Angionetics is a private, newly-formed, San Diego-based biotechnology company focused on the development of Generx™ [alferminogene tadenovec], a phase 3 angiogenic gene therapy product candidate for the treatment of Myocardial Ischemia and Refractory Angina, and other medical indications including Cardiac Syndrome X.
INVESTMENT THESIS

- **Global Leader in Angiogenic Gene Therapy.** With clinical success, Generx will be the first cardiovascular gene-base therapeutic in the world for a large addressable market as a treatment for otherwise healthy patients.

- **Current Management Team.** Responsible for leading Generx from pre-clinical Bench Lab at the University of California to FDA-cleared Phase 3 clinical study. The team has a century of collective experience in fields of gene therapy, cardiovascular, biologics, and commercial development.

- **Novel Mechanism of Action.** Generx provides new and innovation angiogenic “medical revascularization” a for well characterized CAD patients who are most likely to respond and benefit.

- **Late-Stage Clinical Development.** FDA-cleared Phase 3 AFFIRM study preceded in the U.S. by four completed studies. Globally, over 650 patients enrolled, 455 patients treated with Generx, at over 100 medical centers with over 2,500 patient years of safety data.

- **Barriers to Entry.** Know-how and trade secrets, plus 12 years of market exclusivity in the U.S under the Patent Protection and Affordable Care Act of 2010. $250 million technology & capital investment.

- **Cost-Effective Manufacture.** Fully-validated cGMP manufacturing process, and product stability enabling cost-effective batch manufacturing. Projected direct manufacturing gross margins > 85%.

- **Fits within Current Medical Practice.** Generx is a ready-to-use, one-time treatment, administered by interventional cardiologists during angiogram-like procedure. Targeted therapeutic cost: $2,000 to $5,000 per dose comparably aligned to the economics of cardiac stents.

- **Pipeline of Follow-on Medical Indications.** Cardidac Syndrome X, Ischemic heart failure, and inversa forms of angina that represent significant unmet medical needs.
MEDICAL REVASCULARIZATION
Microvascular Gene Therapy

TODAY
Myocardial Ischemia
Refractory Angina

TOMORROW
Cerebral Ischemia
Vascular Dementia
LEVERAGING CARDIAC & CEREBRAL PLASTICITY

Natural Disease-Induced Collateral Network Formation

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<th>Candidate</th>
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PHASE 3 CLINICAL STUDY: Ad5FGF-4 ANGIOGENIC GENE THERAPY FOR REFRACTORY ANGINA (AFFIRM)

- **Target Indication:** Refractory Angina

- Diagnosed as stress-induced myocardial ischemia and angina in patients no longer responsive to optimal anti-anginal medical therapy, and who are not candidates for, or continue to experience angina after, mechanical revascularization

- Estimated 1.2 million patients in the U.S.; $3.0 billion addressable market opportunity

- Prior FDA-cleared clinical studies identified increased myocardial perfusion as mechanism of action and identified characteristics of patient responders. FDA dossier includes >2,500 patient years of safety data

**Clinical Development Plan**

- **Phase 3 AFFIRM Protocol:** Cleared by FDA in September 2016, and granted Fast Track status by FDA in February 2017.

- Inclusion criteria and endpoints based on patient responder data from prior studies. Protocol employs optimized delivery method and higher Ad5FGF-4 dose.

- Primary endpoint: Change in angina-limited exercise duration at 6 months. Secondary endpoints: Angina frequency, nitrate usage, angina classification, quality of life
PHASE 2 CLINICAL STUDY: Ad5FGF-4 ANGIogenic GENE THERAPY FOR CARDIAC SYNDROME X

- **Target Indication**: Cardiac Syndrome X

- Cardiac Syndrome X (CSX) is typically defined by the triad of angina on exertion, ischemia (ST segment depression) on stress testing, and absence of obstructive coronary artery disease on angiography.

- Diagnosis of exclusion. Other conditions, such as coronary spasm, and valvular heart disease must be ruled out.

