**GENERX**<sup>®</sup>

#### Investor Presentation



DNA-Based Non-Surgical Angiogenic Therapy

# Generx®

(alferminogene tadenovec)

# Angiogenic Therapy

Regenerative Medicine for Interventional Cardiology

#### **Forward Looking Statements**

This presentation may contain forward-looking statements, including comments concerning clinical trials and product development programs, evaluation of potential opportunities, the level of corporate expenditures, the assessment of Cardium's technology by potential corporate partners, capital market conditions, timing of events, cash consumption and other subjects. Actual results could differ materially from these forward-looking statements for many reasons, including the risks described under "Risk Factors" in the Company's Annual Report on Form 10-K and Quarterly Reports on Form 10-Q as filed with the Securities and Exchange Commission. No guarantee about future results, performance or achievements can be made. Neither Cardium nor its agents intend to update any of the forward-looking statements after the date of this presentation to conform them to actual results or to changes in expectations.

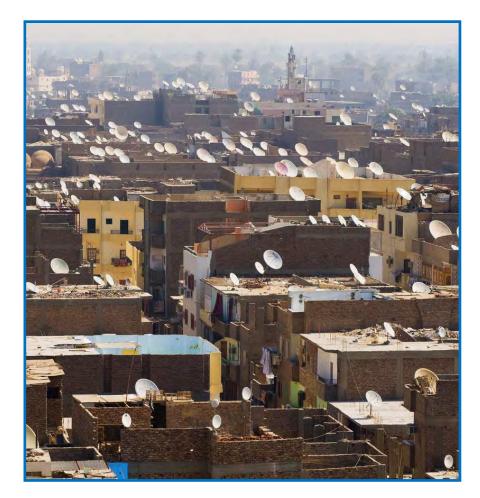


## Scientific Overview and Therapeutic Rationale DNA-Based Cardiovascular Therapeutics

- New regenerative medicine biological tools for interventional cardiology
- Leverages the healing power of cardiac plasticity
- Proprietary, catheterbased intracoronary delivery approach during an angiographic procedure
- One-time non-surgical treatment
- DNA transgene delivery and CAR receptor-based preferential cardiac uptake



- Ischemic injury (coronary heart disease) is a required precursor for effective growth factor DNA-based therapy
- Designed to stimulate microvascular cardiac angiogenesis
- Driven by upstream regulatory gene that stimulates a cascade of other important growth factors
- First DNA-based biologic to advance to U.S. FDA Phase 3 (with fast track status) and Registration / Phase 3 Study in Russia





Developing new and innovative, cost-effective advanced care for coronary heart disease patients in international markets



Generx Cardio Chant

# Generx<sup>®</sup> Highlights

- Generx [Ad5FGF-4] represents a new therapeutic class of regenerative medicine DNA-based biologics for interventional cardiology that is being designed to stimulate the natural growth of microvascular circulation for the treatment of patients with myocardial ischemia due to advanced coronary disease. Generx is administered one-time, using a cardiac catheter.
- Generx is being currently developed, in markets outside the U.S., as treatment alternative for patients who may <u>not</u> have access to costly and invasive advanced mechanical revascularization procedures, including coronary artery bypass surgery and angioplasty/stents, or may no longer be optimal candidates for these procedures.
- Ad5FGF-4 has been evaluated in four clinical studies in North America and Western Europe at over 100 medical centers with over 650 patients participating in these studies. Data from the clinical studies have been published in leading peer reviewed medical journals.
  - The product appears safe and capable of improving microvascular circulation in certain patients, as measured by SPECT imaging, and improvements using standard ETT assessments.

# Generx<sup>®</sup> Highlights

- An independent 10-year clinical study (n=845) by Swiss researchers, published in the American Heart Association's journal Circulation, have reported that patients with high levels of collateral circulation in the heart have a statistically significant mortality advantage when compared to patients with low collateral flow.
- Generx was cleared by the FDA to initiate the AWARE Phase 3 clinical study (with Fast Track status) for certain refractory patients. Ad5FGF-4 is the only DNA-based cardiovascular biologic to be cleared for Phase 3 clinical study by the FDA.
  - The AWARE clinical trial was inactivated by Cardium based on economic considerations due to the patient recruitment challenges for a small targeted population group in the U.S. where by-pass surgery and angioplasty are commonly available to patients of all ages.
- Generx will be evaluated in a Phase 3 / registration study (the Aspire Study) for 100 patients with advanced coronary artery disease at up to six major medical centers in the Russian Federation in connection with a commercialization plan covering the marketing and sale of Generx in Russia. Ad5FGF-4 will be marketed and sold in Russia under the trade name "Cardionovo."

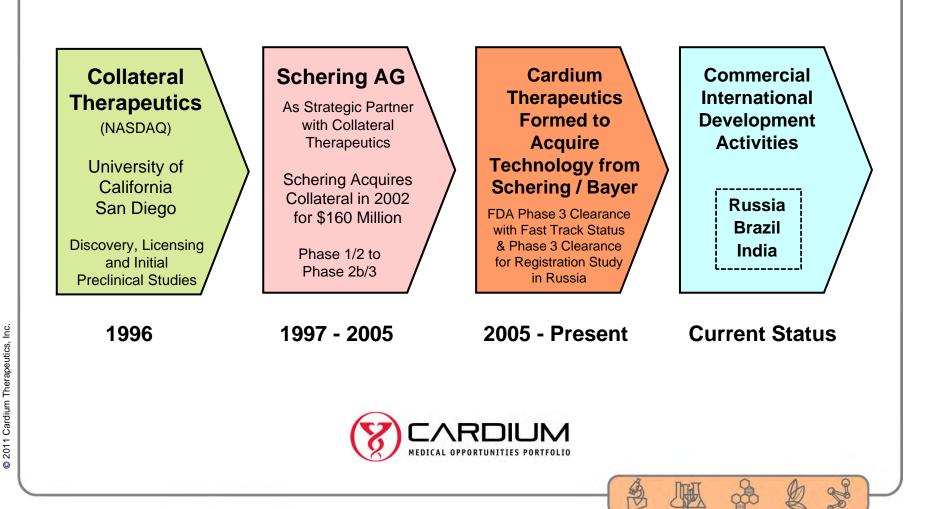


# Generx<sup>®</sup> Highlights

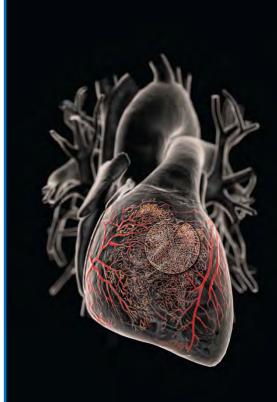
- Recent discoveries from Cardium-sponsored preclinical studies at Emory University showed that induced transient ischemia (i.e. balloon catheterbased occlusion/ reperfusion as in an ordinary angioplasty, but at lower pressure) substantially increases Generx's DNA vector's transfection efficiency to heart muscle cells. These new findings offer the opportunity to further enhance angiogenic response and lower response variability in patients.
  - These findings have now been integrated into the Russian-based ASPIRE clinical study protocol.
- A senior group of current Cardium physicians and business executives have worked on the Generx research and development effort from the initial development (1996) to the present.
- During the Generx development cycle, over \$250 million has been invested in the product formulation, manufacturing and clinical study by Collateral, Schering and Cardium.
- As a DNA-based bio-reactor manufactured product, Generx is projected to have favorable gross margins and offers the potential to generate substantial revenue in large markets with coronary artery disease.

© 2011 Cardium Therapeutics, Inc.

