had undetectable levels of apoB-100 (<35 mg/dL). Because further activity was not measurable, dosing was discontinued and patients progressed directly into follow-up. All eight patients were evaluable per protocol, and the primary endpoint data presented in tabular form below was derived from patients' visit 14 days after the last dose, or study day 78 for this dose cohort.

All patients in this dose cohort achieved LDL-C levels below the recommended 100 mg/dL target for patients in the High Risk category (see Adult Treatment Panel III Recommendations below). Six of eight, or 75% of patients achieved LDL-C levels below the optional lower target of 70 mg/dL. Post dosing, LDL-C levels for patients in this dose cohort ranged from 24 mg/dL to 97 mg/dL.

There were no drug-related serious adverse events in the study, and the most common drug-related adverse events were painless mild to moderate injection site reactions. Elevations in liver transaminases (ALT) were observed in this high-dose cohort; five of the eight patients dosed at 400 mg/week, including all four patients with undetectable levels of apoB, experienced modest ALT elevations at or above three times the upper limit of normal (3xULN). No patients experienced ALT elevations greater than 5xULN; the maximal ALT observed was 241 IU/L.

Importantly, no patients evidenced liver chemistries that would suggest risk of liver injury (extremely high ALT or ALT elevations together with elevations in bilirubin greater than 2xULN). The mild increases in ALT at the 400 mg/week dose likely reflect extreme lipid-lowering activity, not toxicity, and are consistent with perturbations in liver chemistries seen with statins. As predicted from animal studies with this drug and cumulative experience with other second-generation antisense drugs, there were no effects on kidney function. Patients in this dose cohort remain in follow-up.

According to Evan Stein, M.D., Ph.D., Director, Metabolic and Atherosclerosis Research Center, Cincinnati, Ohio, lead investigator in the study, "The clinical evidence supporting the activity and tolerability of ISIS 301012 has accumulated to a point at which it seems clear that ISIS 301012 is likely to play an important role in the management of high cholesterol. The drug's pronounced activity, its predictability, its reduction of all atherogenic lipids and triglycerides, as well as the opportunity for assured patient compliance with infrequent subcutaneous dosing are all attractive attributes. ISIS 301012 has broad potential in a variety of hyperlipidemic populations, and I'm looking forward to participating in its further development."

Henry Ginsberg, M.D., Professor of Medicine at Columbia University in New York commented, "These new results are important because the outstanding results at 400 mg/week with good tolerability indicate that the 200 and 300 mg/week doses should have excellent safety profiles along with the outstanding therapeutic activity."

Mark Wedel, M.D., J.D., Isis' Chief Medical Officer, added, "We have been able to define the full dose-response range of a drug through 400 mg/week, although with the potent and broad lipid-lowering activity we have seen at 200 and 300 mg/week, we do not expect to need to advance the 400 mg/week dose in registration studies. We continue to be encouraged by the performance of ISIS 301012, and look forward to initiating a longer-term Phase 2 study in patients with routine high cholesterol in combination with statins in which we will define induction and maintenance doses. We expect induction doses to be 200 to 300 mg/week and maintenance doses to be 100 to 200 mg/week. In addition, later this year we will begin our registration program for familial hypercholesterolemia."

Jeff Jonas, M.D., Executive Vice President, Isis Pharmaceuticals, said, "In less than 10 weeks with 400 mg/week of ISIS 301012, we were able to reduce apoB to undetectable levels in many of these patients. These levels are similar to those seen in patients with familial hypobetalipoproteinemia (FHBL), a genetic disorder that causes very low apoB levels. To have rapidly achieved these levels with only modest elevations in ALT and no evidence of liver dysfunction is remarkable and further confirms the exciting potential of the lower-dose induction and maintenance regimens we plan."

