# Synta Announces Publication of Elesclomol Mechanism of Action Results in AACR Journal Molecular Cancer Therapeutics

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Oxidative stress induction triggers cancer cell death

LEXINGTON, Mass.--(BUSINESS WIRE)--Aug. 22, 2008--Synta Pharmaceuticals Corp., (NASDAQ: SNTA) today announced the publication of new findings in the American Association for Cancer Research journal, Molecular Cancer Therapeutics that describe the novel mechanism of action of elesclomol: driving programmed cell death (apoptosis) in cancer cells through the selective induction of oxidative stress. Elesclomol is currently in a global, pivotal Phase 3 clinical trial (SYMMETRY(SM)) in combination with paclitaxel for the treatment of metastatic melanoma.

"These results confirm that elesclomol powerfully and selectively induces apoptosis in cancer cells by increasing the level of reactive oxygen species (ROS) beyond sustainable levels," said James Barsoum, Ph.D., Senior Vice President, Research, Synta Pharmaceuticals. "Elevated ROS levels and susceptibility to further increases in ROS are fundamental characteristics of cancer cells that differentiate them from normal non-cancerous cells. Exploiting this special vulnerability represents a novel approach to selectively targeting and killing cancer cells. The findings also suggest that elesclomol can substantially enhance the efficacy of certain other anti-cancer therapies when given in combination. These results collectively indicate the potential of oxidative stress induction as a new therapeutic option for treating multiple types of cancers, either as a single agent or in combination. We are excited by the potential of this new mechanism category, particularly for difficult-to-treat cancers such as melanoma that have not been responsive to chemotherapy or other prior approaches."

Oxidative stress occurs when there is an elevated level of reactive oxygen species (ROS) in cells. Superoxide, hydrogen peroxide and hydroxyl radicals are examples of reactive oxygen species. ROS levels can increase in a variety of situations including exposure to bacteria or viruses, a rise in cell proliferation, or an increase in cell metabolism. Prolonged exposure to elevated levels of ROS can initiate a sequence of protective events culminating in the ultimate self-defense mechanism, programmed cell death (apoptosis). Normal, non-cancerous cells have a strong antioxidant capacity which guards against excessive levels of ROS. In contrast, cancer cells operate at a much higher level of oxidative stress and have a greatly diminished antioxidant capacity. The elevated level of ROS and diminished antioxidant capacity leave cancer cells particularly vulnerable to further increases in oxidative stress.

The results of the new in vitro studies demonstrated that elesclomol causes apoptosis in cancer cells through the induction of oxidative stress. The increase in ROS was observed by measuring the levels of reactive oxygen species such as hydrogen peroxide directly and by measuring the increased expression of genes that are induced by the presence of high levels of ROS. Elesclomol demonstrated potent and cancer-specific induction of oxidative stress and apoptosis in multiple

cancer cell types, including melanoma, leukemias and lymphomas as well as breast, prostate, ovarian, colon, and lung. Specifically:

-- Elesclomol rapidly induced the accumulation of intracellular ROS as detected by fluorescent microscopy;

-- Elesclomol robustly induced the expression of many genes regulated by ROS such as heat shock proteins and metallothionein genes, which is a signature transcription profile of cells under oxidative stress; and

-- Pretreatment of cells with antioxidants blocked elesclomol-induced ROS production and apoptosis.

"These new findings highlight the potential of oxidative stress induction," said Dr. Barsoum. "Cancer types that may be especially sensitive to this mechanism are those known to have particularly high levels of oxidative stress, including, melanoma, prostate, breast, ovarian, and hematologic cancers."

The ongoing Phase 3 SYMMETRY trial of elesclomol in metastatic melanoma is expected to have initial results in early 2009. Phase 2 studies of elesclomol in other indications are planned for the fourth quarter of 2008 and in 2009. Synta has a partnership with GlaxoSmithKline for the joint development and commercialization of elesclomol.

About Synta Pharmaceuticals

Synta Pharmaceuticals Corp. is a biopharmaceutical company focused on discovering, developing, and commercializing small molecule drugs to extend and enhance the lives of patients with severe medical conditions, including cancer and chronic inflammatory diseases. Synta has a unique chemical compound library, an integrated discovery engine, and a diverse pipeline of clinical- and preclinical-stage drug candidates with distinct mechanisms of action and novel chemical structures. All Synta drug candidates were invented by Synta scientists using our compound library and discovery capabilities. Synta has a partnership with GlaxoSmithKline for the joint development and commercialization of its lead investigational drug candidate, elesclomol, which is in a global, pivotal Phase 3 clinical trial for the treatment of metastatic melanoma. For more information, please visit www.syntapharma.com.

About Elesclomol

Elesclomol is a novel, injectable, investigational drug candidate that triggers apoptosis (programmed cell death) in cancer cells. Cancer cells operate at high levels of reactive oxygen species, or oxidative stress. Elesclomol is believed to act by increasing the level of oxidative stress in cancer cells even further, beyond sustainable levels, inducing apoptosis. This mechanism of action, called oxidative stress induction, represents a novel way of selectively targeting and killing cancer cells.

In a double-blind, randomized, controlled Phase 2b clinical trial in 81 patients with stage IV metastatic melanoma, elesclomol in combination with paclitaxel met the primary endpoint, doubling the median time patients survived without their disease progressing, compared to paclitaxel alone ($p = 0.035$). The most common adverse events in the elesclomol plus paclitaxel group included fatigue, alopecia, constipation, nausea, hypoaesthesia, arthralgia, insomnia, diarrhea, and anemia.

A pivotal Phase 3 clinical trial of elesclomol in combination with paclitaxel in patients with stage IV metastatic melanoma (the SYMMETRY(SM) trial) is ongoing; Phase 2 trials in other indications, and in combination with other agents, are planned. Elesclomol has received Fast Track and Orphan Drug designation from the FDA for metastatic melanoma, and the Phase 3 SYMMETRY trial has completed a Special Protocol Assessment process with the FDA. Information about the SYMMETRY trial can be found at www.symmetrymelanomastudy.com, or www.clinicaltrials.gov.

About Metastatic Melanoma

Melanoma, the most deadly form of skin cancer, arises from melanocytes, the pigment-producing cells of the skin. According to the American Cancer Society, melanoma accounts for approximately five percent of all skin cancers but causes about 75% of all skin cancer-related deaths. An estimated 60,000 people will be diagnosed and nearly 8,200 people will die from melanoma this year in the U.S. alone. If diagnosed and surgically removed while localized in the outermost skin layer, melanoma is potentially curable; however, for patients with metastatic disease the prognosis is poor, with limited available treatments and an expected survival of only six to nine months. The incidence of melanoma has increased more rapidly than any other cancer during the past ten years. The FDA has not approved a novel, small molecule drug for the treatment of metastatic melanoma in over 30 years.

Safe Harbor Statement

This media release may contain forward-looking statements about Synta Pharmaceuticals Corp. Such forward-looking statements can be identified by the use of forward-looking terminology such as "will", "would", "should", "expects", "anticipates", "intends", "plans", "believes", "may", "estimates", "predicts", "projects", or similar expressions intended to identify forward-looking statements. Such statements, including statements relating to the timing and progress of our clinical and preclinical programs and financial guidance for 2008, reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such forward-looking statements, including those described in "Risk Factors" of our Form 10-K for the year ended December 31, 2007 as filed with the Securities and Exchange Commission. Synta undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by law.

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