

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

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of
the Securities Exchange Act of 1934 (Amendment No.)

Filed by the Registrant

Filed by a Party other than the Registrant

Check the appropriate box:

- Preliminary Proxy Statement
 Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))
 Definitive Proxy Statement
 Definitive Additional Materials
 Soliciting Material Pursuant to §240.14a-12

Isis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

- No fee required.
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 Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.
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Supplemental Information Regarding Proposal 4—Advisory Vote on Executive Compensation (“Say-on-Pay”)

This information supplements information contained in Isis Pharmaceuticals, Inc.’s definitive proxy statement dated April 23, 2012, which we refer to as our proxy statement. We and our proxy solicitor, Alliance Advisors, may use the following information to communicate with certain stockholders. References to “Isis”, the “Company,” “we,” “us” or “our” refer to Isis Pharmaceuticals, Inc.

May 29, 2012

Re: Isis Pharmaceuticals, Inc. June 7, 2012 Annual Meeting of Stockholders (“Annual Meeting”) Proposal 4 — Advisory Vote on Executive Compensation

Dear Stockholder:

By now you should have received our Notice of the 2012 Annual Meeting and Proxy Statement. You can also view our proxy statement at: http://www.sec.gov/Archives/edgar/data/874015/000110465912025639/a12-1729_1def14a.htm.

We are writing to ask for your support at the Annual Meeting by voting in accordance with the recommendations of our board of directors on all proposals. **In particular, we are requesting your support on Proposal 4, Advisory Vote on Executive Compensation (“Say on Pay”).** We request that you consider the

The Compensation Committee (the “Committee”) does not target executive pay to the 75th percentile of our peer group.

- **The Committee does not benchmark to the 75th percentile of the smaller group of seven companies that was selected as our peer group (the “Peer Group”).** The reference in the compensation discussion and analysis section of our proxy statement to targeting compensation at the 75th percentile of the biotech/pharmaceutical market relates to our general philosophy of targeting the 50th to 75th percentile of AON’s Radford Global Life Science Survey (the “Survey Data”), which is a summary of compensation data submitted by over 300 life sciences companies. As noted above, the Committee uses comparative market data and other materials to inform and shape the Committee’s decision-making, but does not strictly adhere to quantitative benchmarks.
- **For 2011, our chief executive officer’s base salary was below the median salary of the Peer Group, and for the three years reported in our proxy statement, our chief executive officer’s total compensation was less than 33% of the average total compensation for the Peer Group.** The Committee does not and cannot use the peer group as a means to prop up executive compensation because Isis uses the peer group as a secondary reference and not as the primary means for setting executive compensation. The Committee elected not to increase the base salaries of our named executive officers, including our chief executive officer, for 2012. Lastly, an additional indication that Isis’ peer group does not unduly increase executive compensation is that our CEO’s compensation is in line with (within 3% of) the median total compensation for Institutional Shareholder Services’ own peer group.

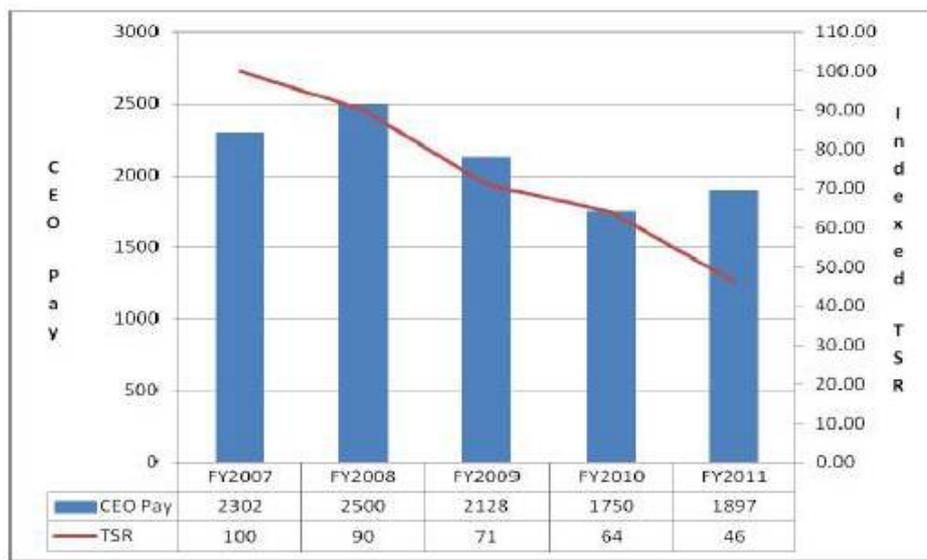
We design our executive compensation program to pay our executive officers for performance.