- CSX angina typically persists for prolonged periods of time compared to other conditions, and is not responsive to short-acting nitrates.

- Estimated 200,000 cases in the U.S. Affects primarily post-menopausal females (~70%).

**Clinical Development Plan**

- **Phase 2 Protocol**: Submit new protocol to FDA under current IND for evaluation of Ad5FGF-4 vs. placebo in patients with Cardiac Syndrome X.

- Measure improvements in angina frequency, cardiac perfusion and quality of life.
DISCOVERY FOCUS: Ad5FGF-4 ANGIOGENIC GENE THERAPY FOR CEREBRAL VASCULAR DYSFUNCTION

- **Initial Focus**: Moyamoya disease & syndrome due to regional cerebral vascular insufficiency & malformations
- Diagnosed by CT and MRI imaging, and angiogram
- Orphan medical indication: one per 100,000 Caucasians, three per 100,000 Asians, 70% female. Develops in young children and adults aged ≈ 40

**Clinical Development Plan**

- **Stage 1**: Adjunctive therapy with surgical intervention via direct injection into cerebral tissue to stimulate neovascularization
- **Stage 2**: Non-surgical, catheter-based delivery during angiographic evaluation to stimulate neovascularization
- **Potential Gateway**: Physiologic therapy to increase cerebral perfusion and slow disease progression, in vascular dementia due to cerebral micro-infarcts, as assessed by the Clinical Dementia Rating Scale
PLATFORM BUILDING BLOCKS

DNA FGF-4 Gene

Adenovector & CAR Receptor Delivery System

One-Time, Non-Surgical Delivery

Localized Transfection

Cardiac Angiogenic Response
GENE THERAPY

Source: Mukherjee, Siddhartha, The Gene, An Intimate History
A bio-engineered gene-based angiogenic therapeutic is shown. The diagram illustrates an Adenovirus serotype 5 construct with an expression cassette that includes a CMV promoter and the human Fibroblast Growth Factor-4 gene. The E1 region is deleted to create a replication-deficient adenoviral vector. The product candidate is referred to as "[Ad5FGF-4] (alferminogene tadenovec)" and is associated with the Generx brand ("Generx [alferminogene tadenovec]").
ANGIOGENESIS

Ad5FGF-4

Coxsackie Adenovirus Receptor (CAR)

FGF-4

VEGF

FGFR

FGF-4

VEGF

FGFR

VEGFR2

Cardiac Myocytes

Vascular Endothelial Cells

ANGIOGENESIS

GENE THERAPY REGULATION OF MICROVASCULAR NETWORK

Product Candidate
Generx
(alferminogene tadenovec)
GENERX: ARTERIOGENESIS & ANGIOGENESIS

HEMODYNAMIC STIMULUS

- Occlusion/Stenosis
- Pre-existing Collateral
- Peripheral Coronary Pressure - High
- Large Coronary Artery
- Pre-Capillary Arteriole (Resistance)
- Capillary

Adaptation: Arteriole → Artery

ISCHEMIC STIMULUS

- Occlusion/Stenosis
- Large Coronary Artery
- Pre-Capillary Arteriole (Resistance)
- Capillary
- New Collateral
- Ischemic Zone

Adaptation: Capillary → Arteriole

Product Candidate

Generx
(alferminogene tadenovec)
INITIAL GENERX TARGETED MEDICAL INDICATIONS

**Refractory Angina**
1.2 Million
Myocardial ischemia and stable angina despite conventional forms of treatment. Low angiographic risk. Not candidates for PCI and CABG.