## Generx<sup>®</sup>: Historical Perspective



### **Generx® Late-Stage Clinical Development**





#### **Angiogenic Therapy:**

Leading the Revolution into New Frontiers of Cardiovascular Medicine

#### **GENERX**<sup>®</sup>

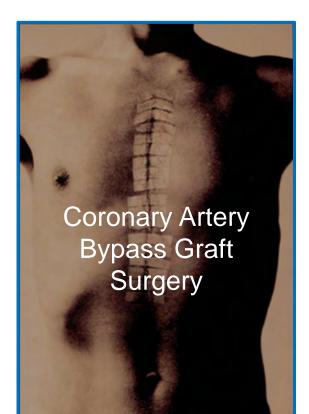


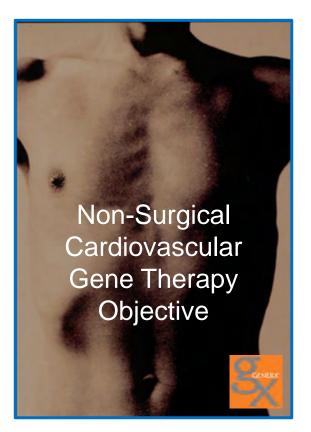
You Tube Cardio-Chant New Global Pathways

> NYSE Amex: CXM www.cardiumthx.com

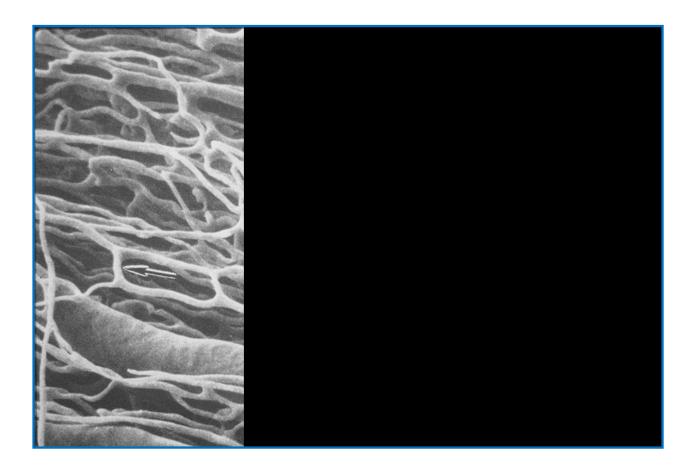


#### Generx<sup>®</sup> Revolutionary Alternative for Heart Disease Patients Without Access to Advanced Surgical Care





# **Cardiovascular Angiogenesis**





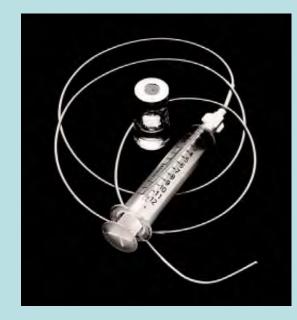
J.

(b)

**B** 

POWERPOINT PRESENTATION > 11

# GENERX<sup>™</sup> [Ad5FGF-4]



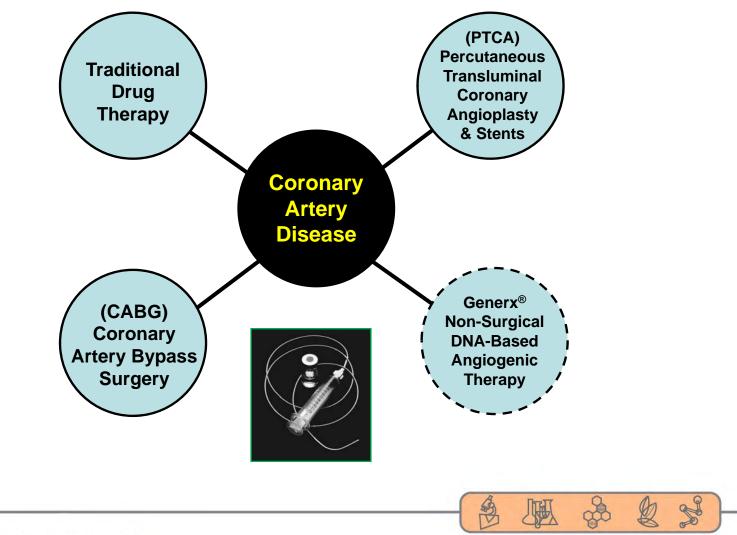
Generx [Ad5FGF-4] represents a new regenerative medicine therapeutic class of DNA-based biologics that is being developed for interventional cardiology that is designed to promote a disease-modifying physiological response which stimulates the growth of microvascular circulation based on the one-time administration, using a standard cardiac catheter, as a treatment for patients with advanced coronary artery disease.

Generx is currently being developed for international markets outside the United States as a treatment alternative for patients who may not have access to costly and invasive advanced care revascularization procedures, including coronary artery bypass surgery and angioplasty/stents, or may not be optimal candidates for these procedures.

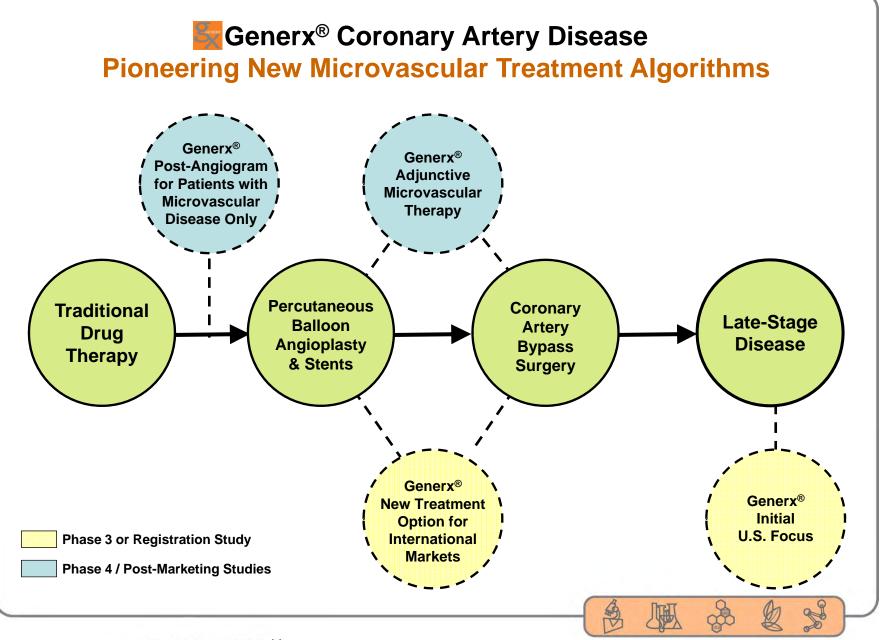


© 2011 Cardium Therapeutics, Inc.

#### **Proposed Therapeutic Positioning: Generx<sup>®</sup> / Cardionovo**



POWERPOINT PRESENTATION > 13



#### Generx<sup>®</sup> [Ad5FGF-4] Product Focus for Russian Federation

Generx is being developed to promote the growth of microvascular circulation in the heart. It is administered by a cardiologist through a cardiac catheter during an outpatient procedure.

The product is a new treatment option for <u>patients with myocardial ischemia due to advanced</u> <u>coronary artery disease that have limited access to advanced medical care</u> including coronary angioplasty and stents as well as coronary artery by-pass surgery or patients who are not optimal candidates for those procedures.

A long-term study (n = 845) has shown that patients with a higher collateral blood flow index may have an improved mortality benefit when compared to patients with a relatively lower collateral blood flow index.

Selected Health Statistics Benchmarks				
Demographic Metrics	United States	Russian Federation	Variance	
Average Life Expectancy - Males	75	<b>57</b> <sup>1</sup>	- 24%	
Cardiovascular Death Rates per 100,000 (Ages 35-74) – <b>Males</b> ²	283	1,555	5.5X	
Cardiovascular Death Rates per 100,000 (Ages 35-74) – <b>Females</b> ²	145	659	4.5X	

<sup>1</sup>R I A Novosti, Feb. 2, 2010. <sup>2</sup>American Heart Association 2009.

POWERPOINT PRESENTATION > 15

© 2011 Cardium Therapeutics, Inc.

