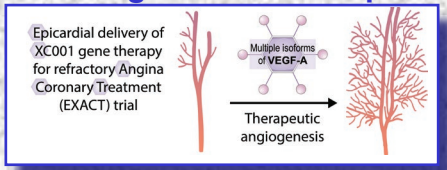
ANGIOGENIC GENE THERAPY FOR REFRACTORY ANGINA: RESULTS OF THE EPICARDIAL DELIVERY OF XC001 GENE THERAPY FOR REFRACTORY ANGINA CORONARY TREATMENT (EXACT) PHASE 2 TRIAL

Thomas J. Povsic, MD, PhD[1]; Kenta Nakamura MD[2]; Timothy D. Henry MD[3]; Jay H. Traverse MD[4]; R. D. Anderson MD,[5]; F. Bakaeen MD[6]; David A. Latter MD[7]; E. Magnus Ohman MD[1]; Mark W. Peterson B[8]; Dawn Byrnes[8]; Carl J. Pepine MD[9]; Ronald G. Crystal MD[10]; Todd K Rosengart MD[11]; Nahush A. Mokadam MD[12]; Howard C. Dittrich MD[8]

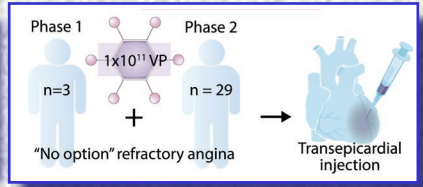
[1]Duke Clinical Research Institute, Department of Medicine, Duke University, Durham, NC; [2]University of Washington, Department of Medicine, Seattle, WA; [3]The Christ Hospital, The Carl and Edith Lindner Center of Research and Education, Cincinnati, OH; [4]Abbott Northwestern Hospital, Minneapolis Heart Institute Foundation , Minneapolis, MN; [5]University of Florida, Heart and Vascular Center, Gainesville, FL; [6]Cleveland Clinic Foundation, Department of Thoracic and Cardiovascular Surgery, Cleveland, OH; [7]University of Toronto, Department of Cardiovascular Surgery, St. Michael's Hospital, Toronto, Canada [8]Xylocor Therapeutics, Malvern, PA; [9]University of Florida, Department of Cardiovascular Medicine, Gainesville, FL; [10]Weill Cornell Medical College, Department of Genetic Medicine, New York, NY; [11]Baylor College of Medicine, Department of Surgery, Houston, TX; [12]Ohio State University Wexner Medical Center, Department of Cardiac Surgery, Columbus, OH

Background and Purpose



- Refractory or "no option" angina (RA) is a debilitating condition with increasing global prevalence.
- Exogenous transduction of vascular endothelial growth factor (VEGF) induces angiogenesis and improves perfusion of ischemic myocardium in preclinical studies.
- XC001 (AdVEGFXC1) is a novel adenoviral-5 vector expressing the three major isoforms of VEGF (-121, -165, -189) in ratios shown to enhance potency and improve safety by increasing expression of heparin binding isoforms.
- EXACT (NCT04125732) is a single-arm, multicenter, open-label, phase 2 trial to explore the safety, tolerability, and preliminary efficacy of trans-epicardial delivery of XC001 to improve exercise capacity and ischemic burden in RA patients.

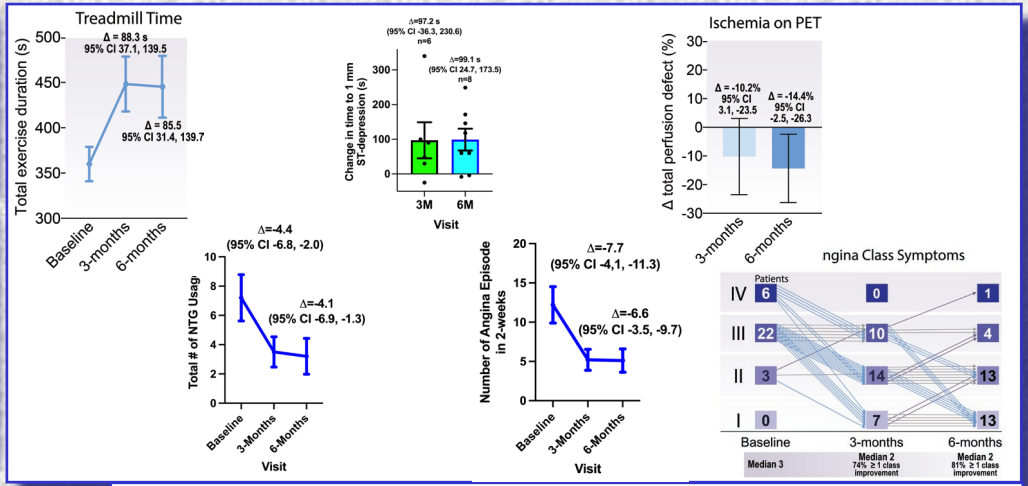
Methods



Patients:
- Stable CCS class II-IV angina
- No recent ACS/stroke
- Maximally tolerated medical therapy
- Anginal limited 90s < ETT < 540s (modified Bruce)
- Ischemia on stress PET
- Lack revascularization options.

Treatment:
- XC001 (1x10[11] viral particles) injected IM via surgical transthoracic epicardial access in 15 0.1 ml injections

Results



- Thirty-two patients included (3 from final dosing cohort Ph 1, 29 Ph 2)
- Mean/median ages of 64/64, 34% female) were enrolled at 13 sites between March 2021 and July 2022. Median anti-anginal use was 3, 75% had prior revascularization with CABG and 88% with PCI.
- Fifty-five serious adverse events (SAEs) were observed in 21 patients (66%). None were attributed to study drug. Twenty-one SAEs in 14 patients were related to the surgical procedure, all of which were expected. One non-CV death occurred in month 3 following respiratory infection (Covid) deemed unrelated to surgery or study drug.
- Compared to baseline:
  - Δ total exercise time 85.5 seconds (95% CI 31.3-139.7) at 6-months
  - total myocardial ischemic deficit in the treated region on PET decreased by 14.4% (95% CI, 3.01–25.73)
  - Angina frequency and nitroglycerin use measured during a two-week diary decreased by 6.6 episodes (95% CI, 3.5–9.7) and 4.1 doses (95% CI, 1.3–6.9), respectively.
  - Canadian Cardiovascular Society angina grade decreased from 3.1 to 1.8, mean difference 1.3 classes (95% CI, 1.0–1.6)
  - Seattle Angina Questionnaire Frequency score improved from 41.3 to 67.4, mean difference of 26.1 (95% CI, 16.3–35.9).

Conclusions

VEGF gene therapy with XC001 administered via minimally invasive transepicardial delivery appears:
- Generally well tolerated
- No IP related SAEs
- SAEs related to surgical procedure all expected and resolved
- Improvements in objective and subjective measures including total exercise time, myocardial perfusion, angina frequency and quality of life support a clinically meaningful biologic effect. This therapy warrants study in larger randomized studies.