Cardiac "Gene" Therapy

An Update
The 12th Annual Meeting of the Indiana Chapter of the American College of Cardiology
11/15/2008

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Disclamer:
I personally have no financial relationship with any company mentioned today.
The Care Group, LLC does have a contract with Cardium to participate in the AWARE Trial

The Point

Add to the therapeutic armamentarium for ischemic CV disease allowing us to treat patients resistant to or who are not candidates for current approaches (i.e., medial therapy or invasive revascularization)

What's Necessary

- ✓A candidate gene
  - ✓ Eg. VEGF, FGF, etc.
- ✓A vector – i.e., a means of delivery
  - ✓ A virus, plasmid, etc.
- ✓A route and mode of delivery
  - ✓ Epicardial transmyocardial
  - ✓ Endocardial
  - ✓ Intravascular
  - ✓ Transvascular
  - ✓ Intravenous

Really Gene Product Therapy

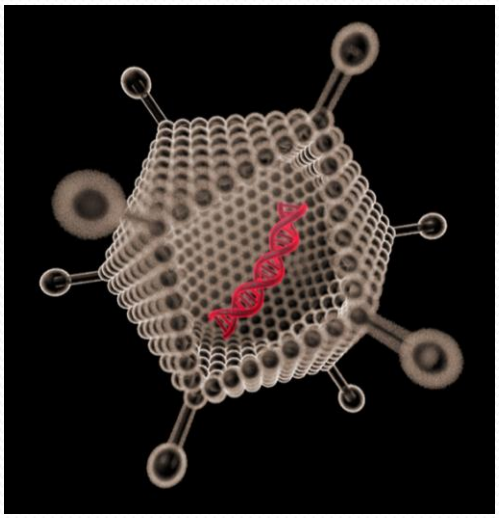
- Looking to utilize the product of a gene to induce angiogenesis
- NOT looking to alter or “repair” the native genome

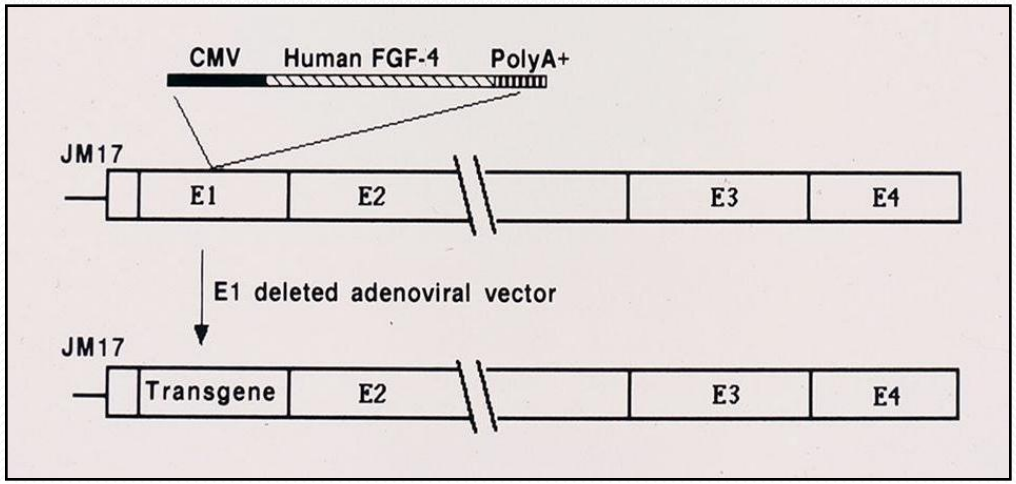
FGF-4 Gene

- Regulates angiogenesis
- Signal peptide - secreted
- Binds to extracellular matrix proteins
- Abundant FGF-4 receptors found in cardiac tissue
- Upstream growth factor that can recruit and stimulate responses in downstream target cells