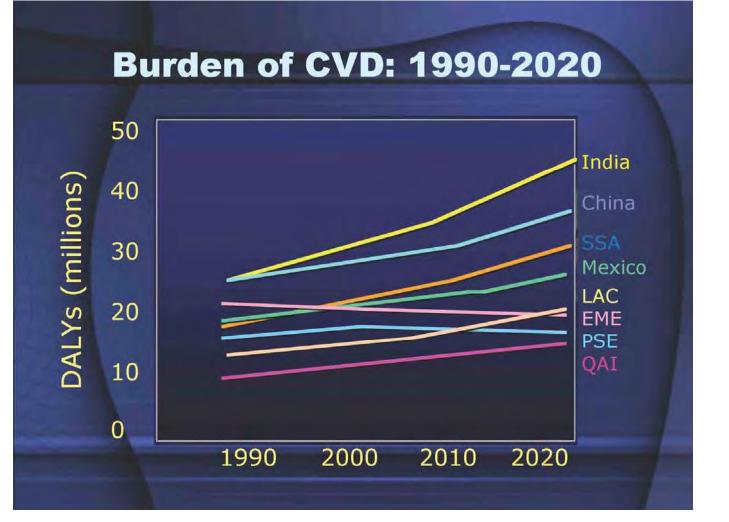
y

# Why Generx<sup>®</sup> for India? 64.0 Million Indians are Projected to have Coronary Artery Disease by 2015

Generx [Ad5FGF-4]	Coronary Anatomy and Cardiovascular Disease Issues in India <sup>1</sup>
<ul> <li>Simpler administration and cost effective treatment compared to bypass and stents</li> </ul>	<ul> <li>Involvement at younger age</li> </ul>
<ul> <li>First non-surgical revascularization therapy</li> </ul>	Smaller coronary arteries
<ul> <li>Stimulates the growth of microvascular circulation in patients with coronary artery disease</li> </ul>	<ul> <li>Diffuse distal disease</li> </ul>
<ul> <li>Women and patients with more advanced disease demonstrated significant treatment effect based on distal disease</li> </ul>	<ul> <li>Multi-vessel disease</li> </ul>
<ul> <li>New "induced transient ischemia" techniques may reduce treatment variability in earlier stage patients</li> </ul>	<ul> <li>Higher incidence in women</li> </ul>
<sup>1</sup> Source: Cardiovascular Disease Trends in India Naresh Terhan, Escorts Heart Institute and Research Centre	

#### CONFIDENTIAL

y



Source: Cardiovascular Disease Trends in India Naresh Terhan, Escorts Heart Institute and Research Centre

# Generx<sup>®</sup> Potential Economic Opportunity

	Target Revenue per Dose				
Unit Volume Opportunity per Economic Region	Level I \$2,000 / dose	Level II \$3,000 / dose	Level III \$4,000 / dose		
50,000 doses	\$100 Million	\$150 Million	\$200 Million		
100,000 doses	\$200 Million	\$300 Million	\$400 Million		
150,000 doses	\$300 Million	\$450 Million	\$600 Million		
200,000 doses	\$400 Million	\$600 Million	\$800 Million		

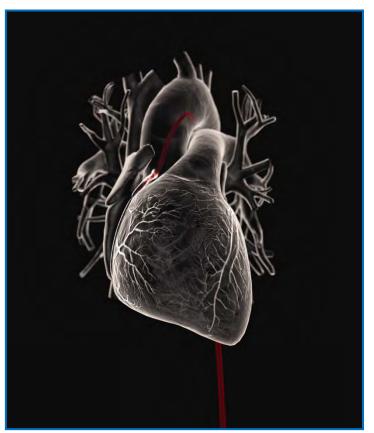
Y

Ø

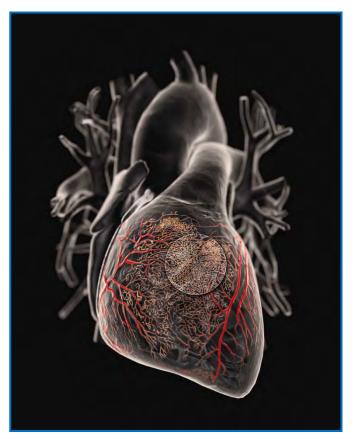
and the



#### Catheter-Based Intracoronary Delivery

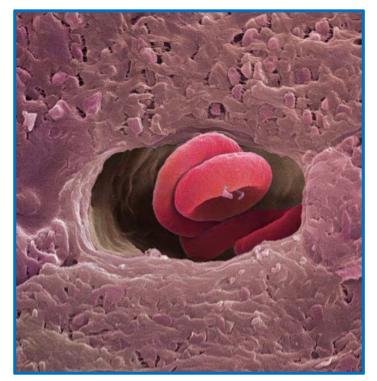


#### Focus on Enhancing Angiogenic Microvascular Circulation





# Generx<sup>®</sup> Understanding the Beauty of Cardiac Physiology



Colored magnification: x3000 at 6x7cm size.



#### Microvascular Pathways

When infused into the coronary arteries using a non-surgical cardiac catheter, the Generx product candidate travels through the coronary microvascular circulation into the small caliber capillaries where it is believed to be taken up by the myocardium.



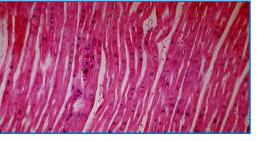
## The Therapeutic Process of Cardiac Microvascular Angiogenesis

Generx has been evaluated in studies of over 650 patients (including 450 Generx-treated patients) in four multi-center, double-blind, placebo-controlled clinical studies at 100 medical centers. Generx is the most clinically advanced DNA-based cardiovascular angiogenic growth factor therapeutic in the world.

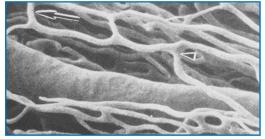
#### **One-Time Treatment**



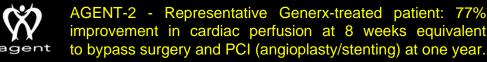
Generx [Ad5FGF-4] (alferminogene tadenovec)

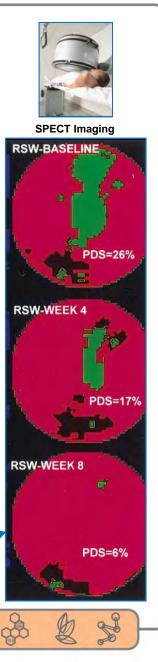


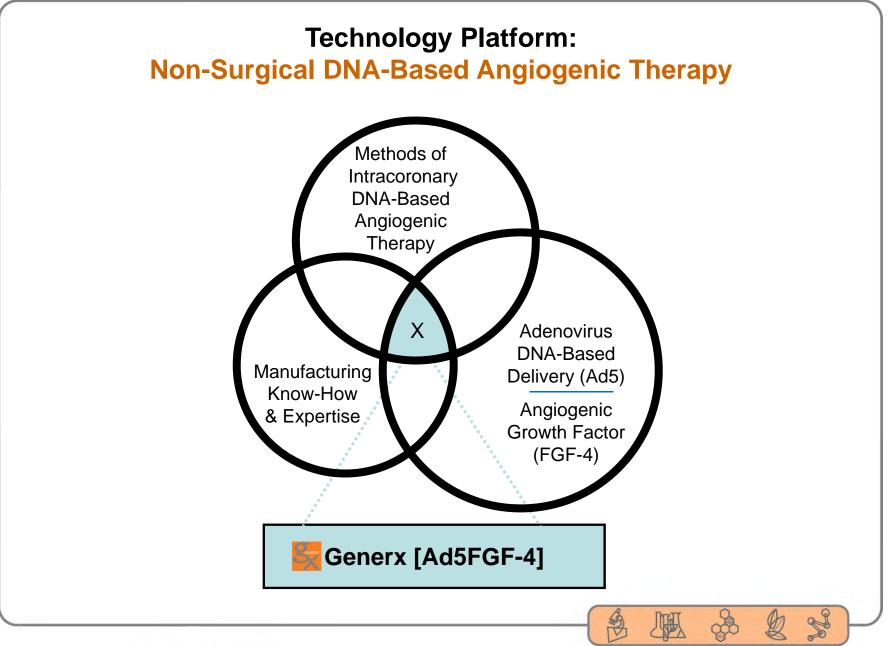
**DNA-Based Delivery** 



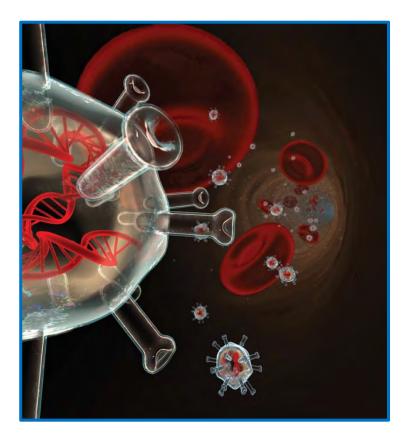
Angiogenic Response







# Generx<sup>®</sup> Pioneering DNA-Based Regenerative Medicine

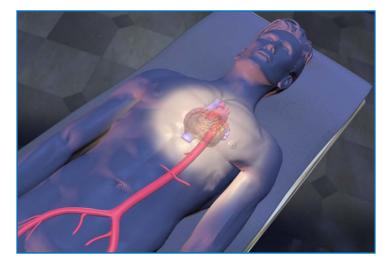




DNA-based therapy is designed to enable a patient's own cells to produce a therapeutic protein directly where it is needed in the body. The Generx product candidate is designed to induce localized angiogenic growth factor production following its onetime delivery to stimulate the growth of microvascular circulation.



