

# **The ASPIRE Trial: Phase 3 Registration Trial Incorporating Preclinical and Clinical Lessons Learned in the Past Decade**

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# Outline

## 1. Rationale for Therapeutic Angiogenesis

## 2. Lessons from the Past 10 Years

- Collective Experience of the Field
- Experience with Ad5FGF4
  - Preclinical (FGF4 activity and Ad5 Vector Delivery)
  - Clinical (AGENT Trials)

## 3. ASPIRE Trial

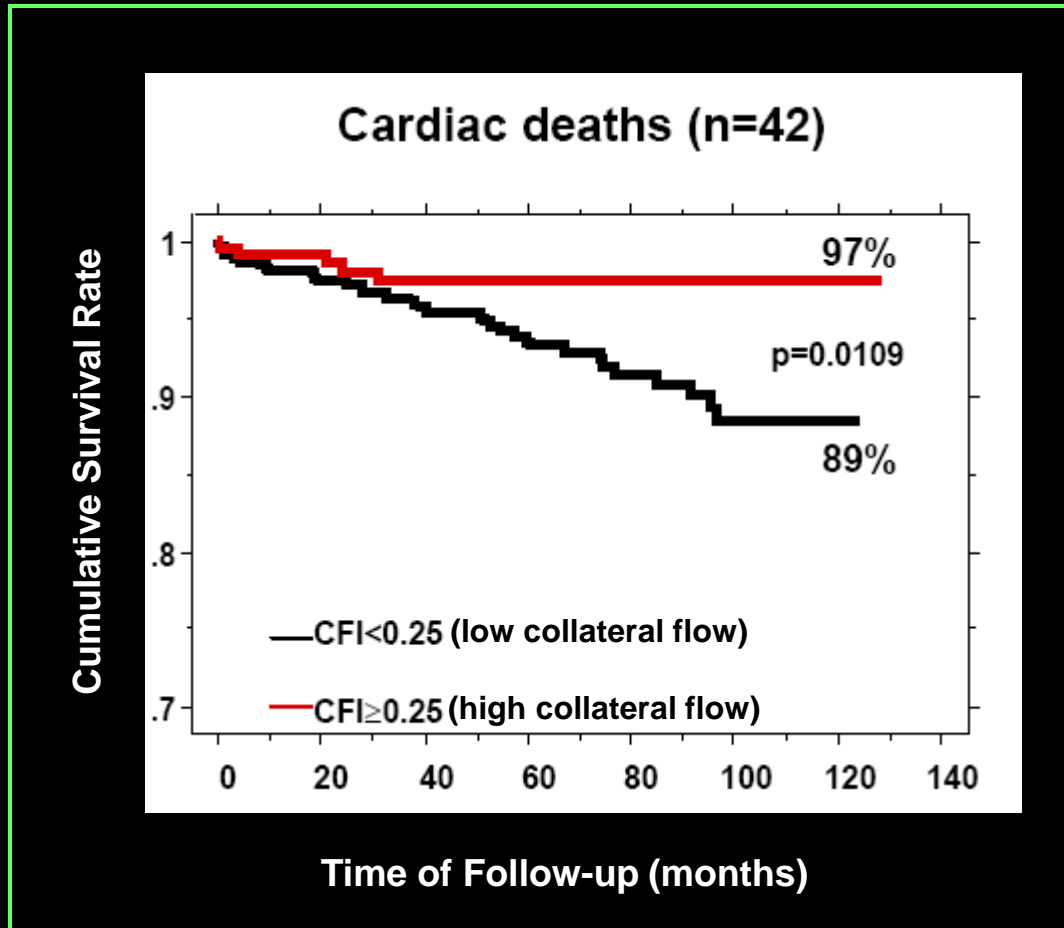
## **Therapeutic Angiogenesis:**

**“The use of angiogenic growth factors (recombinant proteins or genes) to expedite and/or augment collateral artery development in myocardial or hindlimb ischemia to improve blood flow and function.”**

**J.M. Isner et al., JCI 1994, 93:662-670**

# Beneficial Effects of Collateral Vessels: Rationale for Therapeutic Angiogenesis

## 10-Year Follow-up in Patients with Heart Disease



### CARDIAC DEATHS:

10 year follow-up  
(n = 845)