**Cardiac Syndrome X**
(Subset of Refractory Angina)
200,000
Angina with evidence of myocardial ischemia in the absence of flow-limiting stenosis on coronary angiography. 20-30% of patients undergoing angiography for chest pain.
REFRACTORY ANGINA: FACTS & FIGURES

• 1.2 Million Refractory Angina patients in the US\(^1\), and an estimated \(>100,000\) new cases each year\(^2\)

• 30% of patients diagnosed with angina still have angina following implantation of a PCI stent\(^3\)

• At 6 and 12 months following PCI, 31% and 29% of patients respectively have abnormal stress tests\(^3\)

• 72% survival 9 years after initial diagnosis of Angina\(^4\)

• From 2001-2011, stent procedures in the United States went down \(~30\)% and bypass surgeries went down \(~50\)%\(^5\)

References:
1. McGillion et al., Canadian J. Cardiol. 28:S20-S41 (2012)
THERAPEUTIC OBJECTIVES

- Enhance Physical Exertion
- Improve Cardiac Perfusion
- Reduce Angina and Medication Usage
- Offer New Therapeutic Options
STRATEGIC POSITIONING
For a Large Unaddressed Segment of the Angina Market
Recent Clinical Research Findings: COURAGE, BARI 2D, STICH, PROMISE

**Ongoing Clinical Research:**
International Study of Comparative Health Effectiveness with Medical and Invasive Approaches [ISCHEMIA: 8,000 Patients]

- **Optimal Medical Therapy**
  - Small Molecule Drugs

- **Medical Revascularization**
  - Angiogenic Therapy

- **Mechanical Revascularization**
  - Percutaneous Coronary Intervention & Bypass Surgery

- **Low Angiographic Risk**
  - Well-Controlled Angina Symptoms

- **High Angiographic Risk**
  - No Prophylactic Benefit for Lower Risk Patients
Generx is designed to easily fit within the current practice of medicine, as a ready to use, one time treatment, which is administered by interventional cardiologists using standard cardiac balloon catheters, during an approximately one-hour, out-patient, angiogram like procedure.
MEDICAL REVASCULARIZATION
Microvascular Gene Therapy

CARDiAC SPECT IMAGING

Perfusion
Reversible Perfusion Defect

Before Treatment

4 Weeks Post-Generx Treatment

8 weeks Post-Generx Treatment

AGENT-2 Clinical Data

Product Candidate
Generx
(aferminogene tadenovec)

Grines et al., J Am Coll Cardiol; 2003; 42(8):1339-47.
CURRENT TREATMENT PARADIGM: THERAPEUTIC PRINCIPALS OF MYOCARDIAL ISCHEMIA

Increase of Cardiac $O_2$ SUPPLY

- Intermittent Thrombolytics
- Blood Rheology
- Coronary Sinus Reduction
- Coronary Flow Redistribution

O$_2$ Carrying Capacity

- $FIO_2$
- Hb

Coronary Blood In-Flow

- PCI Stent
- Bypass Surgery

Decrease of Cardiac $O_2$ DEMAND

- Allopurinal: Oxidative Stress Reduction
- Trimetazidine: 3-KAT Inhibition
- Perhexline: CPT1/2 Inhibition

Metabolic Modulation

- Ranexa (Ranolazine)
- Metabolic Modulation

Heart Rate Contractility LV Wall Tension

- $I_{na}$ Inhibition
- Calcium Channel Blockers
- Nitrates
- Nicorandil
- β-Blockers
- Ivabradine

CURRENT TREATMENT PARADIGM: THERAPEUTIC PRINCIPALS OF MYOCARDIAL ISCHEMIA

FIO$_2$: $Hb$

O$_2$ Carrying Capacity

Coronary Blood In-Flow

Bypass Surgery

PCI Stent

Product Candidate GenerX (aferminogene tadenovec)
DISRUPTOR STRATEGY: GENERX TREATMENT ALGORITHM
Based on FDA-Cleared U.S. Phase 3 Clinical Study Design

Coronary Artery Disease
(16.5 million)

Angiographic Risk Assessment

Low Risk
(1.2 Million\(^1\))

High Risk
(800,000)

Optimal Medical Therapy

Medical Revascularization

Bypass Surgery
(200,000)

PCI Stent
(600,000)

No Angina
(7.8 Million)

Angina
(8.7 Million)

Controlled Symptoms
Uncontrolled Symptoms

Coronary Artery Disease
(16.5 million)