ISIS 301012 as a Single Agent

This randomized, double-blinded, placebo-controlled, dose-escalation trial treated patients with high cholesterol (baseline median LDL-C ranging from 154 - 206 mg/dL) for three months with ISIS 301012 as a single agent. In April 2006, results for the first three dose cohorts through 200 mg/week were presented, and in November 2006, results for the 300 mg/week cohort were presented. In today's poster, the data from the 400 mg/week dose cohort were presented,

with median reductions of 70% in LDL-C, 65% in non-HDL-C, 56% in TC and 53% in TG. These data demonstrate that in contrast to statins, ISIS 301012 causes linearly increasing reductions of

atherogenic lipids as doses are increased. At doses which decreased LDL-C and apoB more than 50%, there were modest reductions in HDL-cholesterol (HDL-C) when measured via the protocol-specified liquid detergent homogenous assay that was non-standardized; these results were contradicted when samples were re-evaluated in a blinded manner by a CDC Part III-standardized reference laboratory performing the more accurate dextran-sulfate precipitation assay. The ratios of apoB to apoA-1 (the protein components of LDL-C and HDL-C particles, respectively) and TC to HDL-C, which are indicators of cardiovascular risk, showed dose-dependent favorable decreases throughout the dose range.

Table 1: ISIS 301012 as a Single Agent, Summary of Results. Median % changes from baseline at primary endpoint*.

	Placebo	50 mg/week	100 mg/week	200 mg/week	300 mg/week	400 mg/week
# of patients	10	8	8	8	8	8
ApoB	7%	-22% (p=0.07)	-23% (p=0.001)	-47% (p=0.0002)	-61% (p=0.0003)	> -70% (p<0.0001)**
LDL-C	2%	-12% (p=0.33)	-22% (p=0.01)	-42% (p=0.0002)	-62% (p=0.0003)	-70% (p<0.0001)
VLDL-C	-17%	-14% (p=0.43)	-14% (p=0.93)	-54% (p=0.006)	-52% (p=0.04)	-63% (p=0.03)
Non-HDL-C	4%	-17% (p=0.25)	-21% (p=0.02)	-44% (p=0.0002)	-54% (p=0.0003)	-65% (p<0.0001)
HDL-C (1)	2%	9% (p=0.28)	5% (p=0.40)	-1% (p=0.72)	-15% (p=0.009)	-18% (p=0.07)
HDL-C (2)	14% (n=4)	NA	NA	NA	11% (n=7)	7% (n=8)
ApoA-1	0%	8% (p=0.01)	5% (p=0.19)	-2% (p=0.96)	-14% (p=0.06)	-9% (p=0.12)
TC	6%	-12% (p=0.33)	-15% (p=0.09)	-34% (p=0.0002)	-46% (p=0.0003)	-56% (p<0.0001)
Triglycerides	-13%	-7% (p=0.65)	-22% (p=0.54)	-46% (p=0.02)	-43% (p=0.04)	-53% (p=0.02)
ApoB:ApoA-1	11%	-22% (p=0.007)	-26% (p=0.002)	-46% (p=0.0002)	-51% (p=0.0003)	-69% (p<0.0001)
TC:HDL-C	-4%	-14% (p=0.10)	-18% (p=0.006)	-34% (p=0.0006)	-35% (p=0.001)	-53% (p<0.0001)

p value = vs. placebo

*Primary endpoint analysis was 14 days post last dose, Day 99 for 50-300 mg/week cohorts, Day 78 for 400 mg/week

**4 of 8 patients in this dose group reached the limit of detectability for apoB

HDL-C (1) measurements were by a non-standardized liquid detergent homogeneous assay

HDL-C (2) measurements were by the more accurate dextran-sulfate precipitation assay performed in a CDC Part III-standardized reference laboratory

NA = data not available

Table 2: ISIS 301012 as a Single Agent, Patients at Target. Number of patients (%) in each cohort at target lipid levels at the primary endpoint*.

