Synta Presents Results on Ganetespib and Hsp90 Inhibitor Class at the AACR-EORTC-NCI Molecular Targets and Cancer Therapeutics Conference

November 15, 2011

–Ganetespib highly effective in models of multiple oncogene addicted tumors–

–Ocular toxicities common in 2nd generation Hsp90 inhibitors associated with drug distribution properties–

–Results from a Phase 1 canine clinical trial of ganetespib pro-drug published in PLoS ONE–

LEXINGTON, Mass.--(BUSINESS WIRE)--Nov. 15, 2011-- Synta Pharmaceuticals Corp. (NASDAQ: SNTA) today announced that preclinical results presented at the AACR-EORTC-NCI Molecular Targets and Cancer Therapeutics Conference show that ganetespib, a potent Hsp90 inhibitor, is highly effective in overcoming mechanisms of resistance in models of multiple oncogene addicted tumors.

“The results presented today and published in PLoS support the potential of ganetespib activity in a broad range of tumor types, including erlotinib-resistant non-small cell lung cancer,” said Vojo Vukovic, M.D., Ph.D, Chief Medical Officer, Synta. “In the clinic, some 2nd generation Hsp90 inhibitors have shown high rates of ocular toxicity. In contrast, ganetespib has a low rate of ocular toxicity. The study of Hsp90 inhibitor distribution profiles within the retina presented today suggests that ocular toxicities seen with Hsp90 inhibitors are likely compound-specific and not a class effect."

The study showed that the retina/plasma exposure ratio and drug elimination rate profile play crucial roles in ocular toxicity seen with many 2nd generation Hsp90 inhibitors. These results suggest that drug distribution properties may explain the differences in level of ocular toxicity observed in the clinic with different Hsp90 inhibitors.

Ganetespib is a potent inhibitor of heat shock protein 90 (Hsp90) that is structurally unrelated to first-generation, ansamycin-family Hsp90 inhibitors such as 17-AAG or IPI-504, and has shown superior activity to these agents in preclinical studies. Ganetespib is currently being evaluated in a broad range of cancer clinical trials, including the global Phase 2b/3 GALAXY Trial™ in non-small cell lung cancer. In these trials ganetespib has shown anti-tumor activity in heavily pretreated patients with lung cancer, breast cancer, and other tumor types and has been well tolerated without severe liver or common ocular toxicities seen with other Hsp90 inhibitors.

Ganetespib highly effective in multiple oncogene addicted tumors

Poster Presentation: November 14, 3:30 p.m. ET
Title: *Ganetespib, a unique resorcinolic Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile in preclinical models.*

Permanent Abstract Number: B105

In *in vitro* studies ganetespib displays potent activity against drug resistant non-small cell lung cancer (NSCLC) cells. HCC827 NSCLC cells express the EGFR receptor and are highly sensitive to the EGFR inhibitor erlotinib. Activation of the c-MET receptor by its ligand hepatocyte growth factor (HGF) or amplification of the receptor by sustained exposure to erlotinib renders cells resistant to erlotinib. By inducing the degradation of EGFR and c-MET simultaneously ganetespib displays equipotent anticancer activity in both erlotinib sensitive and resistant NSCLC cells.

To determine whether these effects of ganetespib *in vitro* translated to antitumor efficacy *in vivo*, the activity of ganetespib was evaluated using a variety of doses and schedules in a series of xenograft models. Ganetespib exhibited potent antitumor efficacy in oncogene-driven xenograft models of solid and hematological malignancies.

Tumor penetration and the microregional activity of ganetespib were also assessed and showed that *in vivo*, ganetespib penetrates hypoxic regions of tumors and provides strong evidence that ganetespib efficiently distributed within the extravacular compartment, resulting in the sustained inhibition of proliferation and induction of apoptosis throughout the tumors.

Additional results showed ganetespib has a favorable hepatic and cardiac safety profile *in vivo*.

Ocular toxicities common in 2nd generation Hsp90 inhibitors may be successfully minimized

Poster Presentation: November 15, 3:30 p.m. ET
Title: *A critical role for the tissue distribution profile in heat shock protein (Hsp) 90 inhibitor-induced ocular toxicity in rats.*
Permanent Abstract Number: C212

The Hsp90 molecular chaperone controls the folding of key signaling molecules required to maintain normal cell function in many organs, including the retina. Ocular toxicities, including blurred vision, flashes, delayed light/dark accommodation, and photophobia have emerged as commonly-occurring adverse events in human clinical trials of certain second-generation Hsp90 inhibitors, observed in the majority of patients. These adverse retinal effects are believed to be due to drug-induced photoreceptor degeneration and cell death.

This study examined the relationship between retinal drug distribution profiles and photoreceptor degeneration in common Hsp90 inhibitors. 17-DMAG, 17-AAG, and STA-9056 (an Hsp90 inhibitor with comparable *in vitro* activity to 17-DMAG) were compared for retinal tissue exposure and plasma and cerebrospinal fluid levels. In contrast, both ganetespib and 17-AAG have shown clinical activity with a much lower incidence of ocular toxicity. 17-DMAG, for which visual changes have been reported in clinical subjects, produced marked photoreceptor cell death and was associated with a slow elimination rate and a high retina/plasma (R/P) ratio. In contrast, and consistent with the absence of clinically-reported visual changes, 17-AAG did not produce detectable photoreceptor injury. 17-AAG showed 94% drug elimination from the retina within 6 hours and a low R/P ratio. STA-9056 exhibited a drug distribution profile more comparable to 17-AAG than 17-DMAG: a moderately low R/P ratio, 79% retinal elimination within 6 hours and minimal degenerative effects within the eye.

These findings suggest that the retina/plasma exposure ratio and elimination rate profiles play

important roles in ocular toxicity observed with certain Hsp90 inhibitors.

Phase I Evaluation of STA-1474, a Prodrug of the Novel HSP90 Inhibitor Ganetespib, in Dogs with Spontaneous Cancer

In addition to the data presented at the AACR-EORTC-NCI Molecular Targets and Cancer Therapeutics Conference, Synta announced the publication of results from a Phase 1 canine study of STA-1474, a pro-drug of ganetespib, in dogs with spontaneous cancers. The study, performed in the lab of Dr. Cheryl London, DVM at Department of Veterinary Biosciences, The Ohio State University, Columbus, Ohio showed that STA-1474 exhibits both biologic and anti-tumor activity in dogs with spontaneous cancer. Results appeared in the on-line edition of the journal PLoS ONE (www.plosone.org).

About Hsp90

Hsp90 is a chaperone protein required for the proper folding and activation of cellular proteins, particularly kinases. Many of these “client proteins” of Hsp90 – such as ALK, AKT, BCR-ABL, BRAF, KIT, MET, EGFR, FLT3, HER2, PDGFRA, VEGFR – have been shown to be critical to cancer cell growth, proliferation, and survival and are the targets of clinically validated cancer drugs. In preclinical studies, inhibiting Hsp90 causes the degradation of multiple client proteins and leads to cancer cell death.

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, including the global Phase 2b/3 GALAXY trial in non-small cell lung cancer. In these trials, ganetespib has shown anti-tumor activity in heavily pretreated patients with lung cancer, breast cancer, and other tumor types and has been well tolerated 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 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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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, development and progress of our clinical and preclinical programs, 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, 2010 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.

Source: Synta Pharmaceuticals Corp.

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