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Alnylam Presents Phase I Data for ALN-VSP, an RNAi Therapeutic for the Treatment of Liver Cancers, at American Society of Clinical Oncology (ASCO) Meeting

RNAi Therapeutic Demonstrates Evidence for Anti-Tumor Activity in Advanced Malignancy Patients

Biopsy Samples Show Drug Delivery and Proof of RNAi Mechanism in Both Hepatic and Extra-Hepatic Tumors



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CAMBRIDGE, Mass.--(BUSINESS WIRE)-- [Alnylam Pharmaceuticals, Inc.](#) (Nasdaq:ALNY - News), a leading RNAi therapeutics company, announced today the results from its Phase I clinical trial with ALN-VSP, a systemically delivered RNAi therapeutic for the treatment of advanced solid tumors with liver involvement. The data are being presented at the ASCO meeting in a [poster](#) titled "Phase I dose-escalation study of ALN-VSP02, a novel RNAi therapeutic for solid tumors with liver involvement," in the Developmental Therapeutics – Experimental Therapeutics poster discussion session being held on Saturday, June 4, 2011 from 2:00 to 6:00 p.m. CDT. In this Phase I study, ALN-VSP was generally well tolerated, demonstrated evidence for anti-tumor activity, and was found to mediate RNAi activity in both hepatic and extra-hepatic tumors.

"We are very pleased with the Phase I results with ALN-VSP which include safety and tolerability of multiple doses of ALN-VSP, as well as evidence for anti-tumor activity in this very advanced, heavily pre-treated cancer patient population. In particular, we have seen multiple patients achieve stable disease or better, including a patient with endometrial cancer metastatic to the liver who has achieved 70% tumor regression so far and continues on study after having been on drug for over one full year," said Jared Gollob, M.D., Senior Director of Clinical Research at Alnylam. "It is also notable that DCE-MRI results appear to show an anti-VEGF effect with ALN-VSP in approximately 50% of evaluable patients, including those who have been previously exposed to anti-VEGF drugs. Finally, analysis of tumor biopsy samples has demonstrated siRNA delivery and proof of RNAi mechanism in both hepatic and extra-hepatic tumors."

Results from this Phase I study show that ALN-VSP was generally well tolerated. ALN-VSP was administered to 41 patients at doses ranging from 0.1 to 1.5 mg/kg; a total of 182 doses have been administered, including to one patient who has received 24 doses at 0.7 mg/kg over the course of more than one full year, and continues to receive treatment in the study. The most common adverse events were grade 1-2 fatigue (24% of patients), nausea (17% of patients) and fever (15% of patients), with no clear dose dependence. There were also no dose-dependent changes in liver function tests. Grade 2 infusion-related reactions were observed in 15% of patients, or 3% of total doses administered; these reactions responded to slowing of the infusion of drug, and no patients discontinued therapy because of an infusion reaction. Dose-limiting toxicities included: liver failure and death in one patient with extensive hepatic metastases and prior splenectomy/partial hepatectomy at 0.7 mg/kg which was deemed possibly related to study drug; transient grade 3 thrombocytopenia in two patients at 1.25 mg/kg; and grade 3 hypokalemia in one patient at 1.5 mg/kg. Based on these safety data, the recommended dose for advancement of ALN-VSP into Phase II studies is 1.0 mg/kg.

ALN-VSP demonstrated evidence of anti-tumor activity in advanced malignancy patients. Patients participating in the study were heavily pre-treated, having received an average of 4.3 prior treatment regimens for their metastatic cancer, including both chemotherapy and anti-angiogenic drugs. Fifty percent (12 of 24) of patients evaluable for response attained stable disease (SD) or better with ALN-VSP doses greater than or equal to 0.7 mg/kg, compared to only 8% (1 of 13) at doses less than or equal to 0.4 mg/kg. Results include one major ongoing response in a patient with endometrial cancer and multiple liver metastases treated at 0.7 mg/kg. This patient, whose treatment is ongoing after over one full year, has so far had a partial response (PR) with an approximately 70% reduction in tumor burden. Sixty four percent (7 of 11) of patients achieved SD at the recommended Phase II dose of 1.0 mg/kg and 45% (5 of 11) continue to receive drug on study. In addition, DCE-MRI results were suggestive of an anti-VEGF effect. In approximately 50% of evaluable patients, the average decline in Ktrans (measure of blood flow) in liver tumors where this parameter was measured was greater than or equal to 40%, an effect that

is comparable to what has been observed with other anti-VEGF drugs in solid tumors (Cannistra *et al.*, *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S, 2006; and Siegel *et al.*, *Journal of Clinical Oncology*, Vol 26, No 18: pp. 2992-2998, 2008).