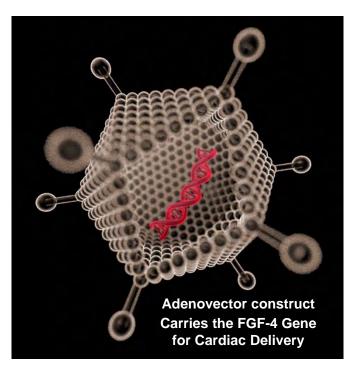
# Generx [Ad5FGF-4] Proprietary Intracoronary Administration of DNA-Based Cardiovascular Growth Factor Therapeutic





- Non-surgical delivery by intracoronary administration by interventional cardiologist during an angiogram procedure
- Utilizes standard balloon catheter which can be easily integrated into diagnostic angiogram procedures or with other percutaneous coronary interventions
- New induced transient ischemia / reperfusion techniques are designed to enhance DNA uptake and expression in the heart
- 40% administered to right coronary circulation and 60% to left coronary circulation





Research Studies: Intracoronary Administration	Coronary Extraction Rate
Pre-Clinical Porcine Study Giordano et al. <i>Nat Med</i> 1996;2:(5):534	98% (mean)
Phase 1/2 Clinical Study – AGENT Trial Grines et al. <i>Circulation</i> 2002;105:1291	87% (median)

## DNA-Based Adenovector Cassette

- Demonstrated CV Safety Database with FDA
- Established FDA
   Manufacturing Standards
- High Cardiac Transfection Levels due to a Binding Affinity with CAR Receptors and Enhanced by Ischemia
- Transient Expression -Does Not Integrate into Host Genome
- Manufacturing in High Titer
- Easily Manipulated
- Relatively Low Cytotoxity
- Mutagenesis Improbable
- Very Favorable Manufacturing Cost

# Generx<sup>®</sup> FGF-4 Gene

-	Regulates angiogenesis
	Signal peptide – secreted FGF protein
<b>√</b>	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
	Appears to require ischemia induced co-factors to augment the angiogenesis process



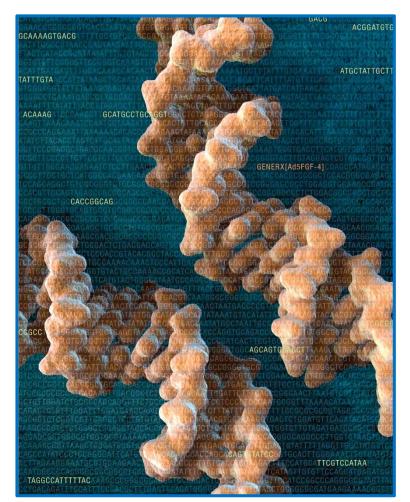
y

Ø

a

W

## Generx<sup>®</sup> Leveraging the Power of Biology

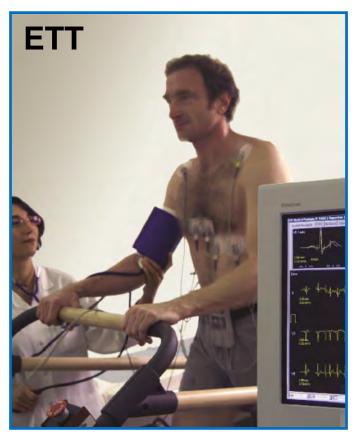




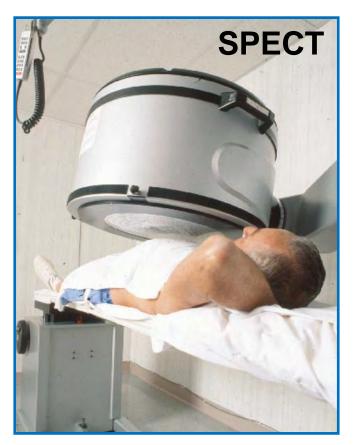
This illustration utilizes computer models of DNA-based on data generated by x-ray crystallography, a technique for determining the structure of a molecular sample, together with a portion of the DNA sequence of Generx (Ad5FGF-4), Cardium's lead clinical product candidate.

Digital illustration of DNA.

## Clinical Efficacy Measures

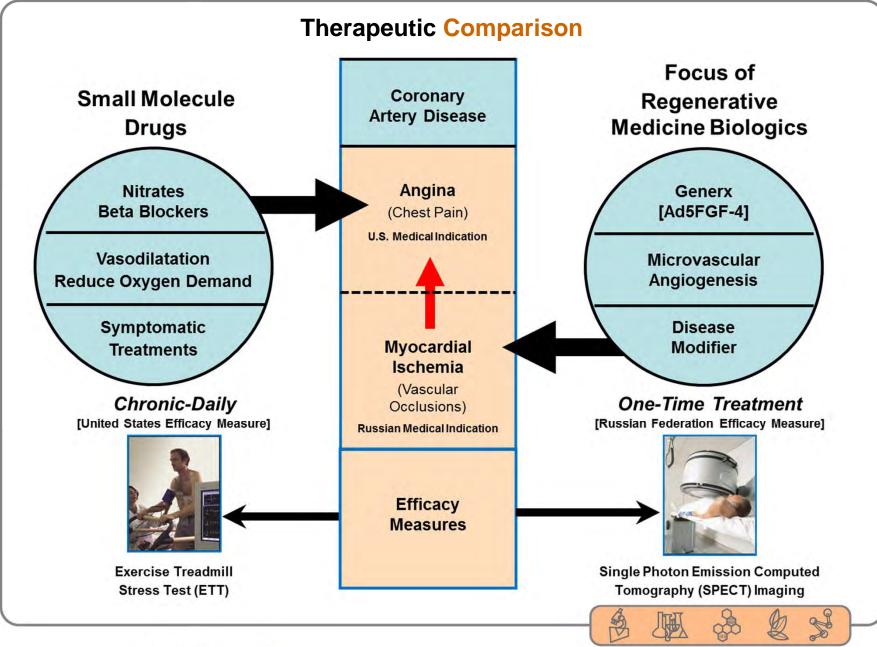


Exercise Treadmill Stress Test [United States Efficacy Measure]



Single Photon Emission Computed Tomography Stress Test [Russian Federation Efficacy Measure]

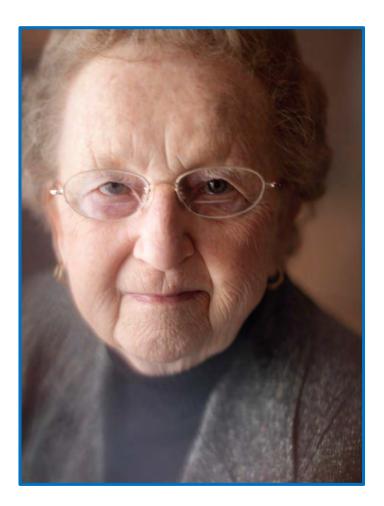




# Generx<sup>®</sup> [Ad5FGF-4] Clinical Studies

Year	Study Name	Region / County	Clinical Study Phase	Patient Status	Clinical Endpoint	Number Patients Recruited
1999	AGENT-1	U.S.	Phase 1/2 Dose finding & safety	Class 2 – 3 Angina	Exercise Treadmill Time	79
2001	AGENT-2	North America	Phase 2a Mechanism of Action Study	>9% Reversible Reperfusion Defect	SPECT Imaging	52
2004	AGENT-3	North America	Phase 2b/3	Class 2 – 4 Angina	Exercise Treadmill Time	300
2004	AGENT-4	Western Europe & South America	Phase 2b/3	Class 2 – 4 Angina	Exercise Treadmill Time	252
2008	AWARE	U.S.	Phase 3 (Fast Track Status)	Class 3 – 4 Angina	Exercise Treadmill Time (Time to ST Segment Depression)	U.S. Beta Tested
2011	ASPIRE	Russian Federation	Phase 3 Registration Study	>9% Reversible Perfusion Defect	SPECT Imaging	100*
				тс	DTAL	783
Preparing to	o intiate			(		3 8 3

#### Generx<sup>®</sup> Patient Pioneers





Marilyn L. was a trial participant in the AGENT-3 clinical trial. She received a one-time treatment of Generx, our DNA-based angiogenic product candidate for patients with recurrent angina due to coronary artery disease.