Study Product: Ad5FGF-4

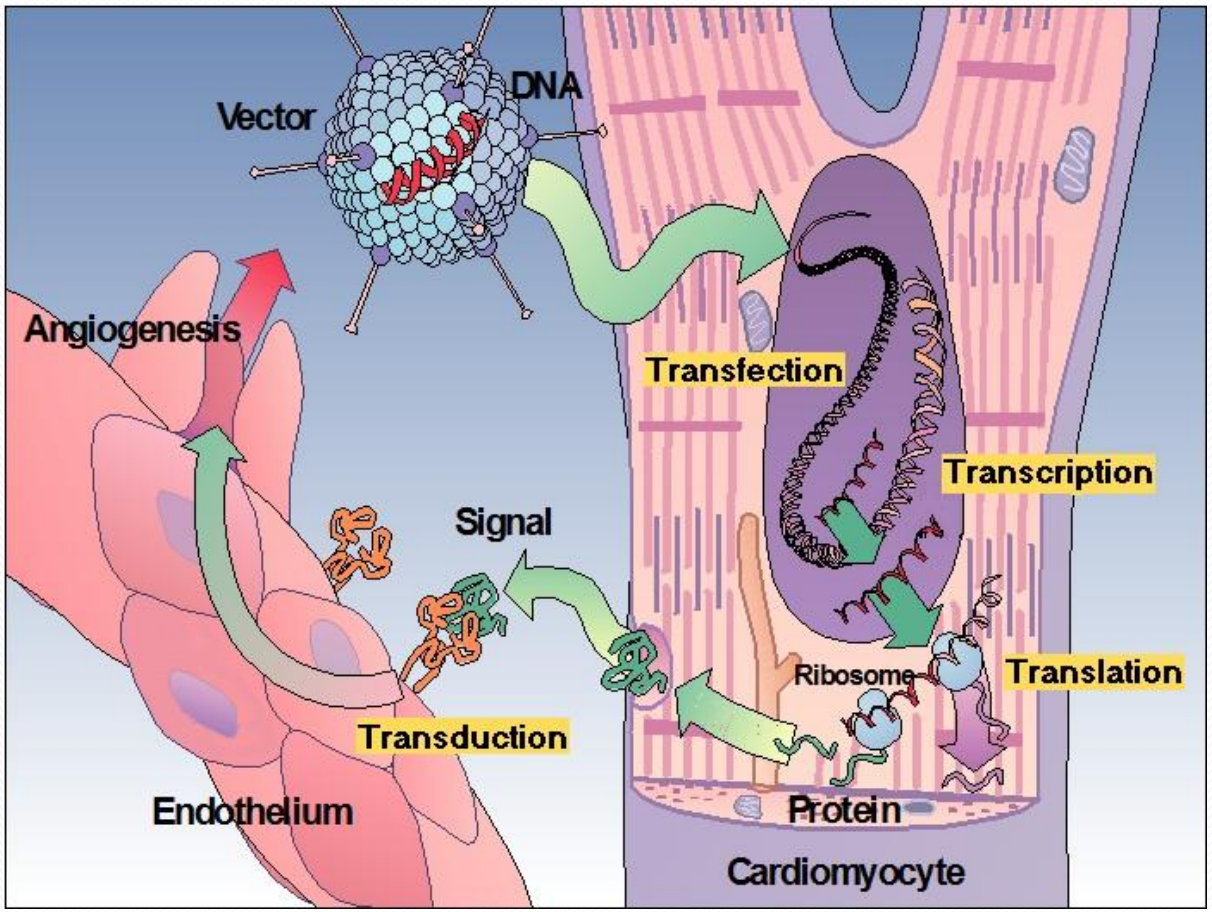
- Recombinant angiogenic gene transfer product
  - First generation E1-deleted recombinant adenovirus (human serotype 5)
  - Human fibroblast growth factor-4 (FGF-4) transgene driven by CMV promoter





