Alnylam Pharmaceuticals (NASDAQ: ALNY) is a leader in the field of RNA interference, or RNAi. RNAi, a breakthrough discovery in biology, is a naturally occurring mechanism within cells for selectively silencing and regulating specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. Alnylam is working to harness the RNAi mechanism to silence genes whose activity is implicated in the cause or pathway of human disease. Working both independently and with top-tier industry and scientific collaborators, Alnylam is building a deep pipeline of RNAi therapeutics to treat a wide range of diseases.

Alnylam maintains a leadership position in this promising field, with a goal of realizing RNAi’s full potential for therapeutic applications. RNAi’s unique mechanism of action enables the targeting of previously “non-druggable” genes. The company’s expertise in designing and optimizing RNAi molecules, together with its leading position in intellectual property relating to RNAi, has enabled Alnylam to form major alliances with world-class companies including Medtronic, Novartis, Biogen Idec, Roche, Takeda and Kyowa Hakko. In these alliances and independently, Alnylam is applying its expertise in RNAi to address multiple therapeutic areas. The company’s product platform enables rapid generation and optimization of potent small interfering RNAs (siRNAs) – the molecules that mediate RNAi – for virtually any disease target. Alnylam was founded by scientific pioneers in the field of RNAi and has assembled a management team with significant product development experience. With strong financial resources and the support and commitment of its top-tier collaborators, Alnylam has made excellent progress in building a pipeline of RNAi therapeutics.

### Clinical Programs

**Respiratory Syncytial Virus (RSV)**

ALN-RSV01, an RNAi therapeutic for the treatment of RSV, is Alnylam’s lead development program. RSV infects nearly every child at least once by the age of two years and accounts for more than 300,000 hospitalizations per year in the U.S due to respiratory infection in children and people with compromised immune systems, and others. Since initiating the ALN-RSV01 therapeutic program in 2005, Alnylam has made rapid progress.

Alnylam previously completed Phase I human clinical trials of ALN-RSV01 using both intranasal and inhaled formulations and these trials demonstrated that ALN-RSV01 was safe and well tolerated in healthy volunteers. In February 2008, Alnylam announced it had achieved human proof-of-concept with an RNAi therapeutic, a first for the industry. Results from the company’s Phase II GEMINI study demonstrated that ALN-RSV01 was safe and well-tolerated, and demonstrated statistically significant anti-viral efficacy with an approximately 40% reduction in RSV infection rate and 95% increase in infection-free subjects.

In April 2008, Alnylam initiated a Phase II clinical trial to assess the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. Those receiving ALN-RSV01 will have drug administered by inhalation via nebulizer which is the expected delivery formulation for commercialization. As a secondary objective, this trial will be the first to evaluate the anti-viral activity of ALN-RSV01 in a naturally acquired RSV lower respiratory tract infection. ALN-RSV01 is expected to advance into the pediatric patient population in the second half of 2008.

In June 2008, Alnylam and Kyowa Hakko announced they formed an exclusive alliance to develop and commercialize ALN-RSV01 in Japan and other major markets in Asia. Alnylam retains all development and commercialization rights worldwide excluding Asia.

### Development Programs

**Liver Cancers**

Despite many advances in the treatment of cancer with targeted small molecules and antibody therapeutics, the clinical impact of these therapies is generally measured in only months of survival benefit. Worldwide, primary liver cancer is one of the most common forms of cancer, with more than 600,000 people diagnosed each year. The overall five-year relative survival rate from primary liver cancer is about 10 percent, making it the cancer with the second poorest five-year survival rate. Alnylam is developing a systemically delivered RNAi therapeutic, ALN-VSP, for the treatment of liver cancer and potentially other solid tumors. ALN-VSP targets VEGF and KSP, two well-validated genes involved in the growth and development of tumors in a wide variety of cancers. This program is an IND candidate for 2008.

### Hypercholesterolemia

Hypercholesterolemia is an additional program being developed by Alnylam. Alnylam is collaborating with researchers at UT Southwestern Medical Center to evaluate new approaches for reducing LDL-cholesterol levels using RNAi therapeutics directed to a disease target called proprotein convertase subtilisin/kexin type 9, or PCSK9. The collaboration will utilize systemic RNAi technologies developed by Alnylam such as those recently presented at the XVI International Symposium on Drugs Affecting Lipid Metabolism that showed an RNAi therapeutic successfully reduced levels of LDL/“bad” cholesterol by approximately 50%. These were the first data in non-human primates demonstrating PCSK9 antagonism.

![Clinical Programs Table](image)

Various statements in this document regarding Alnylam Pharmaceuticals’ business which are not historical facts are forward-looking statements that involve risks and uncertainties. For a discussion of such risks and uncertainties, which could cause actual results to differ from those contained in the forward-looking statements, see “Risk Factors” in our most recent quarterly report on Form 10-Q.
Select Pre-clinical and Partnered Programs

Huntington’s Disease
In January 2008, Alnylam announced that it advanced an RNAi therapeutic development program targeting the huntingtin gene for the treatment of Huntington’s disease. Huntington’s disease is an autosomal dominant neurodegenerative genetic disease that afflicts approximately 30,000 patients in the U.S., with an estimated 150,000 additional patients having a 50 percent risk of developing the disease. The disease is caused by mutations in the huntingtin gene leading to expression of a toxic mutated protein. This program, designated ALN-HTT, is in partnership with Medtronic, Inc. The product is expected to consist of an RNAi therapeutic targeting the Huntington’s disease gene that will be delivered by Medtronic’s implantable infusion pump.