**High Flow:**  
5 (2%) Deaths

**Low Flow:**  
37 (6%) Deaths

67% ↓  
Cardiac Deaths

# **Collective Experience of the Field of Therapeutic Angiogenesis**

# Overview Perspective: Gene Therapy Clinical Studies in Coronary Artery Disease

Trial	Therapeutic (Target) Application	Therapeutic Agent	Administration	Control Treatment	n	Primary Endpoint	Results
<b>KAT</b> (Phase 2)	Therapeutic angiogenesis in CAD (CCS II-III)	AdVEGF <sub>165</sub> or plasmid / liposome VEGF <sub>165</sub>	Intracoronary injection at the angioplasty site	Ringer's lactate	103	Improved myocardial perfusion at 6 months	Positive (adenovirus group only)
<b>REVASC trial</b> (Phase 2)	Therapeutic angiogenesis in CAD (CCS II-IV)	AdVEGF <sub>121</sub>	Intracoronary injection via mini-thoracotomy	Best medical treatment (no placebo treatment)	67	Time to 1 mm ST-segment depression on ETT at 26 weeks	Positive
<b>Euroinject-One trial</b> (Phase 2)	Therapeutic angiogenesis in CAD (CCS III-IV)	Naked VEGF <sub>165</sub> Plasmid	Percutaneous Intramyocardial injections	Placebo plasmid	74	Improved myocardial perfusion at 3 months	Negative
<b>Genesis</b> (Phase 2)	Therapeutic angiogenesis in CAD (CCS III-IV)	Naked VEGF-2 (VEGF-C) Plasmid	Percutaneous Intramyocardial injections	Vehicle	295 (404 planned)	ETT at 3 months	Stopped at interim analysis
<b>NOVA</b> (Phase 2)	Therapeutic angiogenesis in CAD (CCS II-IV)	AdVEGF <sub>121</sub>	Percutaneous Intracoronary injection	Vehicle	129 (planned)	ETT at 26 weeks	Stopped
<b>Northern</b> (Phase 2/3)	Therapeutic angiogenesis in CAD (CCS II-IV)	AdVEGF <sub>121</sub>	Percutaneous Intramyocardial Injections	Vehicle	120 (planned)	Change in myocardial perfusion in stress/rest at 12 weeks	Ongoing (not recruiting)

# State of the Therapeutic Angiogenesis Field

*While early Phase I clinical studies achieved promising results with growth factors administered as recombinant proteins or as single-agent gene therapies, more rigorous phase II and III clinical trials have come up with disappointing results so far.”*

*“... successful navigation through Phase II and III clinical trials will require an iterative exchange between clinical and preclinical experts.”*

*Gupta et al. Human Studies of Angiogenic Gene Therapy, Circ. Res. 105: 724-736, 2009*

# Complex Biology of Angiogenesis / Arteriogenesis

*“It seems likely that combinations of angiogenic factors, or single factors (e.g. HIF-1a, Sonic Hedgehog) that activate numerous angiogenic pathways (“master switches”) are required...”*

*Gupta R, Tongers J, Losordo DW: Human Studies of Angiogenic Gene Therapy, Circ. Res. 105: 724-736, 2009*

# Complex Biology of Angiogenesis / Arteriogenesis

***“... simply augmenting a single growth factor may not be sufficient, and “dumping” many different growth factors at the same time may not lead to optimal response either.” “One solution maybe a gene that acts as a master switch to start the well-timed cascade of events.”***

*Teng CJ, Lachapelle K. Reappraisal of recent clinical trials of angiogenic therapy in myocardial ischemia. Asian Cardiovasc Thorac Annals 13: 90-97, 2005*

# Lessons from Generx (Ad5FGF4) Development

# AGENT Studies Overview

	AGENT-1 Phase 1/2	AGENT-2 Phase 2	AGENT-3 Phase 2/3	AGENT-4 Phase 2/3
Enrolled (Placebo/Active)	79 (19/60)	52 (17/35)	416 (139/277)	116 (38/78)
Doses (vp)	5 Doses 3.2 x 10 <sup>8</sup> to 3.2 x 10 <sup>10</sup>	10 <sup>10</sup>	10 <sup>9</sup> , 10 <sup>10</sup>	10 <sup>9</sup> , 10 <sup>10</sup>
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**

# Potential Cause(s) of “Failure” of AGENT-3 and -4

- 1. Principle is flawed (single GF)**
- 2. Insufficient vector delivery to target sites**
- 3. Inappropriate clinical end-point(s) chosen**
- 4. Insufficient therapeutic effect/benefit**

