

# 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): **December 3, 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 1.01. Entry into a Material Definitive Agreement.**

On December 3, 2007, Regulus Therapeutics LLC ("Regulus"), a joint venture between Alnylam Pharmaceuticals, Inc. ("Alnylam") and Isis Pharmaceuticals, Inc. ("Isis") formed to discover, develop and commercialize microRNA therapeutics, announced today the appointment of Kleanthis G. Xanthopoulos, Ph.D., as President and Chief Executive Officer. Dr. Xanthopoulos will also be a Senior Vice President of Isis.

Under Dr. Xanthopoulos' offer letter dated November 30, 2007 (the "Offer Letter"), Dr. Xanthopoulos is eligible to receive the following compensation from Isis or Regulus:

- a one-time signing bonus of \$200,000 (\$100,000 to be paid by Regulus and \$100,000 to be paid by Alnylam);
- a base salary of \$400,000 per year;
- an at-risk opportunity to earn a year-end management by objective bonus (MBO);
- an option to purchase 60,000 shares of Isis' common stock at an exercise price of \$17.68 per share; and
- healthcare and retirement benefits offered to all Isis' employees.

In addition, the Offer Letter contemplates a severance agreement with the following severance benefits:

- in the event his employment is terminated without cause by Isis, he will be eligible to receive up to 18 months of salary continuation; and
- if as a result of a specified change in control of either Isis, Alnylam or Regulus, his employment is terminated without cause by Isis or the acquirer, or he elects to terminate his employment because of constructive termination, he will be eligible to receive up to 18 months of salary continuation.

The description of the Offer Letter and Dr. Xanthopoulos' compensation set forth above is qualified in its entirety by reference to the full and complete terms set forth in such letter, a copy of which is filed as an exhibit to this Current Report on Form 8-K and incorporated by reference herein.

**Item 9.01. Financial Statements and Exhibits.**

(d) Exhibits.

- 10.1 Offer Letter dated November 30, 2007 between the Company and Kleanthis Xanthopoulos.
- 99.1 Press release dated December 3, 2007

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**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: December 1, 2007

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

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- 10.1 Offer Letter dated November 30, 2007 between the Company and Kleanthis Xanthopoulos.
- 99.1 Press release dated December 3, 2007

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November 30, 2007

Kleanthis Xanthopoulos  
6305 El Camino Del Teatro  
La Jolla, CA 92037

Dear Kleanthis,

It is my pleasure to extend to you an offer to join Regulus Therapeutics, a joint venture between Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, as President and CEO reporting to me. In this position, you will receive an annualized salary of \$400,000 and be eligible for an incentive bonus targeted at 30% of your base salary (established by your Isis Senior Vice President Level). You will also receive \$25,000 annually as a consultant to Alnylam. In addition, you will receive a one-time signing bonus of \$200,000 (\$100,000 to be paid by Regulus and \$100,000 to be paid by Alnylam) payable your first week of employment.

As additional incentive, the management of Isis Pharmaceuticals and Alnylam Pharmaceuticals will *each* grant you an option to purchase 60,000 shares of common stock. The exercise price for the Isis options will be the fair market value on your first day of employment. Isis' options will be non-qualified options and vest over a four-year period and contain the other terms described in Isis' Stock Option Plan. Alnylam's stock options will be non-qualified options and will be subject to the standard terms and conditions of the 2004 Alnylam Stock Option Plan, and the exercise price will be equal to the closing price of the common stock on your first day of employment at Isis. These options will vest over four years at the rate of 25% after twelve months of full-time active employment and then an additional 6.25% for each additional quarter of full-time active employment until after four full years when the option is fully vested.

Vesting of both Isis and Alnylam options will terminate December 31, 2009 (one year after Regulus becomes a C Corporation) as long as you continue to be an employee of Isis or Regulus.

Provided you are still an employee of Isis or Regulus on January 1, 2009, you will receive an option to purchase 5% ownership in Regulus based on a mutually agreed upon valuation at that time, exercisable at a price reflecting such valuation. If we cannot mutually agree on a valuation we will engage a mutually acceptable outside expert to do so.

