

### **Technical Abstract:**

Cardium Therapeutics, Inc. (Cardium) plans to initiate a Phase 3 study (CT-3-001) in female patients with recurrent stable angina pectoris who are not candidates for traditional mechanical revascularization and who are on optimal drug therapy. This study, also known as the AWARE study (Angiogenesis in Women with Angina pectoris who are not candidates for REvascularization), will evaluate the effects of two Ad5FGF-4 dose groups [ $3 \times 10^8$  and  $3 \times 10^9$  viral particles (vp)] on ECG changes diagnostic of myocardial ischemia during exercise treadmill testing (ETT) compared with placebo. Limitations of current therapies for patients with recurrent angina and the overall study design for AWARE are provided below.

Over six million adults in the U.S. have stable angina pectoris (episodes of myocardial ischemia resulting in chest pain) that necessitate medical and interventional therapy (surgical or percutaneous). In patients who are already on optimal medical therapy, using combinations of drugs such as nitrates, beta blockers, or calcium channel blockers, and who are no longer candidates for revascularization procedures, their angina may severely limit their daily activities. New therapeutic options are needed to meet the demands of these patients who have recurrent chronic angina even following surgery and/or other cardiac interventions for revascularization.

Ad5FGF-4 (alferminogene tadenovec) consists of human adenovirus, serotype-5, that has been modified to express the human fibroblast growth factor-4 gene driven by a CMV promoter. The EI region of the wild-type adenovirus vector has been deleted, making the vector replication deficient, and replaced with the expression cassette for FGF-4. Administration of a recombinant adenovirus expressing human fibroblast growth factor-4 (Ad5FGF-4) offers the potential to promote a disease-modifying effect in patients with chronic ischemic heart disease following a single intracoronary infusion. Delivery of the FGF-4 gene to the heart allows for a more sustained production of the angiogenic protein stimulus to potentially produce a permanent change to the heart by stimulating the growth of new blood vessels and thereby relieve ischemia through improved blood flow. There are no currently approved agents that offer this potential to grow new collateral blood vessels.

Ad5FGF-4 has been evaluated in four prospective, randomized, placebo-controlled multi-center clinical studies (AGENT-1 through AGENT-4). The safety database includes 663 patients (213 placebo and 450 Ad5FGF-4) who have been followed for a period of over 1,700 patient years. There have not been any cases of clinical myocarditis, evidence of an increase in heart failure, reports of pathological angiomas or retinal neo-angiogenesis. Long term follow-up safety data collection to assess the risk of delayed adverse events following intracoronary delivery of Ad5FGF-4 is ongoing for AGENT-3 and AGENT-4. In the current follow-up database from the four AGENT studies, there have been no statistically significant differences in the incidence of adverse events during long-term follow-up.

The AWARE study (Protocol CT-3-001) is a randomized, double-blind, placebo-controlled, parallel group Phase 3 study that will enroll approximately 300 female patients with stable angina pectoris who are not candidates for revascularization. The primary objective of this study is to evaluate the effect of Ad5FGF-4 on myocardial ischemia during exercise treadmill testing (ETT). The secondary objectives of this study are to evaluate the effect of Ad5FGF-4 on change in myocardial perfusion by adenosine single-photon emission computed

tomography technetium-99m sestamibi (SPECT), change in functional class using the CCS angina classification, change in other ETT parameters (change in total exercise time and time to onset of angina), change in left ventricular ejection fraction using gated SPECT and on quality of life using the Seattle Angina Questionnaire. The relationship between change in myocardial perfusion and other efficacy endpoints will be evaluated. The safety of Ad5FGF4 will be assessed by adverse events, clinical laboratory evaluations and long-term follow-up to identify clinically important events occurring 12 to 60 months after study product administration.