Adenovector construct carries the FGF-4 Gene for Cardiac Delivery

Mechanism of Action of Study Product



What its Supposed to Do

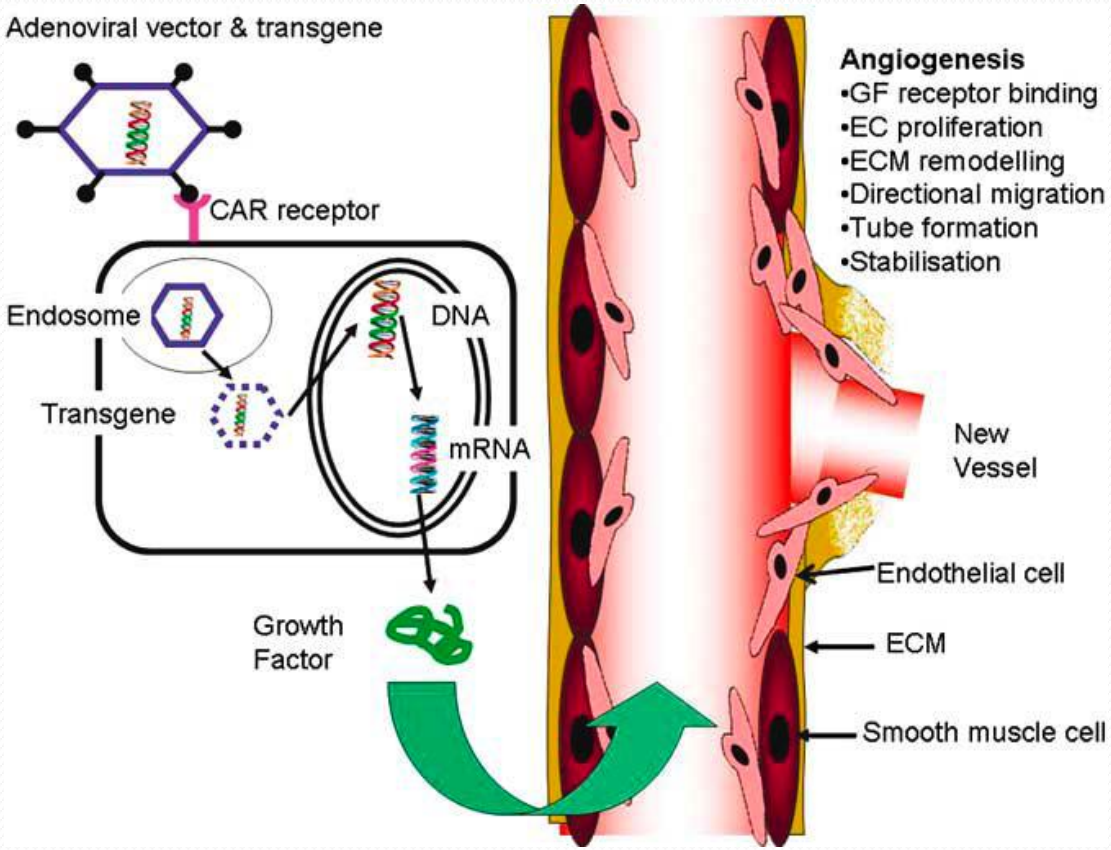


Figure 2 Therapeutic angiogenesis. An example of adenoviral delivery of growth factor transgenes to the vasculature.

From: British Journal of Pharmacology (2007) 152 175–188

Key Summary Points

1. Targeted delivery to the heart.
2. There is a high receptor density for the Ad5 Vector in the heart
3. The Ad5FGF-4 vector DOES NOT integrate into the myocyte chromosomal DNA
4. There is only TRANSIENT expression of the FGF-4
5. This is NOT classical “gene therapy” – there is no insertion of a functional gene into the host genome to replace a defective gene with life-long protein expression

Summary of the AGENT Trials

(Angiogenic GENe Therapy)

Rationale

- Intial Phase I trial of the Ad5FGF-4 construct proved promising
- AGENT-1 - Phase II safety, dosing and pharmacokinetic trial
- AGENT-2 – Scintigraphy study
- AGENT-3 – Phase 2b/3 Trial
- AGENT-4 – Further Phase 2b/3 Trial – terminated early by DSMB

AGENT Studies Overview

	AGENT-1 (Phase 1/2)	AGENT-2 (Phase 2)	AGENT-3 (Phase 2b/3)	AGENT-4 (Phase 2b/3)
Enrolled (Placebo/Active)	79 (19/60)	52 (17/35)	416 (139/277)	116 (38/78)
Doses (vp)	5 Doses 3.2×10^8 to 3.2×10^{10}	10^{10}	10^9, 10^{10}	10^9, 10^{10}
Angina Class (CCS)	2 or 3	2 or 3	2 to 4	2 to 4
Primary Endpoint	ETT	SPECT	ETT	ETT

