Respiratory Syncytial Virus (RSV)

About the Disease
- RSV is a highly contagious virus that causes infections in both the upper and lower respiratory tracts
- RSV is the most common respiratory pathogen in infants and young children
- RSV infects nearly every child at least once by the age of two and is a major cause of hospitalization due to respiratory infection in children, people with compromised immune systems, and others
- RSV infection in the pediatric and adult populations account for ~1M hospitalizations per year in world’s 7 major markets including >300,000 hospitalizations in the U.S.
- RSV infection typically results in cold-like symptoms but can lead to more serious respiratory illnesses such as cough, pneumonia, bronchiolitis, and in extreme cases, death

Incidence
RSV is the most important pathogen associated with acute respiratory infection worldwide. The morbidity and mortality attributable to infection with RSV appears greatest in infants younger than three months of age and in those with known risk factors such as prematurity, underlying cardiac or pulmonary disease, compromised immune systems, and old age. It is estimated that the maximum annual RSV infected population is almost over 18 million patients in the seven major markets, including over 5.5 million elderly, about 3 million adults with underlying disease, over 9.2 million children under four years of age, almost 370,000 premature infants and almost 2,000 bone marrow transplant recipients. When combining the two major overlapping risk groups (elderly and adults with underlying disease), it is estimated that just over 900,000 patients are hospitalized due to an RSV infection in the seven major markets annually.

RSV infection in lung transplant patients is associated with significant morbidity - up to 15 to 20% of infected patients develop acute or chronic lung rejection. These patients are also at risk for an increase in frequency of bronchiolitis obliterans syndrome, a manifestation of chronic rejection that is associated with a high five-year mortality rate.

Current Treatments
A treatment for RSV infection represents a major unmet medical need in children, the elderly and in patients with compromised immune systems. There is no vaccine for RSV and the only available anti-viral has limited utilization and is not highly effective. Despite the number of RSV infections, there are very few drugs on the market to protect against or treat RSV. Current management of RSV consists of supportive care. An effective prophylactic is available for a small number of high risk infants as a monthly injection. However, even after receiving the prophylactic, patients are still at risk of being infected with RSV. Clinicians agree that there is a significant need for novel therapeutics to effectively treat patients infected with RSV.

RNA Interference (RNAi) as a Therapeutic for RSV
The development of potent and specific anti-viral therapies for prevention and treatment of infection has proven difficult using traditional pharmaceutical approaches. The therapeutic benefit of available vaccines and anti-virals is limited by the ability to interact with existing protein targets usually located on the surface of viruses. RNAi anti-viral therapeutics, on the other hand, are not restricted to targeting the viral surface proteins and can be specifically designed to target other highly conserved internal viral proteins essential for replication and infection that have, up until now, been considered “un-druggable.”

Alnylam’s Progress to Date
Since initiating the ALN-RSV01 therapeutic program in 2005, Alnylam has made rapid progress. Our RNAi therapeutic was designed to target the nucleocapsid “N” gene of the RSV genome, a gene that is critical for the replication of the virus. ALN-RSV01 silences the N gene, thereby reducing the virus’ ability to reproduce. Extensive pre-clinical work in animals demonstrated potent and highly specific anti-viral efficacy with molecular proof of an RNAi mechanism of action. We believe the results we have demonstrated to date underscore not only the potential to treat RSV, but the broader potential for RNAi therapeutics in human disease. ALN-RSV01 is being developed in a broad global clinical development program and is partnered with Kyowa Hakko for development and commercialization in Asia.

- 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. The inhaled formulation is delivered via a nebulizer.
- 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 by the second half of 2008.

About Alnylam
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 a wide range of disease areas, including hypercholesterolemia, liver cancers, and Huntington’s disease. 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. To reflect its outlook for key scientific, clinical, and business initiatives, Alnylam has established RNAI 2010 which includes the company’s plan to significantly expand the scope of delivery solutions for RNAi therapeutics, have four or more programs in clinical development, and to form four or more new major business collaborations, all by the end of 2010. Alnylam is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, visit www.alnylam.com.

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.

September 2, 2008