“Both primary liver cancer and metastatic disease of the liver are associated with poor prognosis for patients, and new therapies are clearly needed,” said Dr. Patricia LoRusso, D.O., Professor of Medicine, Director of the Phase I Clinical – Pharmacology Team at the Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine. “This Phase I study with ALN-VSP currently represents, to our knowledge, one of the most comprehensive clinical trials of a systemically delivered RNAi therapeutic and also one of the most extensive experiences with RNAi therapeutics in cancer. The safety data and anti-tumor activity with ALN-VSP are encouraging and I look forward to the further development of this promising agent.”

In this study, 29 tumor biopsies were obtained voluntarily from 15 patients across multiple dose levels (from 0.4 to 1.5 mg/kg) using a CT-guided procedure; these included hepatic (liver) tumor biopsies from 11 patients and extra-hepatic tumor biopsies from four patients. The two siRNAs targeting VEGF and KSP that comprise ALN-VSP were detected in nearly all of the biopsy samples evaluable for drug levels at siRNA concentrations ranging from 0.3 to 142 ng/g tissue. These levels of siRNA are pharmacologically relevant since pre-clinical studies have shown that siRNA tissue levels of 1 ng/g are associated with 50% target gene silencing (Landesman *et al.*, *Silence*, 1:16, 2010). While there was no dose-dependence to the levels of VEGF and KSP siRNAs detected in biopsy samples, this finding was consistent with the high degree of variability in proportion of tumor, fibrotic/necrotic tissue, and normal tissue in biopsy samples, which impacts the quantitative interpretations of molecular results. Using a highly precise polymerase chain reaction (PCR)-based technique known as 5' rapid amplification of cDNA ends (5' RACE), blinded analysis of human tissue samples showed proof of RNAi-mediated target mRNA cleavage. Specifically, three of 15 biopsy samples showed VEGF-derived mRNA fragments corresponding exactly to the predicted RNAi-mediated cleavage product based on the VEGF siRNA sequence ($p < 0.001$) in the post-treatment biopsy sample. The samples that were positive for VEGF 5' RACE included liver tumor biopsies obtained from two patients dosed at 0.4 mg/kg and an extra-hepatic tumor biopsy from one patient dosed at 1.25 mg/kg. KSP 5' RACE assay development is in progress, with further optimization required due to low expression of KSP mRNA in tissue samples.

Pharmacokinetic data from this study showed that C_{max} (peak serum concentration of drug) and area under the curve (AUC) were dose proportional with no evidence of drug accumulation. Pre-clinical animal pharmacokinetic data were predictive for the observed results in man.

“We believe the results from our ALN-VSP Phase I trial represent an important milestone in the advancement of RNAi therapeutics. Indeed, our data demonstrate for the first time both clinical activity and RNAi mechanism for an RNAi therapeutic,” said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. “Clearly, these data are not only important for the continued advancement of our ALN-VSP program, but they also significantly increase our confidence in our entire pipeline of systemically delivered RNAi therapeutics, including ALN-TTR01 which is in a Phase I study for the treatment of transthyretin mediated amyloidosis, and ALN-PCS, which will soon enter clinical trials for the treatment of severe hypercholesterolemia.”

About ALN-VSP

ALN-VSP is a systemically delivered RNAi therapeutic comprising two siRNAs designed to target two genes critical for the growth and development of cancer cells: vascular endothelial growth factor (VEGF) and kinesin spindle protein (KSP), also known as eglin 5 (Eg5). ALN-VSP is Alnylam's first systemic RNAi program and represents the company's first clinical program in oncology. The drug is formulated using a first generation lipid nanoparticle developed by Tekmira Pharmaceuticals Corporation. The company expects to partner its ALN-VSP program prior to initiating a Phase II clinical study, with the goal of initiating this study in 2012.