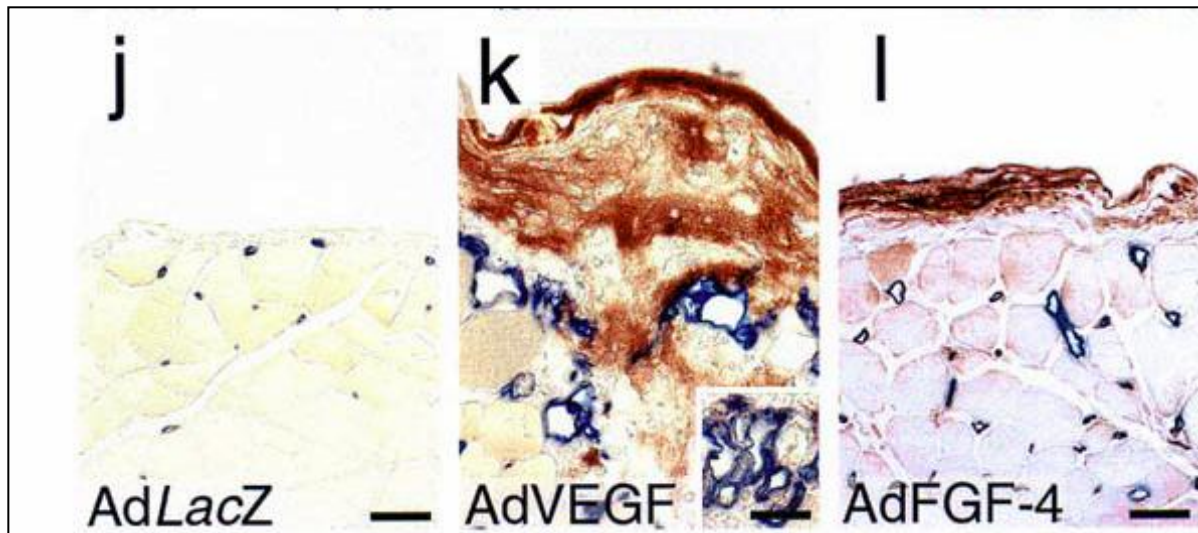
# **Preclinical Lesson #1:**

**FGF4 upregulates  
several angiogenic  
factors**

# Experimental Proof that Ad5FGF-4 Up-regulates Endogenous VEGF and Other Angiogenic Factors

1. Rissanen TT, et al.(2003): FGF-4 up-regulates VEGF and induces vascular permeability, angiogenesis and arteriogenesis in a rabbit hind limb ischemia model
2. Induction of VEGF (and other factors,e.g. NO) by FGF-4 has been documented by others (e.g. Dell'Era et al., 2001; Murphy et al., 2001; Deroanne et al., 1997)

# Upregulation of Endogenous VEGF by Ad5FGF-4 in Rabbit Hindlimb



# **Preclinical Lesson #2**

**Combination of Several Factors Are Needed For Effective Intracoronary Ad5 Vector Delivery to the Heart**

# Intracoronary Ad5Luc Transfection Efficiency in Pig Heart In Situ

<u>Condition</u>	<u>Luc Activity (pg/g)</u>
• Normal	0
• Normal+SNP(i.c.)	0.2+/-0.2
• 75 min occlusion/reperfusion	90+/-27*
• Single 3 min Occlusion	0.6+/-0.6
• Double 3 min Occlusion (infusion during 2 <sup>nd</sup> occl)	36+/-28
• Double 3 min Occlusion+NTG(ic)	82+/-39 *

# Combination of Several Factors Required for Effective Intracoronary Ad5 Delivery to the Heart

- Induced Transient Ischemia
- Prolonged dwell (“residence”) time
- Increase of Capillary Permeability (NO-donor)

