Dose Escalation Study of Encoberminogene Rezmadenovec (Adenoviral Vector With Multiple Isoforms of Vascular Endothelial Growth Factor) in Refractory Angina: Phase 1 Results

Objective: This Phase 1/2 EXACT (Epicardial Delivery of XC001 Gene Therapy for Refractory Angina Coronary Treatment) trial (NCT04125732) investigates the direct administration of encoberminogene rezmadenovec (XC001), a replication-deficient adenoviral serotype 5 vector expressing multiple isoforms of vascular endothelial growth factor (VEGF) including 121, 165, and 189, to the ischemic myocardium of subjects with angina pectoris secondary to coronary artery disease that is refractory to drug therapy and unsuitable for revascularization. This trial is a first-in-human, multicenter, open-label, single arm cardiovascular dose escalation study to assess the safety, preliminary efficacy, and highest tolerated dose for further evaluation in the Phase 2 expansion cohort.
Methods: Twelve patients with refractory angina and Canadian Cardiovascular Society (CCS) Class 2-4 without revascularization options underwent mini thoracotomy with 15 epicardial injections of increasing doses of encoberminogene rezmadenovec (n=3/cohort; $1x10^9$, $1x10^{10}$, $4x10^{10}$, and $1x10^{11}$ viral particles, respectively). Safety and efficacy evaluations were measured as serious adverse events (SAEs) and change from baseline to three months post-treatment including exercise testing, positron emission tomography (PET), and patient-reported symptomatology.
Results: No drug-related SAEs, bleeding complications or ventricular arrhythmias were observed. A total of thirteen SAEs occurred in five subjects through three months of follow up. Six of the thirteen SAEs occurred in four subjects and were attributed to the mini-thoracotomy procedure (atrial fibrillation, chest pain, heart failure, pleural effusion, type 2 MI, wound infection). None were unexpected or resulted in patient death. Changes from baseline to month 3 in Total Exercise Duration (minutes) were -1.58 (-0.15), -0.33 (-0.77), 1.18 (2.72), and 2.36 (2.12) [mean (median)], for cohorts 1-4 respectively (Figure), improvement in CCS angina class 0.7 (0), 1.7 (1.0), 1.0 (1.0), 1.7 (2.0) [mean (median)], respectively and improvement from baseline in PET perfusion defect extent of 1.8 (7.4), 0.2 (-1.2), 1.9 (0.9), 6.9 (6.0), [mean (median)], respectively.
Conclusions: In the Phase 1 portion of this open-label Phase 1/2 study treating refractory angina, epicardial administration of encoberminogene rezmadenovec expressing VEGF appears to be well-tolerated and safe at all tested doses. Further, objective criteria including exercise tolerance and PET scans suggest therapeutic potential with this therapy. This preliminary efficacy evaluation in a small sample size suggests a dose-response across several efficacy variables and supports continued investigation of $1x10^{11}$ viral particle dose in the Phase 2 portion of this trial.

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Change in Total Exercise Duration at 3 Months: Mean Values