Total Patients Enrolled: 663

Ad5FGF-4 Treated Patients: 450

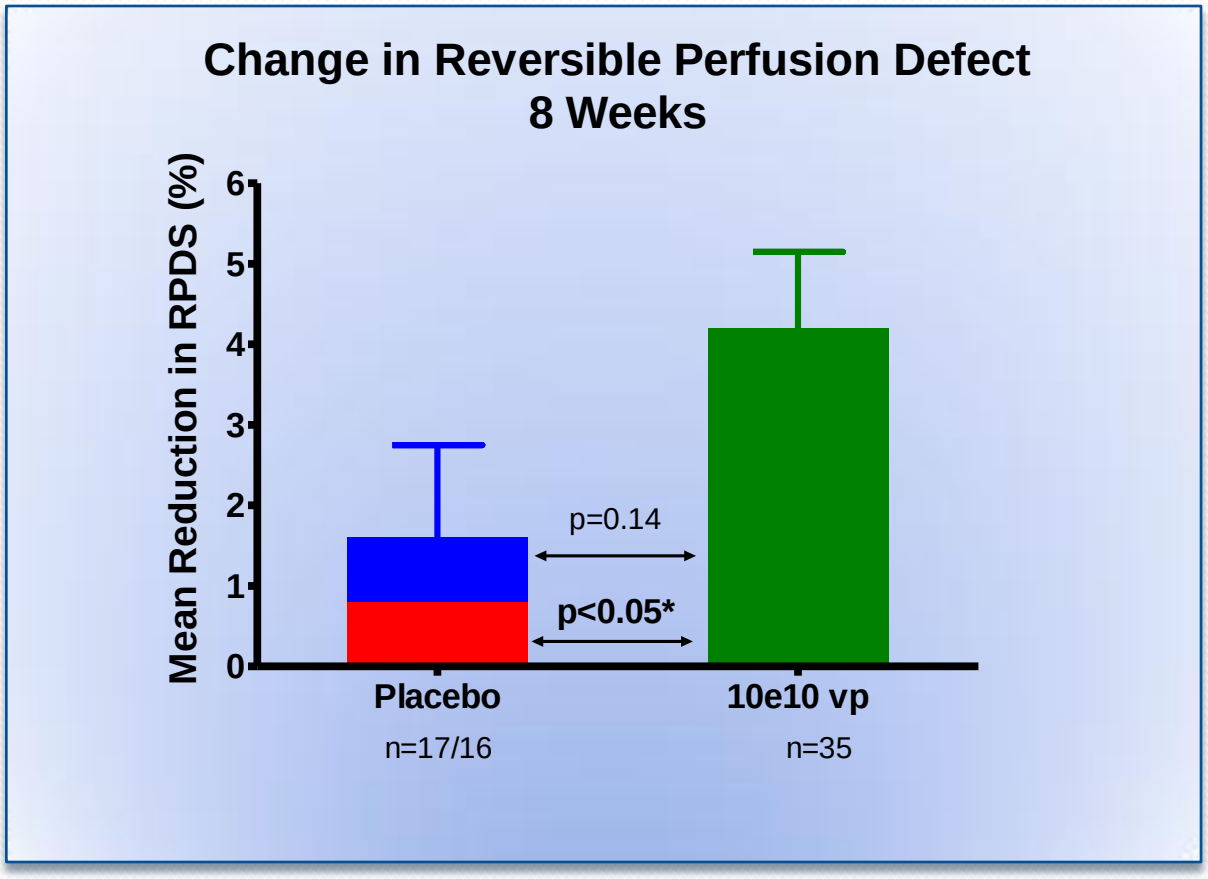
AGENT-1: Safety Results

- No Changes in HR or BP During Administration
- Some Transient Mild Temperature Elevation at Higher Doses
- No Evidence of Dose-Related Liver Toxicity
  - One Patient ($3x10^9$ vp) with Asymptomatic SGPT Elevation (718 U/L) at 1 Wk, Normal by 4 Wk
  - One Patient ($1x10^{10}$ vp) with Transient Mild SGPT Elevation (93 U/L) at 1 Wk
- No Retinal Changes or Undesirable Angiogenesis
- No Myocarditis

AGENT-1: Preliminary Efficacy

- Effects on ETT Duration
  - Pooled Data From Active Groups
    - Positive Effect on ETT Duration
    - Significant Improvement in Patients with Limited Exercise Capacity ($\leq$10 minutes)
  - 1 x 10^{10} vp Group (n=22)
    - Showed Most Consistent Improvement in ETT Duration
    - Chosen as Dose for AGENT-2