Parameter	Target	Placebo	50 mg/wk	100 mg/wk	200 mg/wk	300 mg/wk	400 mg/wk
# of patients		10	8	8	8	8	8
LDL-C	<100 mg/dL	0	1 (13%)	0	4 (50%)	6 (75%)	8 (100%)
	<70 mg/dL	0	0	0	2 (25%)	5 (63%)	6 (75%)
Non-HDL-C	<130 mg/dL	0	1 (13%)	4 (50%)	7 (88%)	7 (88%)	8 (100%)
ApoB	<90 mg/dL	0	2 (25%)	3 (38%)	7 (88%)	7 (88%)	8 (100%)
ALL TARGETS	LDL-C<100		1 (13%)	0	4 (50%)	6 (75%)	8 (100%)
	Non-HDL-C<130 ApoB<90	0	1 (13%)	0	4 (50%)	6 (75%)	8 (100%)

*Primary endpoint analysis was 14 days post last dose, Day 99 for 50-300 mg/week cohorts, Day 78 for 400 mg/week

Table 3: ISIS 301012 as a Single Agent, Laboratory Findings. Number of patients with ALT elevations $\geq 3 \times \text{ULN}$ (no ALTs exceeded $5 \times \text{ULN}$; maximal ALT observed = 241 IU/L).

ALT Elevations Single [†] / Consecutive [‡]	Placebo (n = 10)	50 mg/wk (n = 8)	100 mg/wk (n = 8)	200 mg/wk (n = 8)	300 mg/wk (n = 8)	400 mg/wk (n = 8)
Primary Endpoint Day 1 to 99 (78)	0 / 0	1 / 0	0 / 0	0 / 0	0 / 0	0 / 5*
Primary Follow-up Day 100 to 143	0 / 0	0 / 0	0 / 0	0 / 0	1 / 0	NA
Long term F/U Day 144 to 235	0 / 0	0 / 0	0 / 0	0 / 1	NA	NA

[†]Single = elevation that returned to below $3 \times \text{ULN}$ by the next visit at least 7 days later

[‡]Consecutive = elevation that was observed in two measures at least 7 days apart

*4 of these 5 patients had undetectable levels of apoB

Primary endpoint period was through 14 days post last dose, Day 99 for 50-300 mg/wk, Day 78 for 400 mg/wk

Primary follow-up period was from primary endpoint to 8 weeks post last dose

NA = data not available, cohorts remain in follow-up

Presentation Details

Date: Sunday, March 25, 2007

Session: 1206: Vascular Disease, Hypertension and Prevention — V-cast Poster
Track: ACC.Vascular Disease, Hypertension, and Prevention
Room: Hall H
Presentation: 1206-278
Title: Statin-Like, Dose-Dependent Reductions in LDL-C and Apolipoprotein B With ISIS 301012, an Antisense Inhibitor of Apolipoprotein B, in Subjects With Polygenic Hypercholesterolemia

More about Phase 2 Trials for ISIS 301012

Additional data from two studies in which ISIS 301012 is being dosed in combination with statins and other lipid-lowering therapies are being presented at the ACC. Tomorrow morning, results of an ongoing trial of ISIS 301012 added to maximal lipid-lowering therapies in homozygous familial hypercholesterolemia (FH) patients will be presented, and tomorrow afternoon results of a trial adding ISIS 301012 for five weeks at 400 mg/week in patients with routine high cholesterol on stable statin therapy will be reported, both in oral sessions. Extended three-month treatment periods are planned for subsequent cohorts of 200 and 300 mg/week doses in the statin coadministration study, to be reported later in the year. Also later in the year, results from an ongoing double-blind, placebo-controlled, dose-escalation study in patients with heterozygous FH will be reported.

ISIS 301012 has been granted orphan drug status for the treatment of homozygous FH and Isis plans to begin registration-directed studies for FH in 2007.

About ISIS 301012 and Cholesterol

ISIS 301012 is a second-generation antisense drug that reduces the production of apoB-100, a protein critical to the synthesis and transport of “bad” cholesterol and a target that has proved to be undruggable using traditional, small-molecule approaches. Cholesterol can be carried in the bloodstream in a variety of forms, with high-density lipoprotein, or HDL-C, being the good form, and low-density lipoproteins, or LDL-C, and very low-density lipoproteins, or VLDL-C, being bad forms directly involved in heart disease. Collectively, LDL-C, VLDL-C, and other bad forms of cholesterol are referred to as “non-HDL-C.” The lowering of non-HDL-C is a key component in

the prevention and management of cardiovascular disease. Isis plans to develop ISIS 301012 as the drug of choice for patients who are unable to achieve target cholesterol levels with statins alone or who are intolerant of statins.

