Synta Announces Results on Ganetespib Across a Range of Malignancies at the American Association for Cancer Research (AACR) Annual Meeting

April 4, 2012

–Ganetespib continues to demonstrate promise in overcoming acquired resistance to BRAF inhibitors in melanoma cell lines–

–Antiangiogenic and radiosensitization effects demonstrated in preclinical models of colorectal cancer–

LEXINGTON, Mass.--(BUSINESS WIRE)--Apr. 4, 2012-- Synta Pharmaceuticals Corp. (NASDAQ: SNTA) today announced the presentation of preclinical results on the use of ganetespib, the most advanced heat shock protein 90 (Hsp90) inhibitor in clinical development, in melanoma and colorectal cancer at the 103rd Annual Meeting American Association for Cancer Research (AACR).

“The data presented by our in-house biology group demonstrating that ganetespib is active in tumor cell lines with acquired resistance to BRAF inhibitors not only suggests that ganetespib may be a promising approach to BRAF- driven cancers, including melanoma, thyroid and colon cancers but also are supportive of earlier data where ganetespib is active in other cancer models of acquired resistance,” said Vojo Vukovic, M.D, Chief Medical Officer, Synta. “Additionally, the activity of ganetespib in data presented in preclinical models of colorectal cancers further supports the rationale for combining ganetespib with other therapies in trials going forward.”

Preclinical Data for BRAF-driven Cancers

Title: Overcoming acquired resistance to BRAF inhibitors in melanoma with the HSP90 inhibitor ganetespib.

Poster Presentation: April 4, 8:00 a.m. CT
Abstract Number: 5601
Presenter: David Proia, Ph.D. Synta Pharmaceuticals Corp.

Ganetespib displayed strong anticancer activity in human melanoma, thyroid and colon cancer cells driven by mutant BRAF. Similar to BRAF and MEK inhibitors, ganetespib effectively suppressed the activity of ERK kinase in melanoma cells, a critical component in the BRAF signaling cascade. In vivo, combinations of ganetespib with either BRAF or MEK inhibitors resulted in greater activity than monotherapy. Melanoma cells with high levels of COT, implicated in resistance to BRAF inhibitors, were found to be resistant to both BRAF and MEK inhibitors yet extremely sensitive to ganetespib. Tumor response was associated with ganetespib-induced abrogation of ERK activity and degradation of CRAF, proteins responsible for BRAF-inhibitor resistance.

“Targeting Hsp90 with ganetespib is a promising approach to the treatment of BRAF-driven cancers such as melanoma,” noted Dr. Proia. “BRAF inhibitors have shown considerable antitumor activity in

melanoma, given that mutant BRAF occurs in as many as half of all melanoma. However, BRAF inhibitors have a short disease control, as acquired resistance frequently develops within 7-9 months after start of treatment. By deactivating the cascade of events that underlie resistance, ganetespib could be potentially utilized as a single agent or as part of a combination for BRAF–driven diseases."

The majority of malignant melanomas contain activated PI3K/mTOR. In an effort to maximize antitumor activity ganetespib was further combined with PI3K/mTOR inhibitors. As single agents, ganetespib effectively blocked both ERK and AKT/mTOR signaling; by contrast, PI3K/mTOR inhibitors blocked their targets while activating ERK. Combining ganetespib with PI3K/mTOR inhibitors led to enhanced cytotoxicity in melanoma cells in vitro and decreased tumor burden in human melanoma xenograft mouse models as compared to monotherapy.

Preclinical Colorectal Cancer Data

Title: Antiangiogenic effects associated with the inhibition of HSP90 in colorectal cancer.

Poster Presentation: April 2, 2012 1:00 p.m.
Abstract Number: 2326
Presenter: Bassel F. El-Rayes, M.D., Winship Cancer Institute, Emory University

Ganetespib was found to significantly inhibit two proteins that stimulate angiogenesis, hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor (VEGF), in colorectal cancer cell lines. The antiangiogenic effect of ganetespib was confirmed by data showing blockade of tube formation in human umbilical vein endothelial cells (HUVEC), and inhibition of blood vessel formation in chicken eggs.

"Ganetespib demonstrated significant antiangiogenic actions in preclinical models of colorectal cancer, an effect associated with inhibition of proteins that regulate the formation and growth of new blood vessels in tumor cells," stated Dr. El-Rayes. "Combining ganetespib with chemotherapy may therefore be a rational approach for treatment of colorectal cancer."

Title: Functional inhibition of HSP90 potentiates the effects of ionizing radiation in colorectal cancer.

Poster Presentation: April 2, 2012 1:00 p.m.
Abstract Number: 2872
Presenter: Roberto Diaz, M.D., Ph.D., Winship Cancer Institute, Emory University

HSP90 expression was found to be elevated in human colorectal tumors in comparison to paired normal tissue suggesting that HSP90 contributes to colorectal tumorigenesis. In vitro, ganetespib decreased the proliferation and clonogenicity of human colorectal cancer cell lines in part through the loss of AKT survival signaling. These effects were enhanced by either chemotherapy or ionizing radiation. The findings are consistent with data presented at the 2011 AACR meeting, where ganetespib was shown to synergize with radiotherapy in human cervical cancer tumor xenografts. Taken together, the preclinical findings identify ganetespib as a novel agent to be combined with radiation therapy.

About Ganetespib

Ganetespib (formerly STA-9090) is a potent, synthetic, small-molecule inhibitor of heat shock protein 90 (Hsp90). Hsp90 is a molecular chaperone required for the proper folding and activation of many cancer-promoting proteins, and is recognized as a key facilitator of cancer cell growth and survival. In preclinical experiments, ganetespib has shown activity in multiple tumor models both as a single agent and in combination with certain widely used cancer agents. Ganetespib is currently being evaluated in a broad range of cancer clinical trials. In these trials, ganetespib has shown clinical activity in heavily pretreated patients and has been well tolerated to date with no evidence of severe liver or common ocular toxicities seen with other Hsp90 inhibitors. The most common adverse event seen to date has been transient, mild or moderate diarrhea, which has been manageable with standard supportive care. Information on clinical trials with ganetespib can be found at www.clinicaltrials.gov.

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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Source: Synta Pharmaceuticals Corp.

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