# **Generx<sup>®</sup>: Current Global Clinical Status**

Elements	U.S. Market (AWARE)	International Markets (Initially Russian Federation) (ASPIRE)
Product	<b>Generx<sup>®</sup> [Ad5FGF-4]</b> (alferminogene tadenovec)	<b>CardioNovo [Ad5FGF-4]</b> (alferminogene tadenovec)
Clinical Status	FDA Clearance Phase 3 (with Fast Track Status)	RHA Cleared Phase 3 / Registration Study
Clinical Study Population	300 Women Multi-Center, Randomized, Placebo- Controlled Patient Population	100 Men & Women Multi-Center, Randomized, Controlled Parallel-Group Patient Population
Proposed Medical Indication	Anti-Angina for Refractory Patients who are not Optimal Candidates for Angioplasty / Stents & Bypass Surgery	Myocardial Ischemia as a Treatment Option for Patients Considering Angioplasty / Stents & Bypass Surgery
Clinical Endpoint	Improvement in Exercise Time Based on Treadmill	Improvement in Reversible Perfusion Deficit Based on SPECT Imaging
Clinical Study Status	Currently Inactive	Preparing to Initiate

y

Ø

a

風

## Generx® **Key Peer-Reviewed Scientific & Medical Journals**

ARTICLES		Journal of the American Calager of Cardinage Translations 1997 © 2010 by the American Calager of Cardinage Translations 1998 Traditional by Tanonin Tan. doi:10.1097/077
Intracoronary gene transfer of fibroblast growth		CLINICAL RESEARCH Clin
ctor-5 increases blood flow and contractile function	Angiogenic Gene Therapy (AGENT) Trial in Patients	
in an ischemic region of the heart	With Stable Angina Pectoris	A Randomized, Double-Blind, Placebo-Controlled
0	Cindy L. Grines, MD, Matthew W. Wafkins, MD, Oreg Helmer, MD, William Penny, MD,	Trial of Ad5FGF-4 Gene Therapy and its Effect on
FRANK J. GROBINNO, PEIPE PING, M. DAN MCKEINAN, SHERO NOZAEL ANTHONY N. DIMANA,	Jeffrey Brisker, MD, Jonathan D, Marsur, MD, Andrew West, MD, Jeffery J, Rade, MD,	Myocardial Perfusion in Patients With Stable Angina
WOLIGANG H. DILIMANN, ODLE MATHEU-COTTILIO & H. KIIK HAMMOND	Pran Manon, MRCP, MSc., H. Kaik Hammond, MD, Robert L. Engler, MD	Cindy L. Grines, MD, FACC,* Matthew W. Watkins, MD, FACC,† John J. Mahmarian, MD, Ami E. Islandrian, MD, FACC,§ Jeffrey J. Rade, MD, FACC,J Pran Marrott, MRCP, MSC,
Department of Mullicine, Veterion's Afflin's Mullial Center-Son Diego and University of California, Son Diego,	Stolyround-The angiogenic response to myocardial schemis can be sugmented in scinal models by gote transfer with	Craig Pratt, MD, FACC, + Neal Kleiman, MD, FACC, + for the Angiogenic GENe Therapy (A)
111-4, 3150 La Julla Village Drive, San Diego, California 92163, USA Correspondence should be addressed to H.K.M.	the use of a replication defective adenovirus (Ad) commining a human fibroblait growth factor (FOF) gens. Methods and ReminThe physicitizes of the Angingenic OEEs Therapy (AOESET) will surve to excluse the outery and	Study Group Royal Oak, Michigan; Barlington, Vermont; Hunston, Texas; Birmingham, Alahama; Baltimore, Mary
	underthemic effects of 5 microding dores of AdS-FOH in patients with sugme and to relect potentially rule and effective from three parent moly. Severey was patient with themic molds argues Canadian Cardiovaceular factory	Montville, New Jenny
Increased coronary blood vessel development could potentially benefit patients with lischemic heart disease. In a model of stress-induced myocardial ischemia, intracoronary injection of a	(htt: 2 or 3 underward double-bland randominiation (13) to placebo (ht=10) of AdS-FOIR (ht=60). Safety evaluation	<b>OBJECTIVES</b> The primary objective of this study was to determine whether intracotomary administration of the ademviral gene for fibroblast growth factor (AdSPGF-6) can improve myocardial
recombinant adenovirus expressing human fibroblast growth factor.5 (FGF-3) resulted in messenger RNA and protein expression of the transferred gene. Two weeks after gene	were performed at each wint and some ne medmalitesting (ETT) at baseline and at 4 and 12 weaks. Engis intraconnersy edministration of AdS-FOF4 seems its be safe and we litelar det with no immediate affrates evolus. Forer of <1-day	perfusion compared with placebo.
transfer, regional abnormalities in stress-induced function and blood flow were improved,	duration occurred in 3 particular in the highest door group. Transient, stymptomatic elevations in liter enzyme ( occurred	BACKERDOUND Animal studies and observational clinical studies have shown improvement in perfasion of the ischemic myscardinam using genes encoding angiogenic growth factors; however, randomized
effects that persisted for 12 weeks. Improved blood flow and function were associated with evidence of angiogenesis. This report documents, for the first time, successful amelioration of	in 2 patients in lower-dose groups. Serious adverse events during following (mean, 311 days) were not different betree an placebo and AdS POP4. Overall, patients who received AdS POP4 model to have greater improvements in contrilev	double blind data in humans are lacking. MCIMODS We performed a randomized, double-blind, placebo controlled trial of intracoronary injection
abnormalities in myocardial blood flow and function following in vivo gene transfer.	time at 4 weaks (13 vertue 0.7 minutes, P=NS, n=79). A protocol-specified, subgroup analysis showed the greatest improvement in patients with baseline ETT s10 minutes (1.6 versus 0.6 minutes, P=001, n=50).	of 10 <sup>10</sup> admostral particles containing a gene encoding throblast growth factor (AdD/GF- to determine the effect on mycosofial perfusion. Fifty-two patients with stabile augins and
The state of the second second second states and a second second second second second second second second second	Conchators-Results show evidence of feverable existence affects with Add-FOF4 compared with phoebo, and a	reversible ischemia comprising >9% of the left ventricle on admosine single-photon emission computed transportation (SPECT) impaired parts and busined to use of the second
roteins of the fibroblast growth factor (PGF) family are po- FGF-5 was effective in treating myocardial lichensia: regional trogens that regulate anglogenesis during growth and constructile function and perfusion (assessed before and after	appears to be safe. Augmonate gene transfer with Ad5-F098 shows promise as a new therspecial approach to the meaness of angua pectaric (Oraultation M62)166 1291-1297)	placebo (n = 17). Clinical follow-up was performed, and 51 (98%) patients underwent ( second adenosine SPECT scen after 8 works.
ement. These proteins may also stimulate angiogenesis in simals <sup>14</sup> . The appeal of stimulating angiogenesis to improve ducted without knowledge of which gene the animals had	Key Words angins a anging motion a gran that gay a collateral sirvalities	RESULTS Overall (n = 52), the mean total perfusion defect size at bandine was 32.4% of the left verticle, with 20% revealed indexists and 12.9% over. At right works, AdSTGF: Linjoritar
dai blood flow has led to the delivery of these proteins to received (FGF-5 versus lac2), neary circulation in animal models of myosardial ischemia		resulted in a significant reduction of inchessic defect size (4.2% absolute, 22% relative: p <
action". A prerequisite for achieving cardiac angiogenesis Regional contractile function and blood flow. Thirty-eight	A noise sectors enced by convery ency draws in a possible (~ Seven) choical thick have been conducted	0.001) and placebo-treated patients had no improvement ( $p = 0.32$ ). Although the change in reversible perfasion defect size between AdSPGF-4 and placebo was not significant (4.2% vs