(1) Range 0.6M – 1.8 [mean 1.2M] McGillion et al., Canadian J Cardiology 28:S20-S41 (2012)
other figures, Benjamin et al., Circulation, American Heart Association, Statistics 2017
EMERGING DIRECTIONAL TRENDS IN ISCHEMIA TREATMENT

Mechanical Revascularization to Increase Cardiac O\textsuperscript{2} Supply

Reasons Contributing to the Decline of PCI Stent and Bypass Surgery Use

- More cautious use of PCI stents resulting from a deeper understanding of risks and side effects
- Broad availability of fractional flow reserve diagnostics enhances stent triage and identifies low risk patients
- Improved understanding of “refractory angina” supported by Gilead’s promotion of Ranexa®
- Multiple studies have found no prophylactic benefit of bypass surgery and PCI in patients with low angiographic risk
MARKET RESEARCH:
Integration into the Practice of Medicine

- **Incidence of Refractory Angina:** Cardiologists unanimously agree that there are approximately 1.2 million refractory angina patients in the US, with an estimated 100,000+ new cases diagnosed annually.

- **Clinical Practice Experience:** All survey respondents see patients with refractory angina unresponsive to medical therapy and unsuitable for mechanical revascularization. They also see patients with angina post-mechanical revascularization as well as patients without angiographic evidence of large vessel disease [Cardiac Syndrome X].

- **Post-Mechanical Revascularization Angina:** Estimated to range from 12% to 25% following treatment.

- **Generx Clinical Adoption:** Cardiologists unanimously agree that they would use Generx, if approved by the FDA, for the treatment of refractory angina patients. Most agreed they would also use Generx for angina following a stent or bypass surgery. They also agreed that patients would be receptive to treatment with Generx although some patients may have reservations about “gene therapy.”

- **Generx Pricing Considerations:** Cardiologists were strongly positive, and without reservation, about adoption of Generx in the $3,000 to $5,000 price range, as this is equivalent to the price of stents. There was less agreement for pricing in the $5,000 to $10,000 range with concerns about reimbursement where they felt strong clinical data would be needed to support the higher pricing.

- **Unmet Clinical Need:** All survey respondents felt that there is a need for Generx to treat refractory angina and they would all use it in their daily practice if approved by the FDA.
### Potential Baseline Generx Revenue Model

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<th>Unit Volume</th>
<th>U.S. Market Capture</th>
<th>World Market Capture</th>
<th>Target Revenue per Dose Price Level</th>
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<td></td>
<td></td>
<td><strong>Level III</strong> $5,000 / dose</td>
</tr>
<tr>
<td>150,000 doses</td>
<td>8.3%</td>
<td>1.0%</td>
<td>$300 Million</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200,000 doses</td>
<td>11.1%</td>
<td>1.3%</td>
<td>$400 Million</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>
NEW PATIENT PORTAL

www.MyRefractoryAngina.com
GENERX: REFRACTORY ANGINA
FAST TRACK DESIGNATION OF GENERX BY UNITED STATES FDA

“Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.” - FDA

Generx was granted Fast Track designation on February 7, 2017
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Phase</th>
<th>Status</th>
<th>Clinical Endpoint</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGENT-1</td>
<td>United States</td>
<td>Phase 1 / 2</td>
<td>Refractory Class 2-3 Angina</td>
<td>Exercise Treadmill Time</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose Finding &amp; Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGENT-2</td>
<td>North America</td>
<td>Phase 2a</td>
<td>&gt;9% Reversible Perfusion Defect</td>
<td>SPECT Imaging</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mechanism of Action Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGENT-3</td>
<td>North America</td>
<td>Phase 2b/3</td>
<td>Refractory Class 2-4 Angina</td>
<td>Exercise Treadmill Time</td>
<td>416</td>
</tr>
<tr>
<td>AGENT-4</td>
<td>Western Europe &amp; South America</td>
<td>Phase 2b/3</td>
<td>Refractory Class 2-4 Angina</td>
<td>Exercise Treadmill Time</td>
<td>116</td>
</tr>
<tr>
<td>AWARE &amp; ASPIRE</td>
<td>U.S. &amp; International</td>
<td>Beta Study</td>
<td>Refractory Angina</td>
<td>Exercise Treadmill Time &amp; SPECT Imaging</td>
<td>20</td>
</tr>
<tr>
<td>NEW AFFIRM</td>
<td>United States</td>
<td>Phase 3 Fast Track</td>
<td>Refractory Angina</td>
<td>Exercise Treadmill Time</td>
<td>320</td>
</tr>
</tbody>
</table>