# **Clinical Lessons from the AGENT Trials**

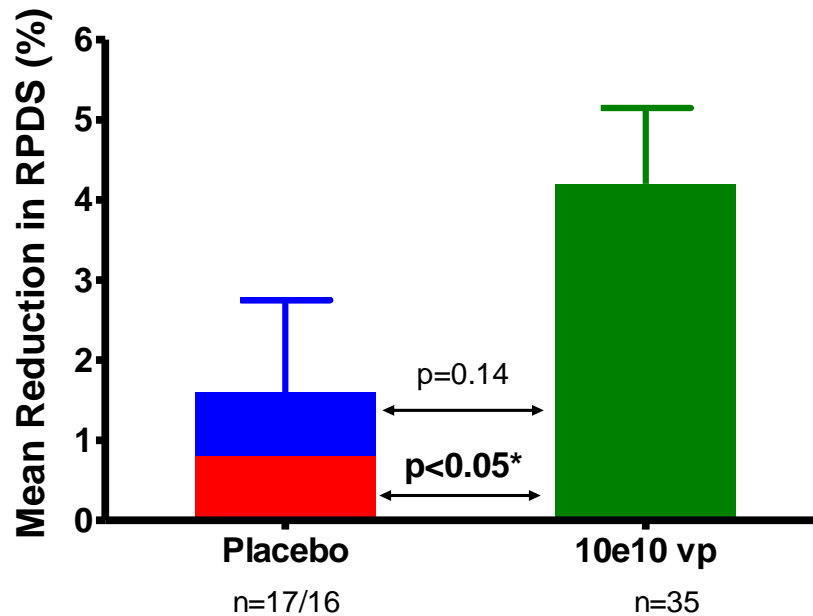
- 1. Primary Clinical End-Point**
- 2. Target Patient Population**
- 3. Extent of Therapeutic Effect**

# **AGENT-2 Study**

**Collateral Flow (Myocardial Perfusion)  
is the Most Relevant and Objective  
Clinical Endpoint**

# AGENT-2: Primary Endpoint

## Change in Reversible Perfusion Defect 8 Weeks




\* Excludes one extreme placebo outlier

# Therapeutic Effect: Comparison of SPECT Results to Revascularization and Medical Therapy

Parameter	Coronary Revascularization	Medical Therapy	Generx (AGENT-2)	
			Placebo	1x10 <sup>10</sup> vp
Number of Patients	83	206	16	35
Age	66±11	68±10	57±9	59±8
Stress defect extent (%)	18±11	16±10	20±8	20±9
Reduction of reversible defect (%)	-5±12	-0.8±7	-0.8±6	-4±6