AGENT-2: Primary Endpoint



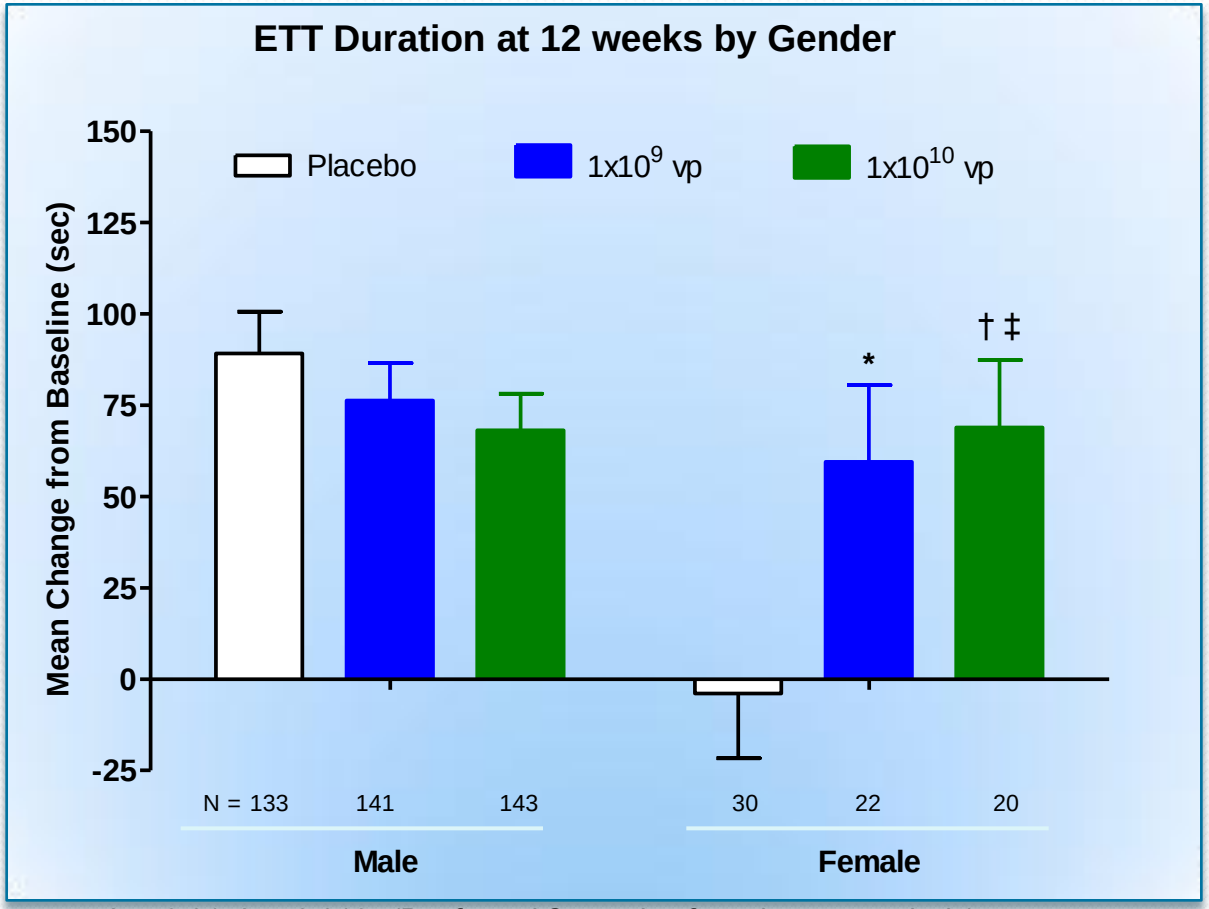
AGENT-3: Overview

- Phase 2b/3 Efficacy Study in the U.S.
- 416 Patients (139 placebo, 137 $1x10^9$ vp, 140 $1x10^{10}$ vp)
- CCS Class 2 to 4 Patients Who Did Not Require Immediate PTCA or CABG surgery
- Results: Interim Analysis Indicated the Study as Designed was Not Expected to Reach Statistical Significance and Enrollment was Discontinued
- A High Placebo Response Observed in Patients with Less Severe Angina