hese proteins, however, has been the need for repeated infu- r injection of the protein coincident with coronary artery aboved impaired wall thickening during atrial electrical stim-	Amujar cause of disability worldwale, affecting memby? that attempted to relieve angina by increasing coronary	1.6%, $p = 0.10$ , when a single outlier was excluded a significant difference was observed (4.2% vs. 0.9%, $p < 0.05$ ). AdSPCT-4 was well tolerated and did not result in any permanent
on. The application of protein-induced angiogenesis for the autation (pacing). Figs receiving lacZ showed a similar degree of pacing-induced dysfunction in the ischemic region before and	million people in the Unded Rules alors. Two general collisional formation. Despite early endosision, transmyo- approaches to the memory of angine have proven effective control have revescularization (TMSR) and interventiar	advene sepadar. CONCLUSIONS Intracoronary injection of Ad5FGF-4 showed an encouraging trend for improved anyocardia
comvents the need for continuous or repeated protein deliv- two weeks after gene transfer. In contrast, two weeks after FGF-	increducing symptoms and increasing electric treachall time : angiogenic protein growth factor therapy with back filter- drage and researchemistics by PTCA or CABO. In picture :	perfusion; however, further studies of thempeutic angiogenesis with AdSTGF-4 will be necessary. () Am Coll Cardiol 2003;42:1319–47) © 2003 by the American College o
s-yield gene transfer to the adult heart has recently been in the ischemic region during pacing (P < 0.0001; Fig. 1). Wall	with connery stary diverse, the body 'mattrid angiogenesis' factor' (VEOF)-165 have been medicative in placebo-	Cardiology Foundation
red using adenovirus vectors <sup>mat</sup> . Adenovirus-mediated thickening in the normally perfused region (the interventricu- nansier does not result in stable incorporation of the trans-	in response to repeated boars of myce with i indemia, can provide collateral bland flow to manche datal to state of angiogical prioritor may have been unsuccessful because	
nto the host genome so transgene expression is transient <sup>40</sup> . transfer (% wall thickening: loc2; pregene 53 ± 8%, post gene ver, for transfer (% wall thickening: loc2; pregene 59 ± 8%, post gene transfer	coronary tomover. In patients who remain outprimates, the initials arguingents response and correctly collideral forms	Myocardial inchemia is a leading cause of death and disabili- ity in the developed world. Established treatment for approaches to improve blood flow to the myo
anspene expression. If effective in achieving a therapeutic $59 \pm 6\%$ .	tim an independ to relieve an or induced inclumin. CAEO mended in angiographic evidence of anhanced	myocardial inchemia has to date consisted of revasculariza-focuated on the biology of enhancing gro
desirable. The demonstration that specific proteins can associated with improved function in the ischemic region was improved regional blood flow. Two weeks after lacZ gene transfer	Remittion of suggenerate prevents in attractive adds in collisions formation, however, effects on convise time tional or alamative approach for the meanward of coronary overs not evaluated <sup>2</sup> Marcover, direct injections into the	tion using either percutaneous or surgical techniques to improve blood supply to the myocardium, or pharmacother reports from uncontrolled pilot studies, two
e in the heart make the prospect of gene therapy for the ent of clinical invocardial ischemia promising. There was a persistent flow deficit in the lschemic region during pacing (Fig. 2). Animals receiving FGF-5 gene transfer, however,	attery discons Animal models of coronary story discore hour muscle by means of an open thoracotomy an epite	apy designed to limit myocadial oxygen demand. Many unds using the ungingenic proteins viscult
g an animal model of myocardial ischemia, we quantified showed homogeneous contrast enhancement in the two regions ree of stress-induced myocardial dysfunction and inade- two weeks later, indicating improved blood flow in the ischemic	have shown that enhancing coronary collater all committees in a more the	patients prove to be ineligible or refractory to the conven- tional therapies, and percutaneous or suggical sevenculariza- (PGF)-2 have reported to significant differen-
egional blood flow, and then performed gene transfer by region $(P = 0.0001)$ .		exercise time in patients with severe ischenic
rorsary injection of a recombinant adenovirus expressing To determine whether improved function and perfusion in the Two weeks later, stress-induced dysfunction and regional ischemic bed were long lasting, five animals were examined	Instant (Carlo B), 2011, and a main marine Danalos (1, 2011, margh ( 2002)). Yene Walan Marone Hayida, Davido Milako (C. J. A. Vaja) da Dyamara of Milatian, Caisariya et Vancen Deshapen (2012). Binara N. Kao (Thina Binara), (1) da Dyamara et Balazian, hain Biyaka Wanavay, Balama, 2013, S. Ja Barat Balazi Dana (2014), (2013) Dania ( Lancina Bandai), (2014) da Dyamara et Milatian (2014) da M. Lange Bandhara Igram,	From the "Separament of Medicine, Section of Cardinage, William Desenter Hospital, Repl Cak, Michigan (Deparament of Medicine, University of Version), be due to the short duration of effect of the prec
low were again measured. We tested the hypothesis that arsifer with $FGF-5$ would ameliorate regional myocardial persistent improvements in function ( $P = 0.005$ ; Fig. 1) and per-	Binasovic Bard China Hamagdor (202) in Department of Barketin, Islaw Boyleis University Indiners, Bitl C.S., P.A., Bower Bard Barketin Control Haw York, WYOR M. J. Barket Industry, Heardin, MY (202), and the Department of Helmin. We (Data Me). Energy Hawliness Agreem, J. M. Done, Cold (1997), H.S.R. 3, L.B.).	Busingina, Vennani, Educational in Modicina, Busina of Contrology, Dar No-modia Unapita, Federa Dalays of Modicia, Housiana, Tonas, Educationals of the overcome by administering the gene, with
ttle dysfunction by improving regional blood flow fusion (P=0.001; Fig. 2). h newly formed blood vessels.	(a) Days, Call (W.F. B.K.R., ALLE). Do Bannard and Bagher as founds of end courds for Calman Hampenio, ho (C.R.), a corporat of the total Da Bagher-part B.R. years on edited of CR bane parchiated to the end initiation of the total Da Bacallian 6 is fore Bacallian C Chained of Chained and a Daffer.	Modutov/toxin d'Cardelog, The University of Adverse in Envirghm, Envirghme, Adverse, Data Hopkin, Solemony, Mergiani, and Horize Lohom- ber Manuel. Manuel Royalin, Solemony, Mergiani, and Horize Lohom- previously shown that interaccountry adversits.
Angiogenesis. In addition to improved regional function and	Liveness of the temp processes of the can anisotrate in the ten to be added to	Theorem and the proof requests to a gass own over an own finding for gene encoding FGF-4 delivered using an ade
blood Bow, there was evidence for angiogenesis after FGF-8 gene measurements were used to assess whether gene transfer of transfer. First, its the initial animals studied, bromodeoxyutidine	E-mail apine (Freement of a Q 2011 Amazon Harr Avecasian Inc	ACENT-2. Increased treadmill exercise time by 1.5 min o Memory resets longer 12, 2022, sense manufig research May 2, 2022, 0.9 min in placebo-treated patients with stab
NATURE MEDICINE, VOLUME 2, NOVER 5, MAY 1996	Chemilation & credital feed Imp. Provide the lateral search and DOL 16 2012-012012 103999	support just 15, 201. An increase of 1 min compared with placebo
	1291	
Pre-Clinical	AGENT-1	AGENT-2

**Nature Medicine** 

Circulation (American Heart **Association Journal**)

Journal of American **College of Cardiology** 

y

Journal of the American College of Cardiology © 2007 by the American College of Cardiology Foundation Published by Eleving Inc.

