

Issuer Free Writing Prospectus
Dated May 31, 2006

ISIS PHARMACEUTICALS, INC.

Conference Call Script:

Azimuth Opportunity Conference Call

Wednesday, May 31, 2006

5:30 AM Pacific / 8:30 AM Eastern

Operator:

Welcome to Isis Pharmaceuticals' Conference Call. Leading the call today from Isis is Dr. Stan Crooke, Isis' Chairman and CEO. Dr. Crooke, please begin.

Stan:

Thank you for joining us today. This morning we announced that we have received a commitment for equity financing from Azimuth Opportunity. Over the next 18 months, we can, if we choose, sell up to \$75 million of common stock at a small discount to market to Azimuth Opportunity. We're particularly pleased to participate with Acqua Capital and Azimuth. We've had a long productive relationship with the principals of these firms and we appreciate their continuing support.

Participating with me are Lynne Parshall, Executive Vice President and Chief Financial Officer.

Lynne will explain the transaction in more detail and its strategic importance to the Company. Before we begin, Lynne, please review our policy on forward-looking statements.

Lynne:

This conference call includes forward-looking statements regarding Isis Pharmaceuticals' business. 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, 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

March 31, 2006, which are on file with the SEC. Copies of these and other documents are available from the Company.

Stan:

Thanks Lynne.

We see this transaction with Azimuth Opportunity as a no-cost insurance policy with a quality group who we know well that allows us to have flexible access to the capital markets. We have had a great year and we believe we will continue to report important progress on our antisense drugs and platform, and in our Ibis division.

Nevertheless, as recent events in the stock market demonstrate, we, like all biotechnology companies, are subject to market dynamics. In a down market, even great news such as the positive Phase 2 data that we reported with our cholesterol-lowering drug, ISIS 301012, may not be enough to assure that we have access to capital at a reasonable price when we need it. This transaction provides us with the flexibility to continue to make progress in all areas of our business and greater ability to take advantage of improved market conditions in the future.

Of course we will continue to be fiscally prudent and we intend to achieve all of our 2006 goals within the financial guidance that we have given.

Lynne will you please review the details of this transaction?

Lynne:

Thanks Stan.

As Stan mentioned, we have received a commitment for up to \$75 million in equity financing from Azimuth Opportunity. Over the next 18 months, we can if we choose, sell common stock to Azimuth at a small discount to market. The discount ranges from 3.8% to 5.3%, based on our stock price. The higher the stock price, the lower the discount, with the maximum discount applying to purchases at 5 dollars per share and the minimum discount applying to purchases at 14 dollars per share or above.

We see this transaction as a no-cost insurance policy that allows us to rapidly take advantage of positive shifts in the market. There are no upfront fees and warrants involved in the transaction.

We will use the net proceeds from the sale of the securities for research, drug discovery and development, capital expenditures and other general corporate purposes, including advancing ISIS 113715, ISIS 369645, and ISIS 353512. In addition, these funds will be used to accelerate the commercialization of Isis' Ibis biosensor system, the IBIS T-5000.

In addition to ISIS 301012, our glucagon receptor and glucocorticoid programs, which we recently financed through our Symphony transaction, and ISIS 113715, our type 2 diabetes drug currently in Phase 2 clinical trials, we have a number of other exciting drugs in our cardiovascular and metabolic programs that we may want to develop. For example, although ISIS 369645, our first aerosol antisense drug for asthma and other lung diseases has been ready for development for several months, we've only recently initiated development activities. We are also evaluating the various opportunities for

development of our antisense drug to inhibit CRP. When we finalize those plans, the availability of these funds will help support those activities.

We also have a significant number of partnered drugs. In some cases, we have the opportunity to participate in the development of these drugs in return for greater ownership. For example, OGX-011, our antisense drug that inhibits clusterin for the treatment of cancers is currently in Phase 2 trials, and is being managed by our partner, OncoGenex. Finally, we are making great progress in commercializing our Ibis biosensor system, the IBIS T-5000 and want to support its successful commercialization plan. So, as you can see, we have exciting opportunities that can better be exploited because of the guaranteed access to capital that this transaction provides.

Having said all that, however, let me reiterate what Stan said. We understand that until market conditions improve, access to any capital is costly. We will continue to be fiscally prudent and use the funding we have to advance the most important assets that we believe will create long-term value for our shareholders. We plan to meet the guidance for 2006 with regard to expenses and net operating loss that we have previously given. We expect a net operating loss, excluding non-cash compensation expense and restructuring costs, in the high \$50 million range. We expect operating expenses to be flat compared to the annualized rate of the last two quarters of 2005, or approximately \$88 million. Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008.

All of this is consistent with the strategy that we have discussed. We are continuing to try to license alicaforsen. We have partnered our other anti-inflammatory and cancer drugs and we've focused our internal programs on metabolic and cardiovascular drugs and advancing routes of delivery, such as aerosol administration.

We will be having an Analyst/Investor Lunch in New York on June 13 to discuss our metabolics program, including our type 2 diabetes drug, ISIS 113715, which is currently in Phase 2 clinical trials. In addition, in the coming months, we will be updating you on the progress we're making in commercializing our Ibis biosensor system. We hope that you share our excitement in these programs and agree that they add great value in addition to our lead cardiovascular drug, ISIS 301012.

Before we move to answering questions, I'd like to point out that because of securities law considerations related to this financing, we will not have the Q&A available on the archived webcast or conference call.

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Isis Pharmaceuticals, Inc. has filed a registration statement (including a prospectus) with the SEC for the offering to which this communication relates. Before you invest, you should read the prospectus in that registration statement and other documents the issuer has filed with the SEC for more complete information about the Isis and this offering. You may get these documents for free by visiting EDGAR on the SEC Web site at www.sec.gov. Alternatively, Isis, any underwriter or any dealer participating in the offering will arrange to send you the prospectus if you request it by calling collect at 760-603-2471 or contacting Isis Pharmaceuticals, Inc., Attn: Linda Powell, Assistant Corporate Secretary, 1896 Rutherford Road, Carlsbad, California 92008.