Adult Treatment Panel III Recommendations

The National Cholesterol Education Program’s Adult Treatment Panel III guidelines for target LDL-C levels High-Risk patients is less than 100 mg/dL, with an optional target of less than 70 mg/dL. For Moderately High-Risk patients, the target is less than 130 mg/dL. Over 20 million people in the U.S. in the High-Risk and Moderately High-Risk categories are failing to meet recommended LDL-C targets using currently available lipid-lowering therapies.

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 17 drugs in development. Isis’ drug development programs are focused on treating cardiovascular and metabolic diseases. Isis’ partners are developing drugs for cancer, and inflammatory and other diseases. Ibis Biosciences, Inc., Isis’ wholly owned subsidiary, is developing and commercializing the Ibis T5000 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 over 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, activity, therapeutic potential and safety of ISIS 301012 in treating high cholesterol. 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, 2006, which is on file with the SEC. Copies of this and other documents are available from the Company.

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apoB-100	369	191	-48%	180	88	-51%	283	201	-29%
LDL-C	651	328	-50%	197	91	-54%	445	301	-32%
VLDL-C	18	12	-33%	33	23	-29%	30	21	-30%
Non-HDL	669	340	-49%	230	114	-50%	475	322	-32%
HDL-C	27	37	40%	29	30	5%	27	29	7%
ApoA-1	86	95	10%	109	106	-2%	89	89	1%
TC	695	377	-46%	258	144	-44%	502	351	-30%
TG	90	60	-33%	163	115	-29%	151	104	-31%
Lp(a)	104	48	-54%	140	112	-20%	108	87	-19%

Presentation Details

Date: Monday, March 26, 2007
 Session: 603: Common Challenges in Preventive Cardiology (7:00 - 8:30 a.m. CT)
 Track: ACC.Symposium
 Room: Auditorium B
 Presentation: 603-8
 Time: 8:15 - 8:30 a.m.
 Speaker: Dr. Evan A. Stein
 Title: High Low-Density Lipoprotein Cholesterol on Three Drugs

More about Phase 2 Trials for ISIS 301012

Additional data from two ongoing studies in polygenic hypercholesterolemia will be presented at the ACC. Results of a study in which patients treated with up to 400 mg/week of ISIS 301012 as a single agent for three months were reported yesterday in a poster session, and results of a study in which patients were treated with up to 400 mg/week of ISIS 301012 added to stable statin therapy for five weeks will be presented in an oral session later today. Extended three-month treatment periods are planned for subsequent cohorts of 200 and 300 mg/week doses in the statin coadministration study, to be reported later in the year. Also later in the year, results from an ongoing double-blind, placebo-controlled, dose-escalation study in patients with heterozygous FH will be reported.

About Familial Hypercholesterolemia

Familial hypercholesterolemia is a dominantly-inherited genetic condition that results in markedly elevated LDL-C levels beginning at birth and heart attacks at an early age. Affected people have consistently high levels of LDL-C, which leads to premature atherosclerosis of the coronary arteries. Treatment for FH is inadequate, and the most severely affected patient may undergo an expensive and time-consuming procedure called apheresis, a process similar to kidney dialysis to remove the "bad" cholesterol from the blood. Homozygous FH is rare, affecting about one in one million people, but heterozygous FH is much more common with a prevalence of approximately one in every 500 people.

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 17 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing drugs for cancer, and inflammatory and other diseases. Ibis Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Ibis T5000 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 over 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, activity, therapeutic potential and safety of ISIS 301012 in treating high cholesterol. 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, 2006, which is on file with the SEC. Copies of this and other documents are available from the Company.

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