AGENT-4: Overview

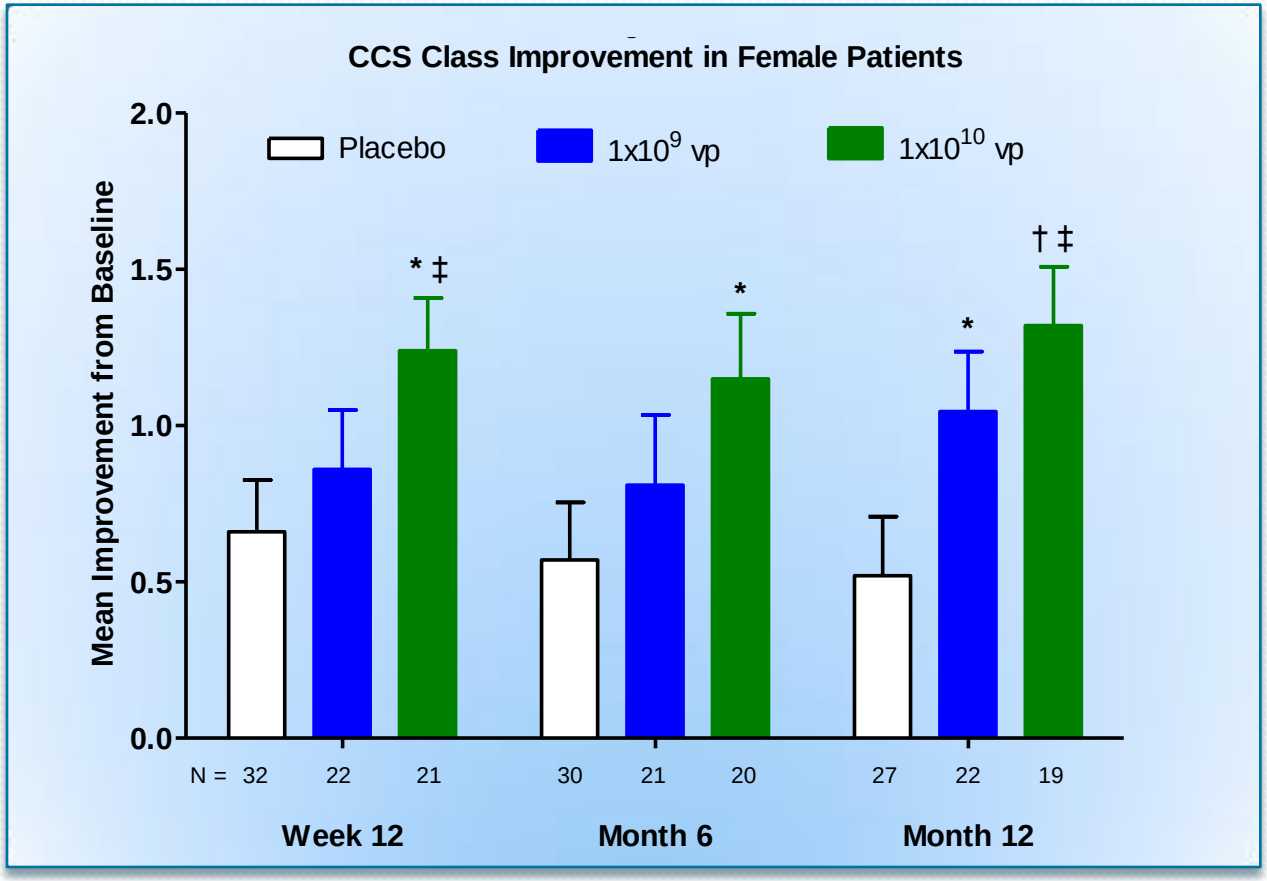
- Phase 2b/3 Efficacy Study in Europe, Latin America, Canada and U.S. (One Site)
- 116 Patients (38 Placebo, 43 $1x10^9$ vp, 35 $1x10^{10}$ vp)
- CCS Class 2 to 4 Patients Who were Not Optimal Candidates for Revascularization
- Results: Enrollment was Discontinued after Interim Analysis of AGENT-3

Exploratory Pooled Analysis AGENT-3 & AGENT-4



* p<0.05, † p<0.01, ‡ p<0.0167 (Bonferroni Correction for subgroup analysis)

Exploratory Pooled Analysis AGENT-3 & AGENT-4



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Summary: Pooled Analysis

- Large Placebo Effect Observed in ITT Population
  - No Treatment Effect Discernable in Male ITT Population
- Significant Improvements in Females
  - ETT Duration
  - Time to 1 mm ECG ST-Segment Depression
  - Time to Onset of Angina
  - CCS Class

Angiogenesis in Women with Angina pectoris who are not candidates for Revascularization