About ALN-VSP Phase I Study Design

The Phase I trial was designed as a multi-center, open label, dose escalation study in patients with advanced solid tumors with liver involvement who have failed to respond to or have progressed after standard treatment. The primary objective was to evaluate the safety, tolerability, and pharmacokinetics of intravenous ALN-VSP. Other secondary and exploratory objectives included:

- assessment of tumor response using Response Evaluation Criteria for Solid Tumors (RECIST), a set of published guidelines that define when cancer patients' disease improves, stabilizes or progresses during treatment;
- quantitation of change in tumor blood flow and vascular permeability as measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI); and,
- analysis of pharmacodynamic effects of ALN-VSP on tumors as measured in patients electing to proceed with voluntary pre- and post-treatment biopsies.

About Liver Cancers

Cancer affecting the liver, known as either primary or secondary liver cancer, is associated with one of the poorest survival rates in oncology and represents a major unmet medical need affecting a large number of patients worldwide. Primary liver cancer, or hepatocellular carcinoma (HCC), is one of the most common cancers worldwide, with more than 600,000 people diagnosed each year. Secondary liver cancer, also known as metastatic liver cancer, is cancer that spreads to the liver from another part of the body due to other common cancers like colon, lung, or breast cancer. Worldwide, more than 500,000 people are diagnosed with secondary liver cancer each year.

About RNA Interference (RNAi)

RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as “a major scientific breakthrough that happens once every decade or so,” and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of a major new class of medicines, known as RNAi therapeutics, is on the horizon. Small interfering RNAs (siRNAs), the molecules that mediate RNAi and comprise Alnylam’s RNAi therapeutic platform, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines with a core focus on RNAi therapeutics for the treatment of genetically defined diseases, including ALN-TTR for the treatment of transthyretin-mediated amyloidosis (ATTR), ALN-PCS for the treatment of severe hypercholesterolemia, and ALN-HPN for the treatment of refractory anemia. As part of its “Alnylam 5x15™” strategy, the company expects to have five RNAi therapeutic products for genetically defined diseases in advanced stages of clinical development by the end of 2015. Alnylam has additional partner-based programs in clinical or development stages, including ALN-RSV01 for the treatment of respiratory syncytial virus (RSV) infection, ALN-VSP for the treatment of liver cancers, and ALN-HTT for the treatment of Huntington’s disease. The company’s leadership position on RNAi therapeutics and intellectual property have enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, and Cubist. In addition, Alnylam and Isis co-founded Regulus Therapeutics Inc., a company focused on discovery, development, and commercialization of microRNA therapeutics; Regulus has formed partnerships with GlaxoSmithKline and sanofi-aventis. Alnylam has also formed Alnylam Biotherapeutics, a division of the company focused on the development of RNAi technologies for application in biologics manufacturing, including recombinant proteins and monoclonal antibodies. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 100 peer-reviewed papers, including many in the world’s top scientific journals such as *Nature*, *Nature Medicine*, *Nature Biotechnology*, and *Cell*. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

Alnylam Forward-Looking Statements

Various statements in this release concerning Alnylam’s future expectations, plans and prospects, including without limitation, statements regarding Alnylam’s views with respect to the potential for RNAi therapeutics, including ALN-VSP, its plan to partner its ALN-VSP program prior to initiating a Phase II clinical study and its goal with respect to the timing of initiating such study, its views regarding the potential of other systemically delivered RNAi therapeutics, including ALN-TTR01 and ALN-PCS, and Alnylam’s expectations regarding its “Alnylam 5x15” product strategy, 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, without limitation, Alnylam’s ability to discover and develop novel drug candidates, successfully demonstrate the efficacy and safety of its drug candidates, including ALN-VSP, in human clinical trials and establish and maintain strategic business alliances, including a partnership for the continued development of ALN-VSP, and new business initiatives, 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.

Contact:

Alnylam Pharmaceuticals, Inc.

Cynthia Clayton, 617-551-8207

Senior Director, Investor Relations and Corporate Communications

or

Media:

Spectrum

Amanda Sellers, 202-955-6222 x2597

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