# Synta Announces Results from Interim Analysis of the Randomized Phase 2b/3 GALAXY Trial Evaluating Ganetespib plus Docetaxel in Second-Line Non-Small Cell Lung Cancer

June 27, 2012

*–2.5 to 3-fold improvement in PFS observed in co-primary endpoints: mutant KRAS and elevated LDH patients–*

*–Improvements in PFS, response rate, and survival events observed in all adenocarcinoma patients–*

*–Results support advancing to Phase 3 stage of GALAXY trial in 2H 2012–*

*–Synta to host conference call and webcast today at 5:00 pm EST–*

LEXINGTON, Mass.--(BUSINESS WIRE)--Jun. 27, 2012-- Synta Pharmaceuticals Corp. (NASDAQ: SNTA) today announced encouraging results from a planned interim analysis of the GALAXY trial, a randomized Phase 2b/3 study designed to evaluate the efficacy and safety of the Company's lead Hsp90 inhibitor, ganetespib, in combination with standard-of-care docetaxel vs. docetaxel alone as second-line treatment for advanced non-small cell lung cancer (NSCLC).

The GALAXY trial is based on a two-stage, operationally adaptive design. The first-stage, randomized, open-label, 240-patient Phase 2b portion of the trial is designed to enroll Stage IIIB/IV NSCLC patients who have progressed following one prior line of therapy, with the goal of determining biomarkers predictive of ganetespib activity. Results will be used to guide choice of patient population for the Phase 3 stage of the trial.

Patients in the GALAXY trial are randomized 1:1 to receive ganetespib plus docetaxel or docetaxel alone. Patients in both arms receive a standard regimen of docetaxel 75 mg/m$^2$ on day 1 of a 21-day cycle; patients in the combination arm receive in addition ganetespib 150 mg/m$^2$ on days 1 and 15. Treatment continues until disease progression per RECIST 1.1 criteria.

The co-primary endpoints of GALAXY are PFS (progression-free survival) in patients with elevated baseline level of serum LDH (lactate dehydrogenase), and PFS in the mutant KRAS population. PFS and OS (overall survival) in all adenocarcinoma patients are key secondary endpoints. Serum LDH levels and tumor KRAS mutation status are assessed by independent central laboratories.

*Elevated LDH:* Elevated baseline LDH occurs in approximately one quarter to one third of advanced cancer patients in clinical trials and is prognostic of poor clinical outcomes in many cancer types, including lung cancer.[1-3] While elevated LDH can result from several conditions, in cancer patients elevated levels of LDH and its isoforms have been associated with tumor hypoxia (lack of oxygen).[4,5] Inhibition of hypoxia pathways has been shown to enhance anti-cancer activity of

taxanes and other chemotherapies.[6] Recent results from trials evaluating agents that target hypoxia-related pathways, including VEGF and mTOR inhibitors, have shown correlation between elevated LDH and improved clinical activity.[7-10] In laboratory experiments, treatment with ganetespib potently suppresses HIF-1alpha, a critical regulator of hypoxic pathways[11] – supporting potential application for ganetespib in combination with taxanes in this patient population.

*KRAS mutation*: Activating KRAS mutations, estimated to occur in 15-30% of NSCLC patients, are also associated with poor clinical outcomes and limited therapeutic options.[12,13] Hsp90 is required for the proper function of a number of key signaling proteins in the KRAS pathway, while inhibition of Hsp90 by ganetespib has shown promising activity in laboratory models of this disease.[14] Recent results from trials evaluating ganetespib monotherapy in lung, colon, and gastric cancers have further suggested promising potential in patients with KRAS mutations.

Based on a target enrollment of 240 adenocarcinoma patients, GALAXY is 90% powered to detect a PFS improvement from 6 to 12 weeks in elevated LDH patients and from 5 weeks to 10 weeks in the mutant KRAS patients. For the key secondary endpoints: in all adenocarcinoma patients, GALAXY is 88% powered to detect an improvement in PFS from 3 to 4.5 months, and 73% powered to detect an improvement in OS from 6 to 8.5 months. All powering assumptions are based on a 1-sided alpha of 0.05. An interim analysis was planned when approximately 50% of patients had been enrolled and had sufficient follow up, defined as one post-baseline scan.

**GALAXY Interim Results**

At the time of this interim analysis, a total of 114 adenocarcinoma and 69 non-adenocarcinoma patients had been enrolled. Following a review earlier this year that determined low likelihood of benefit in the non-adenocarcinoma population, the trial was modified to enroll only adenocarcinoma patients. Results reported below are for adenocarcinoma patients only.

