Sunesis Pharmaceuticals Presents Preclinical Data From Its BTK and PDK1 Inhibitor Programs at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics

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SOUTH SAN FRANCISCO, Calif., Nov. 9, 2015 (GLOBE NEWSWIRE) -- Sunesis Pharmaceuticals, Inc. (Nasdaq:SNSS) today announced that two posters detailing preclinical data from its BTK and PDK1 inhibitor programs were presented on Sunday, November 8th at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics being held in Boston, Massachusetts.

The two poster presentations (Abstracts C198 and C186), titled "SNS-062 is a potent noncovalent BTK inhibitor with comparable activity against wild type BTK and BTK with an acquired resistance mutation" and "PDK1 inhibitors SNS-229 and SNS-510 cause pathway modulation, apoptosis and tumor regression in hematologic cancer models in addition to solid tumors," are available on the Sunesis website at www.sunesis.com.

"These data represent the first peer-reviewed presentations by Sunesis of our two proprietary kinase inhibitor pipeline programs," said Dan Swisher, Chief Executive Officer of Sunesis. "Each shows compelling, anti-cancer activity and a distinct product profile. SNS-062, our novel, second-generation BTK inhibitor, maintains potent preclinical activity in the presence of a cysteine-481 mutation associated with acquired resistance to ibrutinib. In addition, SNS-062 has a kinase selectivity profile distinct from ibrutinib that may confer additional safety and efficacy advantages that we look forward to uncovering in our upcoming clinical studies. SNS-510 and SNS-229, which belong to a novel class of PDK1 kinase inhibitors, show broad activity in a variety of hematologic cancer cell lines, including cell lines resistant to PI3K and AKT inhibitors, that correlates with significant PDK1 pathway modulation and anti-proliferative activity. We believe this program could soon yield a first-in-clinic selective PDK1 inhibitor to test this important pathway in cancer patients. Near term, we look forward to advancing SNS-062 into the clinic in the first quarter of 2016."

Study Results in Detail

"SNS-062 is a potent noncovalent BTK inhibitor with comparable activity against wild type BTK and BTK with an acquired resistance mutation"

For this study, Sunesis researchers explored the potential of SNS-062, a potent, noncovalent BTK inhibitor, to overcome resistance mechanisms of ibrutinib, a BTK inhibitor with validated anti-cancer efficacy in several B-cell malignancies. These resistance mechanisms include mutation of the cysteine in the BTK active site that ibrutinib requires for covalent binding (C481). SNS-062 has a kinase selectivity profile distinct from ibrutinib showing nM binding affinity for BTK, ITK and Tec kinase family members, but does not meaningfully bind EGFR. A lack of EGFR inhibition by SNS-062 may offer safety advantages over ibrutinib, including reduced diarrhea and rash potentially related to inhibition of EGFR.

Prolonged SNS-062 mediated *in vivo* inhibition of BTK correlates with potent anti-inflammatory activity in a BTK dependent B-cell mediated collagen induced rat arthritis model. To assess the activity of SNS-062 and ibrutinib against BTK with acquired resistance mutations, inhibition of wild type (WT) and mutant C481S BTK was evaluated in direct kinase assays. SNS-062 inhibits WT and C481S BTK with similar inhibitory concentrations while ibrutinib potency is reduced 40 fold. Similarly, ibrutinib shows a 100 fold loss of potency in inhibiting pBTK levels in C481S BTK expressing cells while SNS-062 activity is unaffected.

SNS-062 shows good oral bioavailability in multiple animal species with a terminal half-life of three to six hours. Pharmacokinetic, pharmacodynamic and toxicity studies demonstrate that SNS-062 plasma concentrations providing >90% inhibition of BTK can be sustained with acceptable tolerability.

"PDK1 inhibitors SNS-229 and SNS-510 cause pathway modulation, apoptosis and tumor regression in hematologic cancer models in addition to solid tumors"

Phosphatidylinositol (PI) dependent kinase 1, or PDK1, is a master kinase that activates kinases important in cell growth and survival including members of the AKT, PKC, RSK and SGK families and can interact with its substrates through PI-dependent (PH-mediated) or PI-independent (PIF-mediated) mechanisms. For this study, Sunesis researchers characterized two potent PDK1 kinase inhibitors, SNS-229 and SNS-510, with broad preclinical antitumor activity in hematologic cancers.

SNS-229 and SNS-510 belong to a novel class of PDK1 inhibitors that bind the inactive conformation of PDK1 as determined by X-ray crystallography and induce a conformational change that perturbs the PIF-pocket, thereby inhibiting PIF-mediated substrate binding, in contrast to the ATP-competitive PDK1 inhibitor tool compounds GSK2334470 and BX-320.

SNS-229 and SNS-510 were evaluated in more than twenty cell lines derived from hematologic cancers including acute myeloid leukemia, multiple myeloma, B-cell lymphoma, and mantle cell lymphoma. SNS-510 shows strong anti-proliferative activity and induces apoptosis in PI3K and AKT inhibitor resistant cell lines. SNS-229 and SNS-510 are compared to the PDK1 inhibitor GSK2334470 and were up to 30 fold more potent at inhibiting PDK1, S6K, RSK and AKT phosphorylation and up to 50 fold more potent in cancer cell viability assays.

In vivo, SNS-510 shows dose and time dependent inhibition of PDK1 autophosphorylation and up to 90% inhibition of RSK2 and AKT phosphorylation after eight hours, whereas GSK-2334470 and the pan-PI3K inhibitor GDC0941 only show moderate PDK1 and RSK2 inhibition and no AKT inhibition. In PK studies in CD/1 mice, SNS-229 and SNS-510 have good pharmacokinetic properties, with a terminal half-life of four to five hours and an oral bioavailability of >90%.

In an AML xenograft mouse model, both SNS-229 and SNS-510 show dose-related efficacy with >95% tumor growth inhibition and partial regression (>50% tumor shrinkage) in 70% and 100% of animals at the highest dose after 21-day dosing. These studies show that targeting the inactive conformation of PDK1 leads to potent and sustained pathway inhibition resulting in strong tumor growth inhibition and regression.

About Sunesis Pharmaceuticals

Sunesis is a biopharmaceutical company focused on the development and commercialization of new oncology therapeutics for the potential treatment of solid and hematologic cancers. Sunesis has built a highly experienced cancer drug development organization committed to advancing its lead product candidate, vosaroxin, in multiple indications to improve the lives of people with cancer.

For additional information on Sunesis, please visit http://www.sunesis.com.

This press release contains forward-looking statements, including statements related to Sunesis' expected progress in its kinase inhibitor pipeline. Words such as "may," "expect," "intends," "plan," "potential," "will" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Sunesis' current expectations. Forward-looking statements involve risks and uncertainties. Sunesis' actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, the risk that Sunesis' clinical studies for its product candidates may not demonstrate safety or efficacy or lead to regulatory approval, the risk that data to date and trends may not be predictive of future data or results, risks related to the conduct of Sunesis' clinical trials, risks related to Sunesis' need for substantial additional funding to complete the development and commercialization of vosaroxin, and risks related to Sunesis' ability to raise the capital that it believes to be accessible and is required to fully finance the development and commercialization of vosaroxin. These and other risk factors are discussed under "Risk Factors" and elsewhere in Sunesis' Quarterly Report on Form 10-Q for the quarter ended September 30, 2015. Sunesis expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Sunesis' expectations with regard thereto or any change in events, conditions or circumstances on which any such

statements are based.

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