Synta Announces Publication of Ganetespib Results in Molecular Cancer Therapeutics

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–Triazolone-containing chemical structure; lowest molecular weight of class–
–Unique physicochemical properties drive ability to penetrate and induce apoptosis deep into tumor tissue –

LEXINGTON, Mass.--(BUSINESS WIRE)--Dec. 6, 2011-- Synta Pharmaceuticals Corp. (NASDAQ: SNTA) – Synta today announced the publication in Molecular Cancer Therapeutics of ganetespib results including pharmacologic and biological properties that distinguish ganetespib from other Hsp90 inhibitors.

"We believe that certain key physicochemical and pharmacologic properties of ganetespib – including low molecular weight, high potency, and efficient tumor tissue distribution – have contributed to the favorable safety and activity profile observed in the clinic to date," said Keizo Koya, Ph.D., Senior Vice President, Pharmaceutical Development, Synta. "These include observations of durable anti-tumor activity, together with the absence of serious liver toxicities and common ocular toxicity seen with other Hsp90 inhibitors."

The first generation of Hsp90 inhibitors were derived from the natural product geldanamycin, originally identified as an antibiotic. These include 17-AAG and derivatives or analogs with improved solubility such as 17-DMAG and IPI-504. Development of these early Hsp90 inhibitors, however, has been hampered by several drawbacks, including the hepatotoxicity associated with chemical properties of this ansamycin family of compounds. In an effort to overcome these limitations, next-generation synthetic Hsp90 inhibitors such as ganetespib were developed and are now being studied in clinical trials.

Ganetespib is the most advanced of the next-generation, synthetic Hsp90 inhibitors with over 450 patients treated to date; 24 trials completed, ongoing, or initiating in early 2012; the Phase 2b/3 GALAXY trial in second-line non-small cell lung cancer (NSCLC) active in the U.S. and Europe with interim results expected in first half of 2012; and interim data from trials in ALK+ NSCLC, Her2+ breast cancer, and triple-negative breast cancer expected in the second half of 2012. Final results from the 240-patient Phase 2b portion of the GALAXY trial are also expected in the second half of 2012.

"The preclinical results published today show that ganetespib has certain unique characteristics in terms of potency, antitumor activity, and improved safety," said Vojo Vukovic, M.D., Ph.D., Chief Medical Officer. "In the clinic, we have seen compelling evidence of clinical activity, including durable, objective responses following single-agent administration in heavily pretreated patients, together with a well-tolerated, favorable safety profile. With many important clinical results expected, 2012 will be a very exciting year for the ganetespib program."

“Ganetespib, a unique triazolone-containing Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile for cancer therapy” by W. Ying et al can be found at http://mct.aacrjournals.org. A print version of the article will be published in an upcoming edition of Molecular Cancer Therapeutics.

Summary of Results

Results presented at the AACR-EORTC-NCI meeting last month demonstrated that common ocular toxicities seen with some Hsp90 inhibitors, but not observed in clinical trials with 17-AAG or ganetespib, are associated with physicochemical properties including distribution to the eye.

Additional physicochemical properties published today may contribute to the observed improved safety and activity of ganetespib relative to other Hsp90 inhibitors. The molecular weight of ganetespib is 364, considerably smaller than the first-generation geldanamycin derivatives 17-AAG (586), IPI-504 (624), and smaller also than the other synthetic, next-generation Hsp90 inhibitors in Phase 2 development, AUY-922 (466) and AT-13387 (410). Ganetespib is able to enter the ATP binding pocket of Hsp90 in either the open or closed pocket lid conformation, whereas due to their larger size the ansamycin analogs can only occupy the ATP binding pocket in the open pocket lid conformation. Ganetespib contains a unique triazolone-containing moiety. The presence of the triazolone moiety leads to additional hydrogen bond interactions that predict for superior binding affinities between ganetespib and Hsp90. Finally, physicochemical properties including relatively high lipophilicity together with the smaller size lead to improved transport across lipid membranes and into cells, and the important observation that ganetespib is able to penetrate deeply into tumor tissue, far from the nearest blood vessels. The effectiveness of many anti-cancer agents can be compromised by limited drug distribution, and the rapid and dramatic ability of ganetespib to penetrate deep into hypoxic regions and induce apoptosis predicts for enhanced activity.

Additional biologic and pharmacologic properties published today include improved potency relative to 17-AAG (20-fold greater potency across a panel of 57 cell lines); ability to induce cell-cycle arrest (accumulation in G2/M phase) and apoptosis; sustained activity with short exposure times (exposures as short as 5 minutes induced IC50<1uM); activity against drug-resistant phenotypes (ability to overcome resistance to EGFR inhibitors in mutant EGFR lines); and tumor regressions in in vivo models at well tolerated dose levels. Safety findings included absence of any hepatotoxicity signal, in contrast to 17-DMAG; as well as favorable cardiovascular results.

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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Source: Synta Pharmaceuticals

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