- **The stock options granted to our chief executive officer in 2011 directly align the interests of our chief executive officer with the interests of our stockholders and our long-term success.** The amounts disclosed in the executive compensation tables generally reflect the grant-date fair value of stock option awards, but the actual economic value of stock option awards depends directly on the performance of our stock price over the period during which the awards vest and the period during which the options may be exercised. In other words, the stock options are not worth anything if our stock price does not increase above the exercise price. Our executive officers will only realize economic value when our stock price, and consequently stockholder value, increases.
- **We further tie stock option awards to our performance by evaluating company performance, including performance of our stock, when we set the form and size of each subsequent year’s equity awards.** The Committee is mindful that executive compensation should be aligned with our stock price performance, and has consistently adjusted the realizable value of annual equity awards granted to our chief executive officer in line with company performance. Following the decrease in our stock price during 2010, the value of total 2011 equity awards granted to our chief executive officer was reduced relative to the value of his 2010 equity awards.
- **The cash bonus portion of our named executive officers’ compensation is not guaranteed and is totally at risk.** The Committee determines bonus awards based on achievement of goals that were set at the beginning of the year as well as any failures and unexpected accomplishments that occurred through the year. The Committee also reviews the historical accomplishments and failures from previous years to form a comparison for our current year’s successes and/or failures. Cash bonuses are not awarded when threshold levels for payouts are not met. For

example, for 1999, no cash bonuses for executive officers were paid due to the failures Isis faced at the time and for 2004 our chief executive officer’s cash bonus was 64% of the cash bonus he received in 2003 because of disappointing clinical trial results and a resulting corporate performance bonus guideline of 50%. Conversely, in 2007 Isis had a seminal year and we rewarded our employees proportionately to Isis’ success.

Our executive compensation program is designed to appropriately motivate and reward management for the achievement of long-term, strategic objectives that are designed to create long-term value for our stockholders.

- **We mitigate the incentive to take short term risks at the expense of long term value by requiring a four year vesting period for our equity awards and largely using stock options.** We are still a growth stage company. Our business strategy is to discover unique antisense drugs and develop these drugs to key clinical value inflection points so that we can out-license our drugs to partners and generate revenue. This process takes multiple years for each drug so we need to ensure our employees continue to execute our long term strategy. As such, all of our stock compensation vests over a period of four years, with no vesting during the first year. These practices align our employee compensation with our stockholders’ interests because if stockholder value declines over time, so too will the value of the equity compensation. We intentionally do not issue fully vested equity compensation upon the achievement of pre-set metrics because we do not want to reward short term imprudent risk taking to achieve a metric at the expense of long term stockholder value.
- **As noted in our proxy statement and displayed in the following graph, our executive compensation generally tracks total stockholder return and our chief executive officer’s compensation has generally decreased when our stock price has decreased.** The following graphs show the relationship of our chief executive officer’s compensation (\$ in thousands) compared to the total return (TSR) on \$100 invested on December 31, 2007 in our common stock through December 31, 2011.



- **Our long-term success depends on the continued discovery and development of our drugs.** As noted above, our strategy is to build value by discovering and developing our drugs to key inflection points so that we can license the drugs to partners and generate revenue. Thus, the key to our long term success is to keep advancing our drugs towards commercialization. In 2011, Genzyme and Isis worked together to submit the marketing approval applications for KYNAMRO in Europe and the United States, which created the opportunity for the potential approval and commercial launch of KYNAMRO in 2012. In addition, Isis and its partners reported positive clinical data on eight drugs and added six new drugs to its development pipeline. Lastly, by advancing its drugs, Isis generated more than \$23 million in payments from its existing partners and secured a lucrative new collaboration agreement with Biogen Idec to develop ISIS-SMN_{Rx}. These company successes were factors in the Committee’s determination of the amount of executive cash bonuses that were earned for 2011. The Committee determined that 2011 was an exceptional year with successes across the board and very few disappointments, with the only significant one being our stock price.
- **Executing on our strategy in 2011 has already resulted in an over 30% increase in our stock price thus far in 2012.** We too were disappointed with our stock price performance last year, which is in part why the Committee did not increase executive base salaries for 2012. However, we believe meeting the objectives noted above and further described in the section entitled “Evaluation of 2011: Business Highlights” on pages 45 and 46 of our Proxy Statement is one of the primary reasons our stock price has already appreciated more than 30% this year.