Gender Differences in Management

- Females are less likely to:
  - Undergo an exercise ECG to diagnose CAD (in part due to atypical symptoms)
  - Be referred for diagnostic coronary angiography
  - Be prescribed anti-platelet therapy and statins even when the disease is confirmed
  - Be referred for invasive revascularizations even with confirmed CAD and symptoms

Daly C, et al. *Circulation* 2006;113:490-498

Study Overview

Design	Randomized, double-blind, placebo-controlled, parallel group Phase 3 study
Patient Population	300 female patients, stable angina, CCS Class 3 or 4, reversible perfusion defect ≥9% by adenosine SPECT
Dosing*	1:1:1 Randomization Placebo, $3x10^8$ vp Ad5FGF-4, $3x10^9$ vp Ad5FGF-4 Intracoronary administration
Primary Endpoint	Change in time to onset of ECG changes diagnostic of myocardial ischemia during ETT at Month 6
Key Secondary Endpoint	Change in reversible perfusion defect size by adenosine SPECT at Month 6

* Ad5FGF-4 doses correspond to $1x10^9$ and $1x10^{10}$ vp doses in AGENT Program

Inclusion Criteria

- Female patients 18-75 years of age inclusive
- Stable angina classified as CCS 3 or 4
- Treatment with at least two classes of chronic anti-anginal medication, two at the maximally tolerated dose for that patient
- Left ventricular ejection fraction (LVEF) ≥30%

Inclusion Criteria (continued)

- Not a candidate for, or unlikely to benefit from, standard revascularization procedures
  - To be assessed prior to initiating study screening tests
  - Consider ACC/AHA practice guidelines for PCI and CABG surgery
  - Use clinical experience and judgment
  - Protocol **does not require patients to have a 70% critical stenosis** (e.g., diffuse disease, sub-critical stenosis, etc.)

Inclusion Criteria (continued)

- Not a candidate for, or unlikely to benefit from, standard revascularization procedures (cont.)
  - Confirmation required by an independent cardiologist or cardiothoracic surgeon (not a study investigator)
  - Angiogram prior to study product administration is to verify and document:
    - No new unexpected finding
    - Any major coronary artery stenoses
    - Collateral grade

Inclusion Criteria (continued)

- ETT using the modified Bruce protocol
  - ECG changes diagnostic of myocardial ischemia occur during the first 10 minutes of exercise
  - Variability of the time to onset of ECG changes diagnostic of myocardial ischemia is ≤25% or within 60 seconds if the time to onset of myocardial ischemia occurs within the first 4 minutes of exercise as determined by two consecutive screening ETTs

Inclusion Criteria (continued)

- Myocardial ischemia by adenosine SPECT sestamibi
  - Reversible perfusion defect size of ≥9%
  - Determined by SPECT core lab
- Willing and able to comply with the study requirements including long-term follow-up
- Provide written informed consent

Exclusion Criteria - Cardiovascular

- Myocardial infarction within the past 3 months
- Unstable angina or hospitalization requiring intravenous anti-anginal therapy within the 14 days prior to the start of screening evaluations
- Congestive heart failure NYHA Class IV
- Electrocardiogram that precludes accurate assessment of exercise induced myocardial ischemia (*e.g.*, left bundle branch block, WPW syndrome, atrial fibrillation)
- Myocarditis or restrictive pericarditis

