Pharmacyclics Announces Preclinical Results on Texaphrin Therapy at 52nd American College of Cardiology Scientific Session

-- Company Developing Interventional and Systemic Pharmacologic Treatment Approaches to Stabilize Vulnerable Plaque in Coronary Artery Disease --

Chicago, Il.,
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Pharmacyclics, Inc. (Nasdaq: PCYC), announced today that preclinical studies involving treatment with the company’s texaphyrins, motexafin lutetium (Antrin® Injection) and motexafin gadolinium demonstrate the potential utility of the therapies to reduce the numbers of macrophages and stabilize vulnerable plaque in atherosclerotic blood vessels. Company researchers presented the data in oral and poster presentations at the 52nd Annual Scientific Session of the American College of Cardiology (ACC) in Chicago.

“The application of our novel drugs to treat vulnerable plaque is an example of the versatility and diversity of our technology,” said Richard A. Miller, M.D., president and chief executive officer of Pharmacyclics. “Texaphyrins selectively localize in tissues with high rates of metabolism such as cancers and inflammation. The findings presented at the ACC meeting demonstrate selective uptake of texaphyrins in macrophages in atherosclerotic plaque in blood vessels and selective destruction of these vascular macrophages, the culprit cell in vulnerable plaque. Although our primary focus is in oncology, the emerging promise of our drugs for the treatment of cardiovascular disease is becoming increasingly apparent.”

Vascular macrophages play a crucial role in the inflammatory process underlying the formation of atherosclerotic plaque. An increase in macrophages contributes to the instability of vulnerable plaque, subject to rupture in the lining of blood vessels. Disruption of vulnerable plaque has been implicated in the vast majority of acute coronary events, including heart attacks.

In preclinical studies presented at the ACC meeting, texaphyrin-based treatment significantly reduced the differentiation of human monocytes to macrophages in culture, significantly decreased viability of cultured human macrophages by inducing apoptotic death (programmed cell death) of the macrophages, and substantially lowered macrophage density in vulnerable plaque in animal models of atherosclerosis. In one approach, systemic administration of motexafin gadolinium and ascorbic acid led to depletion of macrophages in plaque through the generation of reactive oxygen species, inducers of apoptosis. This treatment has the potential for pharmacologic control of vulnerable plaque without the need for vascular intervention.

“These data suggest that following systemic administration of texaphyrins, various strategies exist to cause activation of the drug at the diseased site and decrease vascular inflammation and stabilize vulnerable plaque,” said Yi-Ping Sun, M.D., a cardiologist and lead cardiovascular researcher at Pharmacyclics, who presented the data at ACC. “We are taking advantage of two key properties of texaphyrins, selective localization and generation of reactive oxygen species, known inducers of cell death by apoptosis.”

Pharmacyclics is developing Antrin phototherapy for use in standard cardiac catheterization settings. Results from a completed Phase 1 clinical trial of phototherapy with Antrin in patients with coronary artery disease (CAD) indicated that the treatment was feasible and well tolerated. Phase 2 trials in patients with high-risk CAD who have vulnerable plaque are now being designed.

The company is also exploring additional ways to treat vulnerable plaque and/or achieving plaque stabilization using its broad technology. As reported at ACC in animal models of atherosclerosis, motexafin gadolinium localizes in vulnerable plaque and reacts with metabolites to generate reactive oxygen species, which leads to depletion of the macrophages. This is a systemic therapy not dependent on interventional approaches.

About Atherosclerosis and Vulnerable Plaque
Atherosclerosis is a major cause of morbidity and death. The disease occurs through build-up of cholesterol and abnormal tissue within blood vessel walls, which often leads to life-threatening blockages of blood vessels to the heart and brain. Abnormal tissue within blood vessel walls consists of connective tissue, smooth muscle cells, and inflammatory cells called macrophages. Although atherosclerosis has long been known to be associated with high levels of circulating cholesterol, inflammation in the vessel wall recently has been shown to be another important factor in progression of atherosclerosis and in plaque rupture, a cause of heart attacks.

Traditionally, vascular plaque is treated with mechanical techniques, such as balloon angioplasty and stents, which maintain
blood flow by physically pushing plaque aside and scaffolding the artery open, respectively. Balloon angioplasty often injures blood vessel walls, leading to a reaction by the vessel that causes renarrowing or restenosis. The use of stents has reduced, but not eliminated, this problem. Many coronary artery disease patients have other sites of unstable atherosclerotic plaque that are at risk of rupturing. Therefore, Pharmacyclics is investigating the potential of texaphyrin therapy, including the combination of Antrin and a nonmechanical technique called phototherapy, to reduce or eliminate these “vulnerable” plaque.

Within the past decade, the medical community's understanding of the causes of heart attacks also has begun to change. New data demonstrate that rupture of non-occlusive, vulnerable plaque causes the vast majority (60 to 80%) of heart attacks. Most vascular plaque that are vulnerable to rupture have a dense infiltrate of macrophages within a thin fibrous cap that overlies a substantial lipid core. The rupture of vulnerable plaque is due to chemicals released by the macrophages and/or mechanical stress such as increased blood pressure. Following rupture of plaque, blood is exposed to the lipid core, an abundance of inflammatory cells, and other components of plaque. This launches a chemical chain reaction that often culminates with a large blood clot (thrombosis) in the coronary artery, and eventually a heart attack. Currently, there are no reliable diagnoses or available treatments for vulnerable plaque. Because patients with cardiovascular disease have vulnerable plaque in multiple locations throughout their coronary arteries and body, a local procedure such as stenting is not likely to be sufficient.

**Texaphyrins in Vulnerable Plaque Therapy**

Antrin Injection is a water-soluble photoactive agent that accumulates selectively in vascular plaque and is cleared readily from the rest of the body. Antrin is injected into the bloodstream, where it accumulates in the multiple sites of plaque throughout the body. These targeted areas are then exposed to far-red light, which is delivered by an optical fiber inserted into the vessel using standard techniques. When activated by the light, Antrin generates a chemical reaction that may selectively eliminate macrophages, causing stabilization or reduction of vulnerable plaque.

Motexafin gadolinium is a systemic treatment that has the potential to stabilize vulnerable plaque throughout the body. This drug localizes in vulnerable plaque and reacts with various metabolites, such as ascorbic acid or vitamin C, to generate reactive oxygen species (ROS). The generation of ROS within vulnerable plaque leads to depletion of inflammatory macrophages and potential stabilization of plaque. Motexafin gadolinium generates reactive oxygen species catalytically by a mechanism of action known as redox cycling.

**About Pharmacyclics**

Pharmacyclics is a pharmaceutical company developing products to improve upon current therapeutic approaches to cancer and atherosclerosis. The company's products are rationally designed, ring-shaped small molecules called texaphyrins that selectively target and disrupt the bioenergetic processes of diseased cells, such as cancer and atherosclerotic plaque. More information about the company, its technology, and products can be found on its web site at www.pcyc.com.

**NOTE:** The statements made in this press release about progress and reports of results from preclinical studies, clinical trial results, clinical development plans, and product development activities other than statements of historical fact, are forward-looking statements. The forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those in the forward-looking statements, including risks associated with the initiation, timing, design, enrollment, and cost of clinical trials; the progress of research and development programs; the regulatory approval process in the United States and other countries; and future capital requirements. For further information about risks that may affect the actual results achieved by Pharmacyclics, please see the company's reports as filed with the U.S. Securities and Exchange Commission from time to time, including but not limited to, its reports on Forms 10-Q and 10-K. Pharmacyclics®, the "pentadentate" logo® and Antrin® are registered trademarks of Pharmacyclics, Inc.

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