***Activity***

The table below lists primary and key secondary endpoints relating to the two co-primary patient populations, as well as the all adenocarcinoma population. Partial response (PR), stable disease (SD), and progressive disease (PD) are assessed per RECIST 1.1 criteria; N/E indicates not available or evaluated at time of analysis. There have been no complete responses (CR) in the trial.

| | Elevated LDH (N=31) | | Mutant KRAS (N=20) | | All adeno (N=114) | |
|---|---|---|---|---|---|---|
| | D (N=15) | G+D (N=16) | D (N=11) | G+D (N=9) | D (N=59) | G+D (N=55) |
| Primary endpoint | | | | | | |
| median PFS | 1.4 mo | 4.2 mo | 1.6 mo | 4.2 mo | 2.9 mo | 4.2 mo |
| *# events (%)* | *12 (80)* | *8 (50)* | *5 (46)* | *3 (33)* | *31 (53)* | *23 (42)* |

| | | | | | | |
|---|---|---|---|---|---|---|
| Best response | | | | | | |
| PR (%) | 0 | 2 (13) | 1 (9) | 2 (22) | 5 (8) | 8 (15) |
| SD (%) | 6 (40) | 7 (44) | 5 (46) | 6 (67) | 31 (53) | 27 (49) |
| PD (%) | 5 (33) | 2 (13) | 3 (27) | 0 | 13 (22) | 7 (13) |
| N/E (%) | 4 (27) | 5 (31) | 2 (18) | 1 (11) | 10 (17) | 13 (24) |
| Overall survival events | | | | | | |
| # deaths (%) | 6 (40) | 4 (25) | 2 (18) | 1 (11) | 13 (22) | 7 (13) |

The sample size in each of these populations is small compared to the total planned sizes. Event rates have not yet achieved maturity for meaningful significance testing.

***Safety***

The adverse event profile was comparable between both arms. The proportion of adenocarcinoma patients with at least one adverse event (AE) was 64% vs. 82%; with grade 3 or 4 AEs was 32% vs. 36%; with AEs leading to treatment discontinuation was 7% vs. 9%; and with AEs with outcome of death were 5.1% vs. 5.5%, for D (N=59) vs. G+D (N=55), respectively. The most common AEs, all grades were neutropenia (48% vs. 44%), diarrhea (10% vs. 40%) and fatigue (19% vs. 26%), for D vs. G+D, respectively. Diarrhea and fatigue were predominantly grade 1 and grade 2; the incidence of grade 3 or 4 diarrhea was 0% vs. 2% and grade 3 or 4 fatigue was 3% vs. 0% in D vs. G+D, respectively. The most common grade 3 or 4 AEs were neutropenia (29% vs. 33%), leukopenia (5% vs. 4%), and nausea (3% vs. 4%).

Trials with some other Hsp90 inhibitors have reported a high incidence of ocular toxicities. In the GALAXY trial to date, there has been one report of ocular-related adverse event (grade 2, blurred vision, transient) in the G+D arm (2%) vs. no reports in the D arm.

**GALAXY Trial Next Steps**

Enrollment completion of the Phase 2b stage and transition to the Phase 3 stage are expected later this year. An additional interim analysis of the Phase 2b portion of the trial, presentation of results at a medical meeting, and a more detailed announcement of plans for the Phase 3 stage of this trial are also anticipated for later this year.

“Ganetespib was designed by our scientists almost ten years ago to improve the potency and safety seen with other Hsp90 compounds, and be the first compound to realize the full potential of chaperone inhibition for treating cancer,” said Safi R. Bahcall, Ph.D., President and CEO of Synta. “The complex biology and broad potential of this new therapeutic class present both an opportunity and a challenge: how can we identify as efficiently as possible which patients, defined by underlying disease biology, are most likely to benefit? In response, our team designed an innovative trial – a highly-powered, Phase 2b ‘learning’ stage followed, in an operationally continuous manner, by a Phase 3 ‘confirming’ stage. We believe that the encouraging results reported today support the therapeutic potential of ganetespib, and the operationally adaptive approach allows us to advance quickly to the next step. We are hopeful that additional development will lead to a new treatment option for patients with this devastating disease.”

“We are encouraged by both the safety profile and the signals of activity seen in the interim results announced today,” said Vojo Vukovic, M.D., Ph.D., Chief Medical Officer of Synta. “The results show

that ganetespib can overcome the liver and common ocular safety concerns seen with other Hsp90 inhibitors, can be added to docetaxel without substantial toxicity, and has potential to enhance the activity of this standard of care treatment. We are excited to advance this program to the next stage of development."

**Conference Call**

Synta management will be hosting a conference call today at 5:00 p.m. (ET) to discuss this announcement. The call can be accessed by dialing (877) 407-8035 or (201) 689-8035 prior to start. A slide presentation will be referenced on the call, which can be found on the Synta homepage at www.syntapharma.com. The live, listen-only webcast of the conference call can be accessed by visiting the "Investors" section of the Synta Pharmaceuticals website, prior to the event.

For those unable to join the live conference call, a replay will be available approximately two hours after the completion of the call, and can be accessed by dialing (877) 660-6853 or (201) 612-7415, and by referring to both account number 286 and conference ID 396810. A replay of the webcast will be archived on the Company's website for two weeks following the call.