Background

Val. 50, No. 11, 2007 18574 0715-1087071 11.00 doi:10.1016/j.uci.200100.010

#### Effects of Ad5FGF-4 in Patients With Angina

An Analysis of Pooled Data From the AGENT-3 and AGENT-4 Trials

Timothy D. Henry, MD, FACC,\* Cindy L. Grines, MD, FACC,\* Matthew W. Watkins, MD, FACC,‡ Nabil Dib, MD, FACC,§ Gerald Barbeau, MD, Randall Moreadith, MD, PHD,¶ Tony Andrasfay,¶ Robert L. Engler, MD¶#

Minucapolis, Minnesota; Royal Oak, Michigan; Burlington, Vermont; Phoenix, Arizonn; Sainte-Foy, Quebec, Canada; and San Diego, California

Objectives The goal of this study was to explore the effects of angiogenic gene therapy.

Precisical studies with intraccorcary soministration of AdSFGF4 (afterminogene tadeovec, Genero, Benero Bisciencia, Richmend, California) vaggested 8 could induce anglogismesia and privile a new clinical approach to the tratment of chronic angina pectore. Two preliminary critical triats provided evidence that it could improve exercise tradomili test (ETT) time and myscardial perfusion. The AdSM (Anglogenic GDNe Therapy)-5 and - 4 triats of a low and high blob of AdSFGF4 for chronic angina ware limitated in the U.S. and of her countries and enrolled 532 patients in a randomized, doubbe-blind, piacebo-controlled fashion. Both studies were halted when an interm analysis of the AGENT-3 triat indicated that the primary and point change from baseline in total ETT time at 12 weeks would not react significance.

Methods We performed a pooled data analysis from the 2 nearly identical triais to investigate possible treatment effects on primary and secondary and points in physicalities subgroups.

Results The effect of placedo was large and not offerent than sorier treatment in man, but the placedo effect in women was negligible and the treatment effect was significantly greater than placedo. We traind a significant, greater specific beneficial effect of ndSPLIP de total Eff. If time, time to a run Straegment depension, time to angen, and canolise darbiensould Society class in women. This is the first clinical réport of a gender difference in response to cardio-angelone: therapy.

Conclusions The potential importance of the observed gender-specific anglogimic response on the climical transition of the tractory anglina is substantial and severives trather investigation. [Emclary and Starky of Intracotonian Ad-PGE-4 in Potents With Stable Adgious. http://www.climicatiniss.gov/ct.pdv/emcVitClistGe4-37, SKR00364437 (Starky and Emcary of Intracomany AdsFGE-4 in Patients With Stable Anglina (ACEM-4), http://www.climicatinis.gov/ct.pdv/emcVitClistGe4-37, SKR00364437 (Starky and Emcary of Intracomany AdsFGE-4 in Patients With Stable Anglina (ACEM-4), http://www.climicatinis.gov/ct.pdv/emcVitClistGe4-37, SKR00364437 (Starky and Emcary of Intracomany AdsFGE-4 in Patients With Stable Anglina (ACEM-4), http://www.climicatinis.gov/ct.pdv/emcVitClistGe4-37, SKR00364437 (Starky 2007); NotTool.582637, NotTool.582637 (AWARE: http://www.climicatinis.gov/ct.pdv/emcVitClistGe4-3867; NotTool.488657 ( J. Am. Coll. Cardiol.2007);55:01324-46) © 2007 by the American College of Catology Poundation

Anging pectoris is a disabling manifestation of coronary artery disease (CAD). In the U.S., 9.3 million people live with chronic angina, and an additional 400,000 people are newly diagnosed each year (1). There are 2 major mecha-

From the "Mannepula Hourd Jonaso Fauncians, Mannepula, Minnestin, William Paumen Hurjah, Berd Link, Mehlang, Hilmeini of Winnes-Humigan, Vannet, Christiwania tod Swei Oli Douali um, Picora, Atama, Wolymai Lucki, Tong Lighten, Canada, Christian Tempolati, In-San Daug-Chillense, and the Alformany of Dalifera, An Hung, Chillense, Byogens, Jinput Schlading, Ohann, Gamman, Hong, Kathana, Tan, Mangella, Mar-Yeng, and Canada. Theogenetic to: Similar Hong, Chillense, D. Morella, Bar-Yeng and Canada. Theogenetic to: Similar Hong, Chillense, D. Morella, Bar-Yeng and Canada. Theogenetic to: Similar Hong, Chillense, D. Morella, Bar-Yeng and Canada. Theogenetic to: Similar Hong, Chillense, D. Morella, Bar-Yeng and Canada. Theogenetic to: Similar Hong, Chillense, D. Morella, Bar-Yeng Manne, 2007. 2007. nistic approaches to the treatment of chronic angina. First, currently approved drag therapy includes bera-blockers, caldiure-channel blockers, long acting nitrates, und, most restrudy, ranolazine. Drug therapy alters the supply/demand relationship between the coronary arterial tree blood flow and cardiar muscle oxygen requirements. Second, revascularization by angiophasy, stent, or bypass surgery either reopens or bypasses blockages in the epicardial vessels. However, many patients continue to have recurrent angins with drug therapy and are not suitable for revascularization procedures (1). New mechanistic approaches are meeded to improve blood flow to the myocardium (2).

In contrast to the mechanisms involved in approved therapeutic methods, the heart's natural responses to isch-

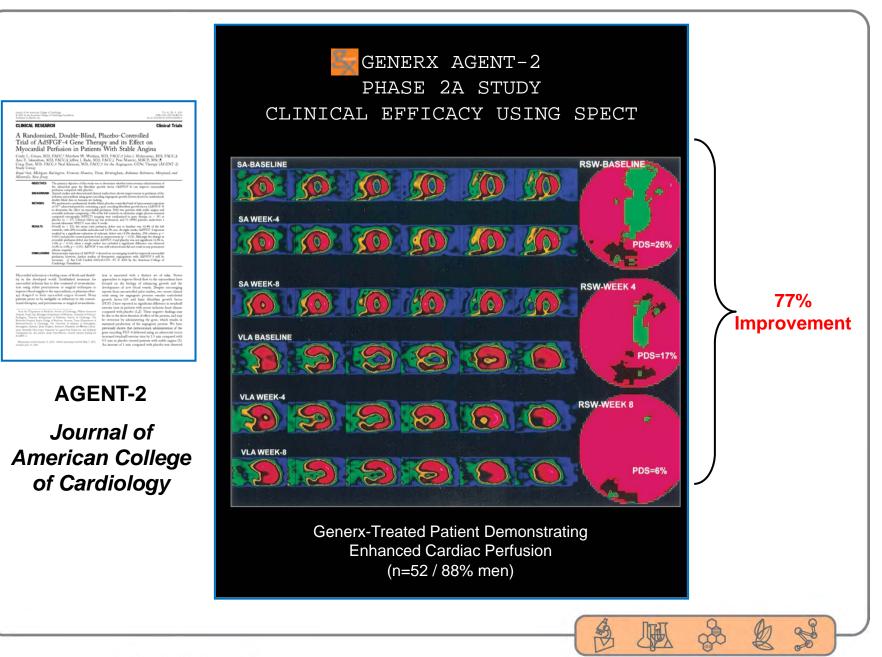
#### Generx<sup>®</sup> AGENT 3 & 4 Summary Research

"We found a significant, genderspecific beneficial effect of Ad5FGF-4 on total ETT time, time to 1 mm ST-segment depression, time to angina and CCS Class in women. This is the first clinical report of a gender difference in response to cardiac angiogenic therapy."

"The potential importance of the observed gender-specific angiogenic response on the clinical treatment of refractory angina is substantial and deserves further investigation."