Additionally, you will be provided the opportunity to enter into a severance agreement having the following terms: 18 months of salary continuation in "change of control" (e.g. Regulus is bought by Isis, Alnylam or a 3<sup>rd</sup> party) resulting in loss of job, elimination of the job or

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constructive termination. The severance agreement will also provide for 18 months of salary continuation if Isis or Alnylam is bought and you suffer a job loss, elimination of the job or constructive termination. The severance agreement will also provide for 18 months of salary continuation if fired for no cause. The severance agreement will contain a customary provision releasing Isis, Alnylam and Regulus from liability. Pending approval of the Isis, Alnylam and Regulus Boards of Directors, we will provide that your options immediately vest, if one of the above mentioned salary continuation events occur.

While you are an employee of Isis you will have the opportunity to participate in Isis' employee benefits program, which includes medical, dental, life insurance and our 401(k) Retirement Plan and your vacation will begin accruing at the rate of three (3) weeks per year based on your anniversary date. If you have any questions, please feel free to contact Shannon Devers at (760) 603-3848.

**On your first day of employment, please complete and bring with you the enclosed Employee Confidential Information and Inventions Agreement. You will also need to bring identification as listed on the back of the enclosed I-9 form, which is required as proof of eligibility-to-work.**

If you accept this offer and the terms herein, please sign below and return the original as soon as possible. You may retain the enclosed signed copy for your records. We are anticipating a start date of Monday, December 3, 2007.

Sincerely,

/s/ Stanley T. Crooke

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Stanley T. Crooke  
Chairman and CEO  
Isis Pharmaceuticals, Inc.

Accepted and agreed:

/s/ Kleanthis Xanthopoulos, PhD

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Kleanthis Xanthopoulos, PhD



## Contacts

### Alnylam Pharmaceuticals

Cynthia Clayton (Investors)  
617-551-8207

Kathryn Morris (Media)  
KMorrisPR  
845-635-9828

### Isis Pharmaceuticals/ Regulus Therapeutics

Kristina Lemonidis  
760-603-2490

Amy Blackley, Ph.D.  
760-603-2772

## **Regulus Therapeutics Appoints Kleanthis G. Xanthopoulos, Ph.D. as President and Chief Executive Officer**

CAMBRIDGE, Mass. and CARLSBAD, Calif., December 3, 2007 – Regulus Therapeutics LLC, a joint venture between Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) formed to discover, develop and commercialize microRNA therapeutics, announced today the appointment of Kleanthis G. Xanthopoulos, Ph.D., as President and Chief Executive Officer. Dr. Xanthopoulos is the co-founder and former President and Chief Executive Officer of Anadys Pharmaceuticals, Inc.

“Kleanthis has had a distinguished and broadly recognized career as a leader in the life sciences industry,” said John Maraganore, Ph.D., Chairman of Regulus, and President and Chief Executive Officer of Alnylam. “We expect his experience in building organizations from research to development stages will be instrumental as we build a leading company focused on advancing microRNA therapeutics.”

“We are delighted that Kleanthis has joined Regulus,” said Stanley Crooke, M.D., Ph.D., Chairman and Chief Executive Officer of Isis. “He has the right combination of entrepreneurial spirit and scientific knowledge balanced with business expertise, to advance the efforts already underway at Regulus.”

“MicroRNAs are an exciting new area of biology, and microRNA therapeutics represent a previously unexplored area of pharmaceuticals research that could lead to the emergence of novel high-impact drugs,” said Kleanthis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. “Indeed, due to their mechanism of action, we believe microRNA therapeutics could have important implications for the treatment of a broad range of diseases including cancer, viral infection, and metabolic disorders. I am very excited to be joining Regulus at this time, as Isis and Alnylam have established a solid foundation of scientific and intellectual property leadership comprising an estate of more than 500 patents and decades of RNA-based research and development on which to build this leading biopharmaceutical company.”

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Before joining Regulus, Dr. Xanthopoulos was a managing director of Enterprise Partners Venture Capital. Prior to that, he was a co-founder and served as President and Chief Executive Officer and Director of Anadys Pharmaceuticals from its inception in May 2000 to November 2006. From 1997 to 2000 he held a variety of positions at Aurora Biosciences Corporation (now Vertex Pharmaceuticals Incorporated) including Vice President, Genomics & Molecular Biology. Dr. Xanthopoulos participated in The National Institutes of Health (NIH) Human Genome Project and was a Section Head of the National Human Genome Research Institute at NIH from 1995 to 1997. He was an Associate Professor of Molecular Biology at the Karolinska Nobel Medical Institute, Stockholm, Sweden from 1991 to 1995, and a Postdoctoral Research Fellow at The Rockefeller University from 1987 to 1990. An Onassis scholar, Dr. Xanthopoulos received his B.Sc. in Biology with honors from Aristotle University of Thessaloniki, Greece, and received both his M.Sc. in Microbiology and Ph.D. in Molecular Biology from the University of Stockholm, Sweden.

Dr. Xanthopoulos is a member of the board of directors of Anadys Pharmaceuticals, Odyssey Thera, Inc., and an executive board member of BIOCUM, Southern California’s life science industry association, where he chairs the Capital Formation Committee.

### About microRNAs

microRNAs are a recently discovered class of genetically encoded small RNAs, approximately 20 nucleotides in length, and are believed to regulate the expression of a large number of human genes. microRNA therapeutics represent a new approach for the treatment of a wide range of human diseases. The inappropriate absence or presence of specific microRNAs in various cells has been shown to be associated with specific human diseases including cancer, viral infection, and metabolic disorders. Targeting microRNAs with novel therapeutic agents could result in novel and broadly acting treatments for human diseases.

### About Regulus

Regulus Therapeutics LLC is a biopharmaceutical company formed to discover, develop and commercialize microRNA therapeutics. The company was created as a joint venture between Alnylam Pharmaceuticals, a leader in RNAi therapeutics, and Isis Pharmaceuticals, a leader in antisense technologies and therapeutics. Isis and Alnylam scientists and collaborators were the first to discover microRNA antagonist strategies that work *in vivo* in animal studies (Krutzfeldt *et al. Nature* **438**, 685-689 (2005); Esau *et al. Cell Metab.*, **3**, 87-98 (2006)). Isis and Alnylam have also created and consolidated key intellectual property for the development and commercialization of microRNA therapeutics. The company, founded in 2007, maintains facilities in Carlsbad, California. For more information, visit [www.regulusrx.com](http://www.regulusrx.com).

### About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the

world's top scientific journals including *Nature*, *Nature Medicine*, and *Cell*. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics; its most advanced program is in Phase II human clinical trials for the treatment of respiratory syncytial virus (RSV) infection. In addition, the company is developing RNAi therapeutics for the treatment of influenza,

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hypercholesterolemia, and liver cancers, among other diseases. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Medtronic, Novartis, Biogen Idec, and Roche. The company, founded in 2002, maintains headquarters in Cambridge, Massachusetts. For more information, visit [www.alnylam.com](http://www.alnylam.com).

#### **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 18 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Ibis Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Ibis T5000™ Biosensor System, a revolutionary system to identify infectious organisms. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. 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](http://www.isispharm.com).

#### **Alnylam Forward-Looking Statements**

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including statements concerning the potential of microRNA therapeutics and the importance of Alnylam's intellectual property, know-how, and other technology in the discovery, development and commercialization of microRNA therapeutics, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including risks related to: Alnylam's approach to discover and develop novel drugs, which is unproven and may never lead to marketable products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to enforce its patents against infringers and to defend its patent portfolio against challenges from third parties; Alnylam's ability to obtain additional funding to support its business activities; Alnylam's dependence on third parties for development, manufacture, marketing, sales and distribution of products; obtaining regulatory approval for products; competition from others using technology similar to Alnylam's and others developing products for similar uses; Alnylam's dependence on collaborators; and Alnylam's short operating history; as well as those risks more fully discussed in the "Risk Factors" section of its most recent quarterly report on Form 10-Q on file with the Securities and Exchange Commission. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam does not assume any obligation to update any forward-looking statements.

#### **Isis Forward Looking Statements**

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Isis' technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus. 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. Such statements are subject to certain risks and uncertainties, particularly those

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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, 2006, and its quarterly report on Form 10-Q for the quarter ended September 30, 2007, which are on file with the SEC. Copies of these and other documents are available from the Company.

Isis Pharmaceuticals is a registered trademark of Isis Pharmaceuticals, Inc. Ibis Biosciences and Ibis T5000 are trademarks of Ibis Biosciences, Inc. Regulus Therapeutics is a trademark of Regulus Therapeutics LLC.

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