Hepatitis C
Regulus Therapeutics (a joint venture between Alnylam and Isis Pharmaceuticals) most advanced program is a microRNA therapeutic that targets miR-122 for the treatment of hepatitis C virus (HCV) infection, a significant disease worldwide where emerging therapies target viral genes and are therefore more prone to resistance. Regulus is targeting miR-122, an endogenous host gene required for viral infection by HCV.

MicroRNA Programs

Regulus Therapeutics, LLC
Regulus Therapeutics is a leading microRNA therapeutics company. In September 2007, Regulus Therapeutics was created as a joint venture between Alnylam and Isis Pharmaceuticals to focus on the discovery, development, and commercialization of microRNA therapeutics. Regulus Therapeutics combines the strengths and assets of Isis’ and Alnylam’s technologies, know-how, and intellectual property with strong leadership from a focused management team and a world-class Scientific Advisory Board chaired by Nobel laureate David Baltimore and including key pioneers in the microRNA field. The company maintains facilities in Carlsbad, California. For more information, visit www.regulusrx.com.

Glaxo Smith Kline
In April 2008, GSK and Regulus Therapeutics announced the first ever microRNA-focused strategic alliance to discover, develop and market novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The alliance provides GSK with an option to license drug candidates directed at four different microRNA targets with relevance in inflammatory disease.

Progressive Multifocal Leukoencephalopathy (PML)
Partnered with Biogen Idec. PML is caused by infection of the central nervous system with a virus called “JC virus” and can occur in certain immune-suppressed patients, including those receiving immunomodulatory therapies. Alnylam and Biogen Idec will initially conduct investigative research into the potential of using RNAi technology to develop therapeutics to treat PML.

Novartis Programs
As part of its major 2005 alliance with Novartis, Alnylam is engaged in the joint discovery of new therapeutics using RNAi across multiple disease areas in the Novartis research portfolio.

In February 2006, Alnylam and Novartis formed a second alliance to jointly advance RNAi therapeutics for pandemic flu.

Alnylam Biodefense
In September 2006, the company established Alnylam Biodefense™ – an initiative to develop RNAi therapeutics targeting biological threats. As part of a public sector-private sector partnership with its Ebola program, Alnylam is working with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), an organization which is uniquely experienced in the handling, safety, and security requirements of specialized biological agents. Alnylam will be producing drug candidates which will be sent to USAMRIID for in vitro and in vivo testing against the Ebola virus. In August 2007, the United States Defense Threat Reduction Agency (DTRA) awarded Alnylam a $38.6M contract to develop a broad spectrum RNAi anti-viral therapeutic for the treatment of viral hemorrhagic fever.

Non-Exclusive Platform Alliances

Roche
In July 2007, Roche and Alnylam entered into a major alliance, valued at over $1 billion, in which Roche obtains a non-exclusive license to Alnylam’s technology platform for developing RNAi therapeutics. The alliance will initially cover four therapeutic areas: oncology, respiratory diseases, metabolic diseases and certain liver diseases. Alnylam and Roche also will collaborate on RNAi drug discovery for one or more disease targets in these therapeutic areas.

Takeda
In May 2008, Alnylam and Takeda formed a strategic platform alliance that provides Takeda with broad, worldwide, non-exclusive access to and enablement with Alnylam’s RNAi therapeutics platform technology and intellectual property in the fields of oncology and metabolic disease, with the right to expand the number of therapeutic fields in the future. The agreement also includes the transfer of platform technology from Alnylam to Takeda, a collaboration and cross-license of delivery technologies between the two companies, and a drug discovery collaboration on certain RNAi therapeutic targets.

Scientific Leadership
By the end of 2010, Alnylam expects to broaden its leadership and significantly expand the scope of delivery solutions for RNAi therapeutics. This will be achieved by the continued scientific leadership of Alnylam scientists and current academic and industry collaborators, but also a significant external effort to form new delivery technology partnerships. Further, this effort will include the significant expansion of the range of tissues and cell types where the company aims to achieve efficient delivery of RNAi therapeutics with both direct and systemic delivery approaches.

Clinical Pipeline
By the end of 2010, Alnylam expects to have four or more RNAi therapeutic programs in clinical development. These include direct and systemic RNAi programs, Alnylam proprietary and 50/50 partnership programs, and siRNA (short interfering RNA) and miRNA (microRNA) therapeutics.

New Business Collaborations
Based on its scientific, clinical, and intellectual property leadership, the company also expects to form four or more new major business collaborations by the end of 2010. These are expected to include completion of additional broad platform alliances similar to the company’s July 2007 partnership with Roche. Completion of these business collaborations is expected to provide the company significant resources and funding to advance Alnylam’s proprietary and 50/50 partnership pipeline programs.

RNAi and Our Approach
The discovery of RNAi has sparked a revolution in biology, representing a major breakthrough in understanding how genes are turned on and off in cells, and providing a completely new approach to drug discovery and development. RNAi has the potential to become the foundation for a whole new class of therapeutics that harness this natural mechanism to achieve high potency and specificity.

RNAi is mediated by small, double-stranded RNA molecules. One method to activate RNAi is with chemically synthesized small interfering RNAs, or siRNAs, which are double-stranded RNAs that are targeted to a specific disease-associated gene. The siRNA molecules are used by the natural RNAi machinery in cells to cause highly targeted gene silencing.

RNAi 2010

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