**[Generx: 622 | Placebo: 381]**   **TOTAL 1,003**
<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical FDA Regulatory Dossier Findings</th>
</tr>
</thead>
</table>
| AGENT-1 ETT Endpoint *(N = 79)* | - Safe and well-tolerated (Treatment Response Correlates to Angina Severity)  
- Significant improvement in ETT vs. placebo when baseline ETT ≤ 10 min *(p=0.01 at 4 wk; p= 0.05 at 12 wk)* |
| AGENT-2 SPECT Endpoint *(N = 52)* | - Safe and well-tolerated (77% Response Rate)  
- Significant cardiac perfusion improvement at 8 wk *(p<0.05 vs placebo)* similar to CABG and PCI procedures  
- Parallel trends for improvements in angina frequency and NTG use  
- Data supports improved myocardial perfusion as Generx mechanism of action |
| AGENT-3 / AGENT-4 Meta-Analysis ETT Endpoint *(N=532)* | - Safe and well-tolerated (Supports “Female Pattern” Angina Thesis)  
- In females, High Dose vs Placebo:  
  - ETT: *(pre-specified)* 12 wk, *(p<0.01)*; 6 mo, *(p<0.01)*  
  - Time to ECG Ischemia: 12 wk, *(p=0.03)*; 6 mo, *(p=0.01)*  
  - CCS Class Improvements:  
    - 12 wk, *(p=0.01)*; 6 mo, *(p=0.04)*; 12 mo, *(p< 0.01)*  
- In Agent-3, males and females exhibited improvement in CCS class at 12 mo *(p<0.05)*  
- Substantial placebo response in men, with endpoint ETT comparable to females (over all “improvement” dampened) |
| ASPIRE SPECT Endpoint *(N = 11)* | - *New* transient ischemia delivery safe and well-tolerated (86% Response Rate)  
- Significant cardiac perfusion improvement at 8 wk *(p=0.01 vs placebo)* similar to AGENT-2 and CABG/PCI |
Clinical & Medical Advancement: Why This? Why Now?

- FDA Phase 3 clearance with expanded and newly-demarcated patient population
- FDA Fast Track designation approved Q1 2017
- Initial strategic partnership completed
- New preclinical research on Ad5 receptor interaction with Generx supports new transient ischemia delivery technology
- New catheter-based gene transfer delivery technology and new data supporting safety & efficacy of higher dose level
- Fundamental research on FGF-4 signaling and angiogenic process confirms VEGF interactions
- Advanced data analytics identifying Generx responders
- New simplified cath lab handling process
- A more clearly delineated refractory angina market opportunity based on Gilead’s promotion of Ranexa
- Research on limitations of mechanical revascularization opens door for “medical revascularization” Generx therapy
Transfection Efficiency Increases in Ischemic Tissue

Hypothesis: CAR Receptor Expression and Vascular Permeability Increase in Ischemic Myocardium

1. Normal Myocardium
   - Endothelial Cells
   - Cardiac Myocytes
   - Tight Cell Junctions

   Under normal conditions, endothelial cells maintain tight cellular junctions and inhibit transfection of the myocardium.

2. Ischemic Myocardium
   - Endothelial Cells
   - Cardiac Myocytes
   - CAR Receptors

   In ischemic myocardial tissue, coxsackie adenovirus receptors (CAR) are exposed in the endothelial cellular junctions.

3. CAR Mediated Transfection
   - