First Patient Treated in Innovative Clinical Study 'Amelia-1', Testing the Novel Investigational Drug Evexomostat Plus a PI3K Inhibitor in Late-Stage Breast Cancer Patients

Amelia™-1 Study is testing if evexomostat can improve patients' safety and clinical response to a PI3K inhibitor plus an estrogen receptor degrader. Evexomostat, a novel MetAP2 inhibitor, controlled PI3K-induced hyperglycemia in the first study patient, consistent with pre-clinical data. Further, ctDNA data shows no evidence of residual PIK3CA mutation in blood after 6 weeks of treatment.

CAMBRIDGE, Mass., September 19, 2023 (Newswire.com) - SynDevRx, Inc. today announced the opening of the Amelia-1 study and data from the first patient treated in its Phase 1b/2 clinical study testing the novel MetAP2 inhibitor evexomostat (aka SDX-7320) in combination with the PI3K inhibitor alpelisib (Piqray®) and the estrogen receptor degrader (SERD) drug fulvestrant (Faslodex®) in breast cancer patients with metastatic disease and the PIK3CA gene mutation (NCT05455619 - Phase 1b/2 Study of the Safety and Efficacy of Evexomostat Plus Alpelisib and Fulvestrant in Postmenopausal Women at Risk for Hyperglycemia With Advanced Breast Cancer and a PIK3CA Mutation Following Endocrine Therapy and a CDK4/6 Inhibitor).

Drugs from the PI3K class, including Piqray, frequently induce hyperglycemia followed by hyperinsulinemia, which can lead to treatment failure[1]. Insulin is an important hormone that controls blood glucose levels, but it has been reported that high insulin levels in breast cancer can cause the tumors to grow faster[2], making treatment more difficult, and can lead to premature disease progression[3]. The aim of the Amelia-1 clinical study is to test whether the combination of evexomostat, a novel MetAP2 inhibitor, combined with standard-of-care therapies Piqray and fulvestrant, will prolong treatment response and reduce the number and severity of hyperglycemic events brought on by Piqray. In a Phase 1 dose escalation clinical study of evexomostat (NCT02743637) in late-stage cancer patients, anti-metastatic and anti-angiogenic properties, as well as insulin-sensitizing effects were noted in patients[4] (Mita et al, 2020).

Hope S. Rugo, MD, a breast cancer specialist at the University of California San Francisco who helped in the design of the Amelia-1 study, is at the forefront of researching PI3K inhibitors for breast cancer patients and has been instrumental in the development of many cutting-edge treatments for breast cancer patients. "Piqray is an effective treatment for breast cancer patients with a PIK3CA gene mutation in the second line treatment setting following a CDK 4/6 inhibitor. However, certain patients

with baseline metabolic complications are at risk for developing severe hyperglycemia, which can interfere with their treatment and reduce Piqray's effectiveness. Based on evexomostat's Phase 1 clinical data, we designed this study to determine whether evexomostat will help to control the hyperglycemia and to prolong treatment. If effective, evexomostat could facilitate increased Piqray clinical usage," Dr. Rugo said. "The research into the role of insulin and insulin resistance in breast cancer, historically overlooked, is gaining momentum, and may soon emerge as a viable cancer treatment target."

MetAP2 inhibitors have a history of clinically demonstrating improvements in insulin resistance[5]. "In our Phase 1 clinical study in late-stage cancer patients, evexomostat (SDX-7320) demonstrated positive effects on insulin resistance in patients presenting with baseline insulin resistance (N=11 out of 32 with baseline insulin resistance), and prevention of new metastases in 89% of evaluable, heavily pre-treated cancer patients (N=24 out of 27 evaluable)," said Bradley Carver, co-founder and Chief Executive Officer of SynDevRx. The most common adverse events (AEs) observed in the Phase 1 (N=32) study were fatigue (44%), decreased appetite (38%), constipation and nausea (each 28%), and diarrhea (22%); all other AEs occurred at an incidence <20%. The majority of AEs experienced in the Phase 1 study were Grade 1 and Grade 2, considered mild to moderate in severity. "While the safety focus of the Amelia-1 study is on controlling glucose and subsequent insulin levels, the study could confirm the potential anti-metastatic and anti-angiogenic effects of evexomostat (SDX-7320) that were observed in our Phase 1 study and the potential synergistic effects with Piqray that were observed preclinically in a breast cancer tumor model[6]. Further, oncologists typically do not consider their patients' metabolic health when designing treatment regimens. This study aims to highlight the potential role of addressing dysregulated metabolic hormones in cancer patients' treatment. The Amelia-1 study is an innovative research study which provides an excellent opportunity to research the possible multi-faceted effects of evexomostat (SDX-7320) for breast cancer patients," said Bradley Carver.

The Amelia-1 study is targeting up to 52 hormone receptor positive (HR+) metastatic breast cancer patients with the PIK3CA mutation to assess the investigational drug's impact on controlling hyperglycemia, which may simplify oncologists' and patients' clinical experience. "Recent scientific data suggests that MetAP2 inhibitors like evexomostat may synergize[7] with and thereby enhance the therapeutic effect of PI3K inhibitors, translating into better outcomes for patients," noted SynDevRx's co-founder and Chief Business Officer James Shanahan. "The PI3K target is mutated or amplified in many cancers, but on-target effects of inhibition have seriously complicated the development of effective anti-PI3K therapies. If our clinical hypothesis is validated, we believe evexomostat could enable PI3K treatment across a broad range of tumor types."

Breast cancer patients interested in more information on the study can visit www.amelia1.com, created in collaboration with www.SurvivingBreastCancer.org and Touch.

1. Hopkins et al., Suppression of Insulin Feedback Enhances the Efficacy of PI3K Inhibitors Nature vol. 560, 499-503 (2018)
2. Gallagher, E.J., et al., Hyperinsulinaemia in cancer. Nat Rev Cancer 20, 629-644 (2020)
3. Yee LD, et al., Metabolic Health, Insulin, and Breast Cancer: Why Oncologists Should Care About Insulin. Front. Endocrinol. 11:58 (2020).
4. Mita M, et al, Cancer Res (2020) 80 (16-Supplement): CT153
5. Proietto, J., et al. Efficacy and Safety of MetAP2 Inhibition in Type 2 Diabetes: A Randomised, Placebo-controlled Clinical Trial. Diabetologia 61, 1918-1922 (2018).
6. Cornelius P, et al, Cancer Res (2020) 80 (4_Supplement): P3-11-13
7. Holzen et al., RNA Interference Screens Discover Proteases as Synthetic Lethal Partners of PI3K Inhibition in Breast Cancer Cells: Theranostics Vol. 12, Issue 9, (2022)

About Evexomostat (SDX-7320)

Evexomostat (SDX-7320) is among the first drugs being developed specifically for cancer patients with metabolic complications, such as insulin resistance, obesity, diabetes, or pre-diabetes. For certain solid tumor types, dysregulated metabolic hormones stemming from metabolic dysfunction can stimulate known oncogenic pathways, making the cancer more aggressive and deadlier. Evexomostat acts by binding irreversibly to its target enzyme MetAP2, triggering multiple downstream effects. Pre-clinical mechanism studies provide evidence that evexomostat inhibits multiple tumor cell cycle signaling pathways, provides synergistic anti-tumor effects in combination with PIK3CA inhibition, reduces angiogenesis, inhibits metastases, controls dysregulated metabolic hormone signaling, regulates key lipids and reverses obesity-induced immune suppression within the tumor micro-environment. Evexomostat is being developed for use in combination with clinically indicated standard-of-care cancer therapies for breast cancer, prostate cancer, and other tumor types.

About SynDevRx, Inc.

SynDevRx is a privately held clinical-stage biopharmaceutical company based in Cambridge, Massachusetts, that is leading the research and development of treatments that address the interactions between cancer and dysregulated metabolic hormones, i.e., metabo-oncology. Obesity, pre-diabetes and type 2 diabetes are known to worsen certain cancer patients' prognoses, but oncologists have no specific tools to treat systemic or cancer treatment-induced metabolic complications, except for diet and exercise. SynDevRx is initiating a series of proof-of-concept clinical studies of its drug candidate evexomostat (SDX-7320) to determine whether improving these hormones together with effects on angiogenesis, metastasis, the tumor's energy and micro-environment will result in better patient outcomes and establish a new and complementary treatment modality for tens of thousands of cancer patients. For more information, visit www.syndevrx.com.

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