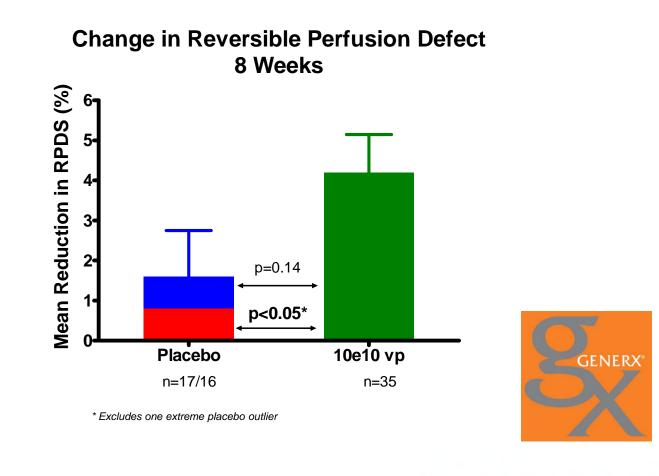
#### JACC September 11, 2007





© 2011 Cardium Therapeutics, Inc.

#### AGENT 2: Primary Endpoint SPECT Imaging Angiogenic Mechanism of Action Study



y

# **AGENT 2 - Comparison of SPECT Results to**

# **Revascularization and Medical Therapy**

Parameter	Coronary Revascular- Medical		Generx /	AGENT-2
Parameter	ization Therapy	Placebo	1x10 <sup>10</sup> vp	
Number of Patients	83	206	17	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. <i>J of Nuclear Cardiol, 2001; 4:42</i>	28-437			

# Generx AGENT 3 & 4 Clinical Studies Clinical Efficacy Using ETT

#### Pooled-Analysis: Protocol-Specified Gender-Based Subgroup

Women	12 weeks			6 months		
n=76	Placebo	10 <sup>9</sup> vp	10 <sup>10</sup> vp	Placebo	10 <sup>9</sup> vp	10 <sup>10</sup> vp
Exercise Duration	-4	+60*	+69*	+7	+75*	+83*
(seconds & percentage ∆)	-1%	+16%	+23%	+2%	+20%	+28%
Angina Onset	+50	+111	+86	+55	+157*	+94
(seconds & percentage ∆)	+26%	+52%	+46%	+28%	+73%	+48%
Time to 1mm ST Segment ↓	+13	+50	+63*	+14	+59*	+86*
(seconds & percentage ∆)	+4%	+16%	+27%	+5%	+19%	+36%

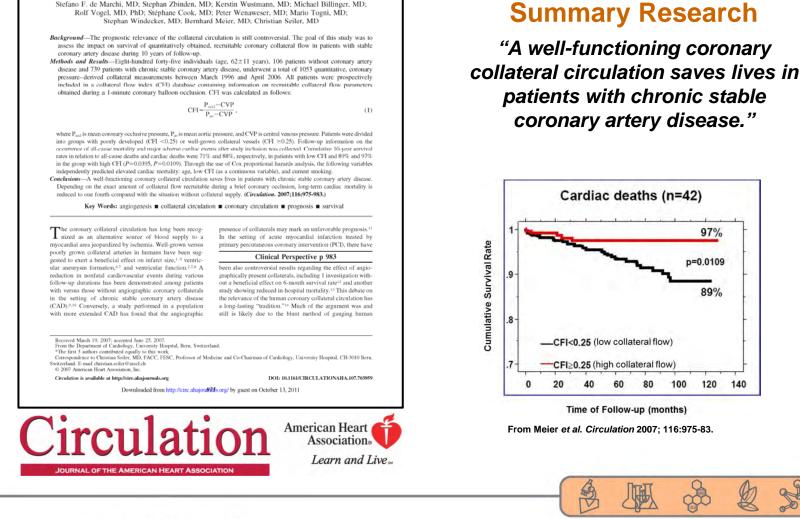
J's

#### AGENT 3 & 4 Clinical Studies: Concordance of Results from Prespecified Pooled Analysis of Gender-Based Subgroup

Women		Generx Ad5FGF-4		
n=76	Time Point	1x10 <sup>9</sup> vp	1x10 <sup>10</sup> vp	
ETT Duration	12 Weeks	p=0.032	p=0.002	
	6 Months	p=0.042	p=0.009	
Time to ECG Ischemia	12 Weeks	NS (0.216)	p=0.031	
	6 Months	p=0.036	p=0.011	
Time to Angina	12 Weeks	NS (0.146)	NS (0.125)	
	6 Months	p=0.003	NS (0.094)	
CCS Class Improvement	12 Weeks	NS (0.222)	p=0.014	
	6 Months	NS (0.341)	p=0.042	
	12 Months	p=0.038	p=0.006	

NS=Not Significant

R



**Beneficial Effects of a** 

**Disease-Induced** 

**Angiogenic Vascularization** 

140

# Inc. © 2011 Cardium Therapeutics,

**Coronary Heart Disease** 

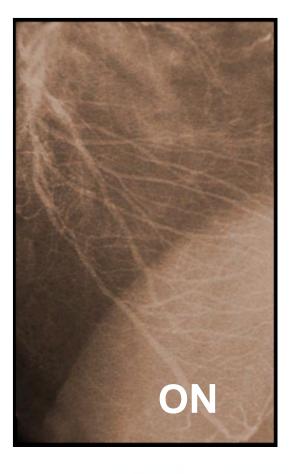
**Beneficial Effect of Recruitable Collaterals** A 10-Year Follow-Up Study in Patients With Stable Coronary Artery

**Disease Undergoing Quantitative Collateral Measurements** Pascal Meier, MD\*; Steffen Gloekler, MD\*; Rainer Zbinden, MD\*; Sarah Beckh, BS; Stefano F. de Marchi, MD; Stephan Zbinden, MD; Kerstin Wustmann, MD; Michael Billinger, MD;

Rolf Vogel, MD, PhD; Stéphane Cook, MD; Peter Wenaweser, MD; Mario Togni, MD;

# Coronary Artery Disease Natural Disease-Induced Angiogenic Vascularization

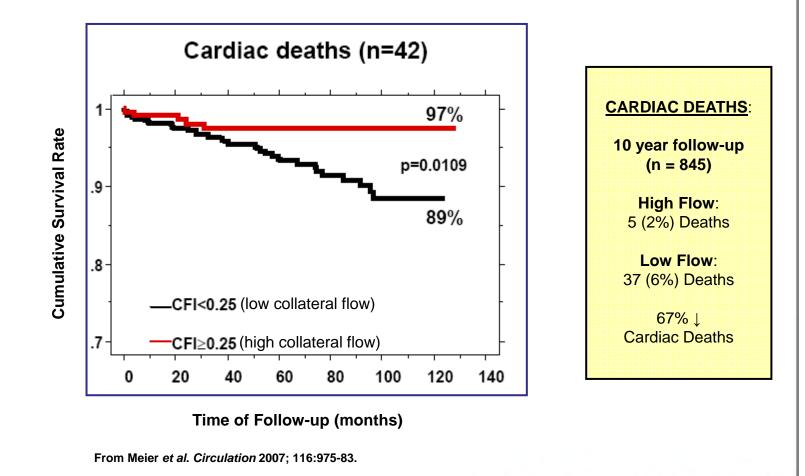




Y

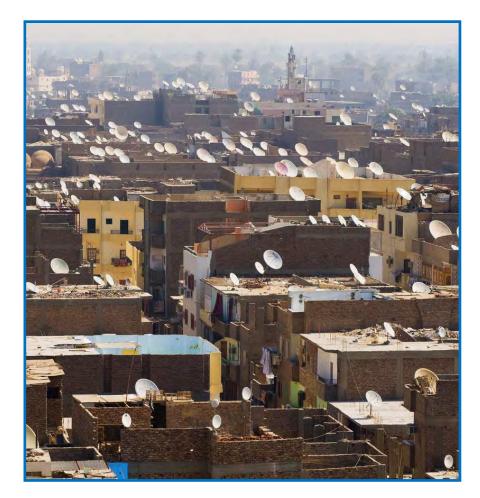
POWERPOINT PRESENTATION > 41

#### Beneficial Effects of Natural Disease-Induced Collateral Vessels 10-Year Follow-up in Patients with Coronary Heart Disease



© 2011 Cardium Therapeutics, Inc.

y





Developing new and innovative, cost-effective advanced care for coronary heart disease patients in international markets



Generx Cardio Chant