From Berman DS, et al.  
*J of Nuclear Cardiol*, 2001; 4:428-437



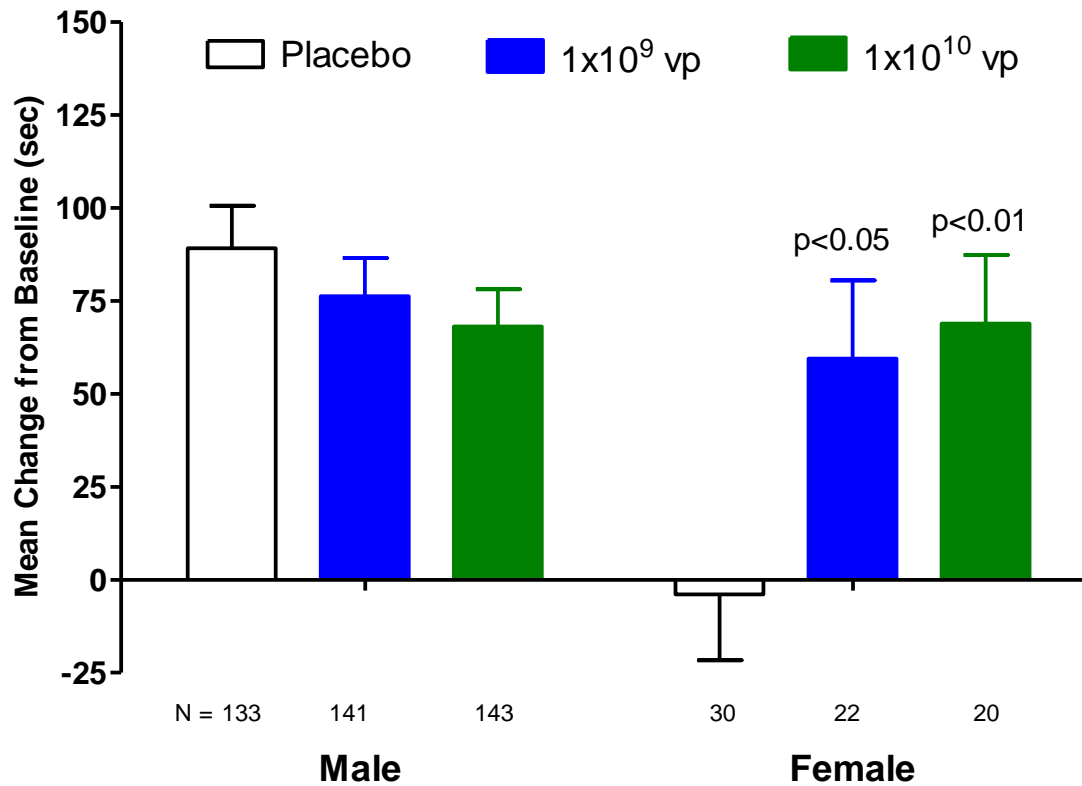


**AGENT-3 & AGENT-4  
Clinical Trials  
Primary End Point: ETT**

**In pre-specified subpopulations, patients with severe disease and limited exercise capacity, Ad5FGF4 had significant effect on ETT**

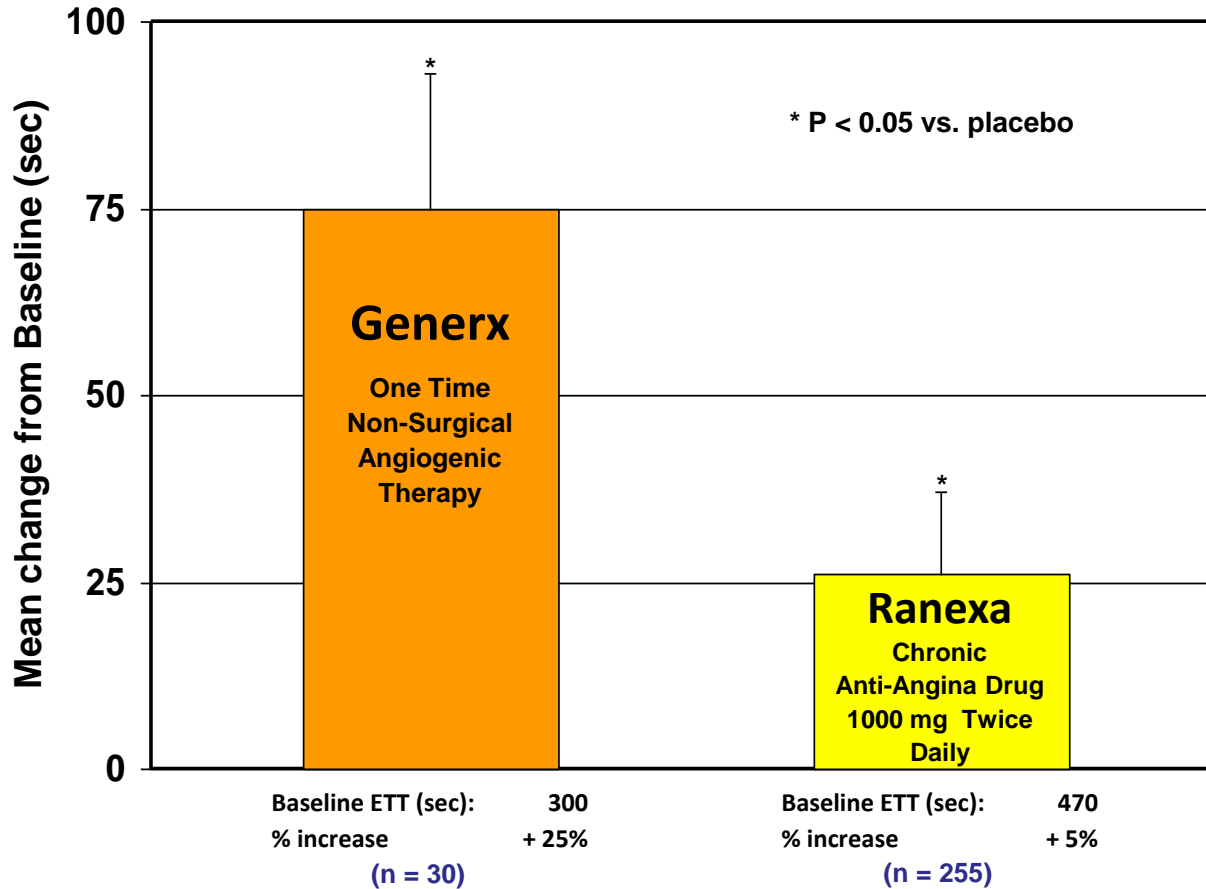
# AGENT-3: Prespecified Subgroup Analysis