The Committee uses comparative market and peer group data to inform and shape the Committee’s decision-making, but does not strictly adhere to quantitative benchmarks.

- **We aim to attract and retain the most highly qualified executives in an extremely competitive market.** Accordingly, the Committee believes that it is important when making its compensation decisions to be informed as to the current practices of comparable publicly held companies with which we compete for top talent. To this end, the Committee reviews market and peer company data, which includes competitive information relating to the mix and levels of compensation for executives in the life sciences industry.
- **Ultimately, in determining the amounts of compensation to be awarded, the Committee relies on its collective business judgment and discretion.** In setting executive compensation for our named executive officers, the Committee takes into account both objective and subjective information, including general economic conditions, industry conditions, our company-wide performance, and challenges confronting us. In addition, the Committee carefully considers each executive’s credentials, length of service, experience and past and expected future abilities to contribute to our financial and operational performance and the development and execution of our strategic plans.
- **We use an objective formula to calculate each named executive officer’s annual cash bonus that imposes a pre-determined maximum annual cash bonus amount.** Each officer’s cash bonus is calculated based on the following formula: Base Salary (x) Target MBO % (x) Company Success Factor (x) Individual Success Factor. The maximum Company Success Factor is 200% and the maximum Individual Success Factor is 160% and our chief executive officer’s Target MBO is 40%. For 2011, the formula was applied by the Committee to determine our chief executive officer’s bonus based on a 135% Company Success Factor, 135% Individual Success Factor for a cash bonus amount of \$535,938. The maximum cash bonus payment our chief executive officer could have earned for 2011 pursuant to the pre-determined objective formula if the Company Success Factor was 200% and the Individual Success Factor was 160% was \$941,016.

In addition to our pay-for-performance philosophy, we are mindful of our stockholders’ concerns and evolving best practices in executive compensation.

- **We have reasonable change of control benefits.** Our change of control agreements require a “double trigger” before we make a cash payment to an eligible executive officer and our policies do not provide for change of control “gross-up” payments.
- **We do not allow perquisites.** Our policies do not provide for perquisites for any employees, including our executive officers.
- **We have responsible equity plan provisions.** We proactively manage the potential dilution resulting from our equity awards. Our annual equity burn has consistently been less than 2%, which is well below the typical equity burn rate for our industry and stage of development. In addition, our 1989 Stock Option Plan and the 2011 Equity Incentive Plan prohibit the repricing of any options outstanding under such plans, unless approved by our stockholders. The Plans also require minimum vesting periods, except in the case of death, disability, retirement, or a change of control.
- **We received strong Support for Say-on-Pay in 2011.** We held our first Say-on-Pay vote last year, and it was supported by over 96% of the votes cast for the proposal.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF PROPOSAL 4—ADVISORY VOTE ON EXECUTIVE COMPENSATION

Engagement of Proxy Solicitation Firm

On May 29, 2012, Isis retained Alliance Advisors to provide proxy solicitation services for Isis in connection with the Annual Meeting. Our agreement with Alliance Advisors provides that Isis will pay Alliance Advisors a fee of approximately \$12,000 for its services and the reimbursement of Alliance Advisors’ reasonable out-of-pocket expenses.

Forward Looking Statement

These materials include forward-looking statements regarding Isis’ collaboration with Genzyme, a Sanofi company, and the development, activity, therapeutic benefit and safety of KYNAMRO™ in treating patients with high cholesterol. Any statement describing Isis’ goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. 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 drugs. 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, 2011 and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

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