XC001 Gene Therapy for the Treatment of Refractory Angina: 6-Month Efficacy and Safety from the Phase 1/2 First-In-Human Study (EXACT Trial)

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Refractory angina (RA) is a debilitating chronic condition of advanced coronary artery disease in which patients have exhausted all available medical or surgical therapies and interventions. RA is characterized by high symptom burden and healthcare resource utilization, poor quality of life, and high rates of hospitalization. XC001 is a replication-deficient, recombinant adenovirus (Ad) 5 containing a human-derived cDNA/genomic hybrid and alternative splicing provides mRNA encoding for multiple isoforms of vascular endothelial growth factor (VEGF) which initiates angiogenesis to bypass coronary artery blockages. XC001 is administered under direct visualization by surgeons via a mini-thoracotomy to ischemic areas of the left ventricle identified by stress imaging studies and angiography which allows for the administration of lower vector genomes maximizing levels in the heart while minimizing systemic levels. Rodent biodistribution data demonstrated that direct epicardial administration resulted in localization of the vector to the left ventricular wall as compared to other highly perfused organs (liver, lung, spleen). XC001 was much more effective in the ischemic mouse hind-limb model at inducing angiogenesis and hind-limb blood flow than comparable vectors expressing only individual VEGF isoforms. XC001's increased ratio of expressed heparin-binding isoforms are designed to have a stronger local angiogenic effect due to their ability to bind to the extracellular matrix more tightly. Reported here are 6-month results from the phase 1/2 first-in-human, open-label, single-arm, sequential dose escalation study (EXACT) with the highest tolerated phase 1/2 dose of 10^{11} viral particles (n=29) demonstrating preliminary safety and signals of efficacy. The majority of subjects showed clinically meaningful improvements from baseline to 6 months post XC001 in the key endpoint of total exercise duration (TED) on a standardized exercise treadmill test read by a blinded core lab (mean (SD) increase of 1.4 (2.3) minutes, p=0.003). Mean (SD) change in angina episodes at 6 months showed a reduction of 6.7 (8.1) episodes (p<0.001) over a 2-week period prior to each visit while at the same time nitroglycerin use decreased (-3.8 (6.9), p=0.008). Canadian Cardiovascular Society (CCS) Class, a measure of angina symptoms, improved in 81% of subjects. There was a 14% reduction (p=0.02) in total myocardial perfusion deficit on Positron Emission Tomography (PET) observed at 6 months. An assessment of treatment success across 5 key endpoints (TED increase of ≥1 minute, angina episode reduction of ≥30%, nitroglycerin reduction of ≥30%, ≥1 class improvement in CCS, and >10% reduction in TPD) showed 93%, 67% and 40% of subjects meeting ≥2, ≥3 and ≥4 endpoint criteria, respectively. No serious adverse events (SAEs) were considered related to XC001 and SAEs related to the administration procedure (38%) were expected

and occurred within 2 weeks of dosing. In summary, multiple EXACT study efficacy endpoints demonstrated that intramyocardial administration of XC001 was associated with improvements in angina symptoms and exercise capacity in RA subjects while cardiac imaging measured by PET provided supportive evidence of a biologic effect.

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