Exclusion Criteria - Cardiovascular

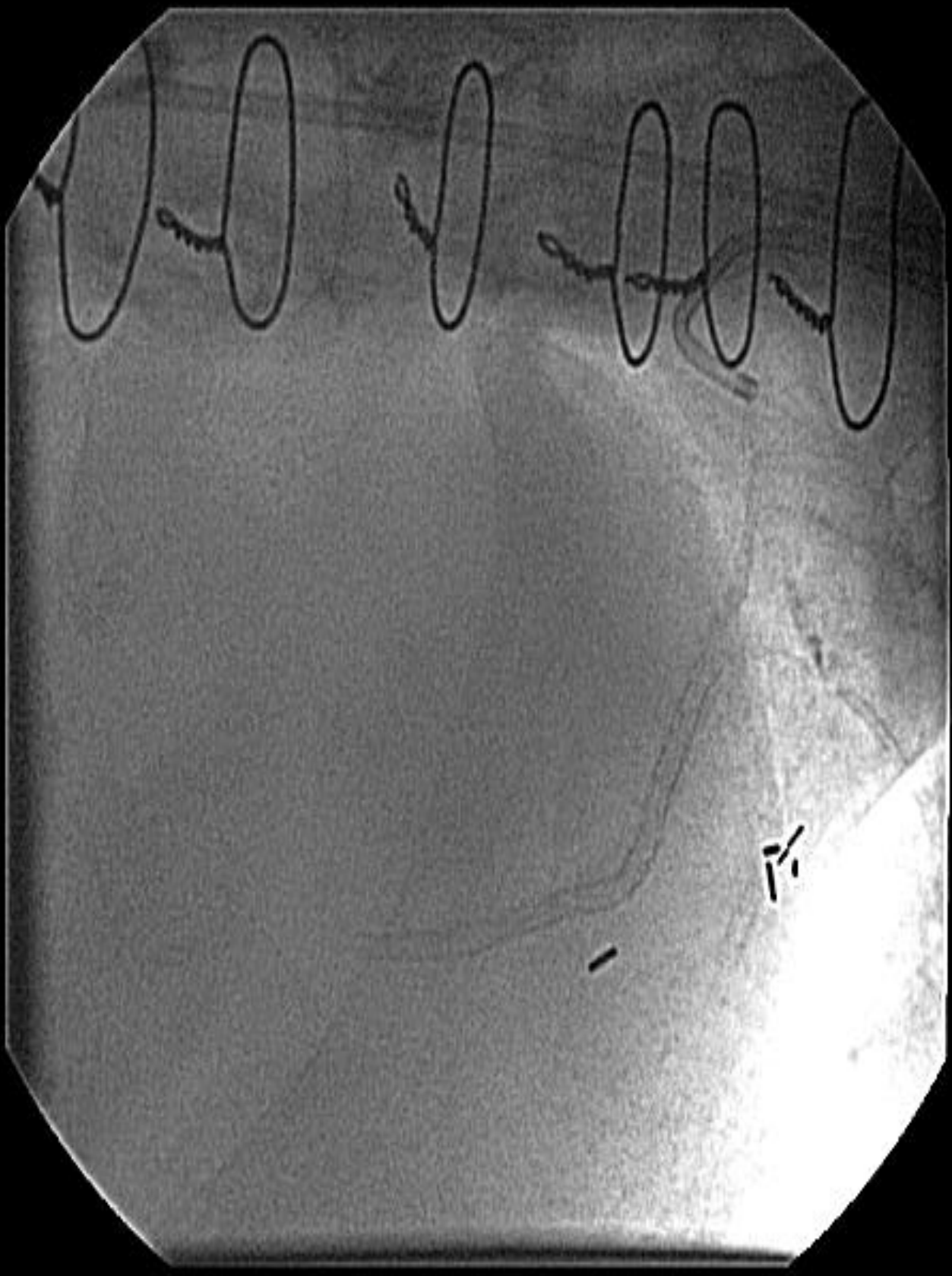
- Left main coronary stenosis ≥70% (unless the patient has a patent graft or collaterals supplying the left coronary circulation) or proximal stenoses ≥70% in all major coronary conduit vessels (coronary arteries and bypass grafts)
- Clinically significant aortic or mitral valvular heart disease
- Coronary ostial stenosis that precludes adequate catheter engagement in any target vessel
- Coronary artery to venous communications, which bypass the coronary capillary bed
- Untreated life-threatening ventricular arrhythmias

Exclusion Criteria - Cardiovascular

- CABG surgery within the past 6 months, unless those grafts are now occluded
- Percutaneous transluminal angioplasty (PTCA) within the past 3 months, unless the dilated vessel(s) are now occluded
- Enhanced external counterpulsation (EECP) within 3 months prior to the start of screening evaluations
- Transmyocardial or percutaneous myocardial laser revascularization within the previous year
- Prior treatment with any cardiovascular gene or stem cell therapy

Exclusion Criteria – Cancer

- History of cancer, other than basal cell carcinoma
  - Any laboratory, physical exam or diagnostic procedure finding suggestive of current malignancy (ACS Guidelines)
- History of colon cancer in a first degree relative unless the patient has undergone a colonoscopy in the past 36 months with negative findings
- History of breast cancer in a first degree relative
- Patient in a family with any documented hereditary cancer syndrome



Thank-you for your attention!