Synta Presents New Data on Mechanism of Action of Elesclomol at AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics

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Copper redox reaction key to elesclomol's ability to generate ROS

LEXINGTON, Mass.--(BUSINESS WIRE)--Nov. 18, 2009-- Synta Pharmaceuticals Corp. (NASDAQ: SNTA), a biopharmaceutical company focused on discovering, developing, and commercializing small molecule drugs to treat severe medical conditions, today presented new data on the mechanism of action of elesclomol, a first-in-class oxidative stress inducer, at the AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics in Boston, Mass.

“Elesclomol has been shown previously to induce apoptosis in cancer cells by increasing the level of reactive oxygen species (ROS),” said Vojo Vukovic M.D., Ph.D., Chief Medical Officer, Synta Pharmaceuticals. “The results presented today provide new details on the underlying mechanism by which elesclomol elevates oxidative stress. Elesclomol binds copper in plasma, facilitates its uptake into cells, and enables a transition between copper oxidation states once inside the cell. These results also point towards the origin of elesclomol’s unusual cancer-cell selectivity – its ability to kill cancer cells with little to no effect on normal cells. Cancer cells and normal cells are well known to have distinct metabolic properties, including the electrochemical properties of the mitochondria where many of these redox reactions take place. Taking advantage of these metabolic and electrochemical differences represents an entirely new and exciting approach, distinct from kinase inhibition or conventional chemotherapy, to selectively target and kill cancer cells. These unique properties of elesclomol are important considerations for future clinical applications. Additional results related to the elesclomol mechanism of action and hematologic applications will be presented at the American Society of Hematology meeting next month.”

The results of the *in vitro* studies demonstrated that:

- Elesclomol binds to copper as Cu(II) outside the cell
- The chelation of copper facilitates the entry of elesclomol into the cell
- Once in the cell, elesclomol promotes a reduction reaction where Cu(II) transitions to Cu(I)
- The redox reaction leads to the generation of reactive oxygen species (ROS)
- This process is necessary for elesclomol’s anticancer activity (ability to induce oxidative stress to the point of apoptosis).

About Elesclomol

Elesclomol is a first-in-class oxidative stress inducer that triggers apoptosis (programmed cell death) in cancer cells. Cancer cells operate at high level of oxidative stress, marked by an elevated presence of reactive oxygen species (ROS) such as oxygen radicals and hydrogen peroxide. In laboratory studies, elesclomol has been observed to increase the level of ROS in cancer cells even further, leading to an increase in pro-apoptotic factors, a decrease in anti-apoptotic factors, the opening of the mitochondrial membrane pores, and ultimately to the initiation of programmed cell death via the mitochondrial apoptosis pathway. This mechanism of action, called oxidative stress induction, represents a novel way of selectively targeting and killing cancer cells.

In preclinical models elesclomol showed potent anti-cancer activity against a broad range of cancer cell types, as well as an ability to enhance the efficacy of certain chemotherapy agents with minimal additional toxicity. In a 21-center, double-blind, randomized, controlled Phase 2b clinical trial in 81 patients with metastatic melanoma, elesclomol in combination with paclitaxel achieved the primary endpoint of improvement in progression-free survival compared to paclitaxel alone. The subsequent Phase 3 trial in 650 patients with metastatic melanoma, the SYMMETRY trial, was suspended in February 2009, based on an interim analysis that identified possible safety concerns. Preliminary results from the SYMMETRY trial were presented at ASCO in May 2009 and Perspectives in Melanoma XIII in October 2009, showing a differential response to treatment with elesclomol based on level of baseline LDH. Clinical trials with elesclomol remain on hold pending further review of the SYMMETRY trial results. Further results related to elesclomol, including survival data from the SYMMETRY trial with one year minimum follow-up, will be presented in the first half of 2010.

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. For more information, please visit www.syntapharma.com.

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