**Figure 2**  
**Change in Total Exercise Time at Week 12 by Gender**



# Effect of Chronic Angina Treatment with Ranexa and Single Intracoronary Administration of Generx (Ad5FGF-4) on ETT Duration at 12 Weeks

(Difference from Placebo)



# Summary of Lessons Learned

1. Well developed collateral network saves lives, providing the most convincing rationale for angiogenic therapy
2. Strong support for use of FGF-4 (as single GF)
3. Effective i.c. Ad5 delivery requires change of product infusion protocol
4. Primary clinical end-point should be change of myocardial perfusion (SPECT)
5. In “responsive” target population (severe disease, limited exercise capacity, >9% RPDS) the extent of therapeutic effect is acceptable

# The ASPIRE Trial

A randomized, controlled, parallel group, multicenter phase 3 study to evaluate the efficacy and safety of Ad5FGF-4 using SPECT myocardial perfusion imaging in patients with stable angina pectoris, conducted in Moscow (Russian Federation)

# Why Russia?

1. Cardiovascular morbidity and mortality are among the highest in the World
2. Limited availability of expensive revascularization procedures (PCI, CABG) across broad patient population
3. Moscow has a number of large, well-established cardiology centers
4. More available patients for enrollment

# Change (vs. AGENT-3 and -4) #1: Dose of Ad5FGF4

- AGENT-1:  $3 \times 10^8$ - $3 \times 10^{10}$  vp
- AGENT-2:  $10^{10}$  vp
- AGENT-3 & -4:  $10^9$  and  $10^{10}$  vp
  
- **ASPIRE:**  $3 \times 10^{10}$  vp

## **Change #2: Patient Population**

**Patients with myocardial ischemia, diagnosed with stable angina pectoris, who are symptomatic despite optimal medical therapy and who have a reversible perfusion defect size of > 9% by dipyridamole SPECT-MIBI**

# Treatment Groups

The study will enroll 100 patients in the following treatment groups in a 1:1 ratio:

Group A: 3x10<sup>10</sup> vp of Ad5FGF-4 and standard-of-care angina medication

Group B: Standard-of-care angina medication

## **Change #3: Primary Endpoint**

**The change in Reversible Perfusion Defect Size (RPDS) as measured by dipyridamole stress single-photon emission computer tomography (SPECT) with technetium-99m sestamibi (MIBI) from Baseline to Month 2**

# Secondary Endpoints

- ◆ Change in patient functional status using CCS angina class at Month 2
- ◆ Change in angina frequency and nitroglycerin use at Month 2
- ◆ Change in quality of life assessed by the Seattle Angina Questionnaire at Month 2
- ◆ Safety of Ad5FGF-4 as assessed by AEs and clinical laboratory testing through Month 2
- ◆ Long-term safety as assessed by SAEs at Month 12

# Change #4: Product Administration

- ◆ Patients randomized to Group A will be scheduled for cardiac catheterization and study product administration
- ◆ Patients will receive Ad5FGF-4 by intracoronary infusion with the dose ( $3 \times 10^{10}$  vp) divided and selectively infused into all patent major coronary conduits (e.g. LAD, LCX, RCA and bypass grafts) combined with balloon occlusion

# Change #4: Product Administration

The *infusion protocol* will be as follows:

1. Placement of a balloon angioplasty catheter in the proximal coronary artery
2. Balloon inflation to 1 atm to occlude the artery for 2 minutes, or until evidence of severe ischemia
3. Five minutes of recovery: after 2 minutes of recovery infusion of 200 ug of NTG into the same artery

## Infusion Protocol (Cont.)

4. Second balloon inflation for 3 minutes as tolerated
5. Infusion of study product through distal lumen during second balloon occlusion at 1.5 ml/min followed by 2 ml flush
6. Repeat procedure for each patent major coronary artery or graft

# Status

- ◆ **Ministry of Health of the Russian Federation Approval of Protocol/Trial**
- ◆ **Study Start: 1Q 2012**

# Conclusions

## Key Insights and Lessons Learned

- **Collateral vessels are cardio-protective and save lives (Meier et al., Circulation 116:975-83, 2007)**
- **Ischemia is an important and perhaps essential element of successful angiogenic therapy. We are pioneering the use of induced transient ischemia during gene delivery**
- **Disease modifying collateral vessel formation is directly measured by SPECT (perfusion), compared to traditional indirect angina pain-based measures, such as ETT, that can be masked by a multitude of commonly used drugs ( NSAIDs, anti-depressants, etc.)**