**About Ganetespib**

Ganetespib is a potent inhibitor of heat shock protein 90 (Hsp90) that is structurally unrelated to first-generation, ansamycin-related Hsp90 inhibitors. 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. Company-sponsored clinical trials with ganetespib include 1) the GALAXY Phase 2b/3 trial evaluating ganetespib in combination with docetaxel as second-line treatment of non-small cell lung cancer (NSCLC), 2) the CHIARA Phase 2 trial evaluating ganetespib monotherapy in ALK+ NSCLC, and 3) the ENCHANT Phase 2 trial evaluating ganetespib as first-line treatment for HER2+ and triple-negative metastatic breast cancer. In addition, ganetespib is being evaluated in investigator-sponsored trials including lung, breast, prostate, gastric, pancreatic, and colorectal cancers as well as ocular melanoma, acute myeloid leukemia and multiple myeloma. Information on these trials can be found at www.clinicaltrials.gov.

**About the GALAXY Trial™**

The GALAXY (**G**anetespib **A**ssessment in **L**ung c**A**ncer with doceta**X**el) trial is a randomized Phase 2b/3 trial comparing the combination of ganetespib and docetaxel versus docetaxel alone in patients with Stage IIIB/IV NSCLC who have received one prior systemic therapy. More information about the GALAXY trial can be found at www.clinicaltrials.gov (NCT01348126).

**About 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. Many of the "client proteins" of Hsp90 – such as ALK, AKT, BCR-ABL, BRAF, KIT, MET, EGFR, FLT3, HER2, HIF-1alpha, PDGFRA, VEGFR 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 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.

**Safe Harbor Statement**

This media release contains 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, developments and progress of our GALAXY trial and our clinical development plans for ganetespib, 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. Those risks and uncertainties include whether the results from the interim analysis of the Phase 2b portion of the GALAXY trial will be consistent with future data from the Phase 2b portion and the Phase 3 stage of the trial; whether the results at the conclusion of the Phase 2b portion of the trial will demonstrate safety and statistically significant efficacy; challenges with respect to patient enrollment or other delays in our clinical development plans; as well as other risks and uncertainties described in the "Risk Factors" section of our Form 10-K for the year ended December 31, 2011, as filed with the Securities and Exchange Commission, including those under the heading “Risks Related to the Development and Regulatory Approval of our Drug Candidates.” Synta undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by law.

**References**

1. Schneider, “Tumor markers in detection of lung cancer,” Advan Clin Chem 42:1-41 (2006)

2. Albain et al., “Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience,” J Clin Oncol 9:1618-1626 (1991)

3. Suh and Ahn, “Lactate dehydrogenase as a prognostic factor for survival time of terminally ill cancer patients: a preliminary study,” Eur J Cancer 43:1051 (2007)

4. Koukourakis et al., “Lactate dehydrogenase-5 (LDH-5) overexpression in non-small-cell lung cancer tissues is linked to tumour hypoxia, angiogenic factor production and poor prognosis,” Br J Cancer 89:877-885 (2003)

5. Azuma et al., “Serum lactate dehydrogenase levels and glycolysis significantly correlate with tumor VEGFA and VEGFR expression in metastatic CRC patients,” Pharmacogenomics 8:1705-13 (2007)

6. Zhou et al., “Warburg effect in chemosensitivity: targeting lactate dehydrogenase-A re-sensitizes taxol-resistant cancer cells to taxol,” Mol Cancer 9:33 (2010)

7. Kim et al., "BEAM: A Randomized Phase II Study Evaluating the Activity of Bevacizumab in Combination With Carboplatin Plus Paclitaxel in Patients With Previously Untreated Advanced Melanoma," J Clin Oncol 30:34-41 (2012)

8. Van Cutsem et al, "Phase III Trial of Bevacizumab in Combination With Gemcitabine and Erlotinib in Patients With Metastatic Pancreatic Cancer," J Clin Oncol 27:2231-2237 (2009)

9. Kelly et al, "Randomized, Double-Blind, Placebo-Controlled Phase III Trial Comparing Docetaxel and Prednisone With or Without Bevacizumab in Men With Metastatic Castration-Resistant Prostate Cancer: CALGB 90401," J Clin Oncol 30:1534 (2012)

10. Armstrong, "Serum lactate dehydrogenase (LDH) is a predictive biomarker for mTOR inhibition in patients with metastatic renal cell carcinoma (RCC)," ASCO 2010, Abstr 324 (JCO in press)

11. Foley et al., "Hsp90 inhibitor STA-9090 induces HIF-1α degradation in the hypoxic regions of solid tumors," AACR April 2010 #2638

12. Johnson, "Association of KRAS and EGFR mutations with survival in patients with advanced lung adenocarcinoma," ASCO 2010 Abstr 7541

13. Socinski, "The emerging role of biomarkers in advanced non-small-cell lung cancer," Clin Lung Cancer. 2010 May;11(3):149-59 (2010)

14. Acquaviva et al., "Targeting KRAS mutant NSCLC with the Hsp90 inhibitor ganetespib," AACR-IASLC, San Diego Jan 2012 (manuscript submitted)

Source: Synta Pharmaceuticals Corp.

Synta Pharmaceuticals Corp.
George Farmer, 781-541-7125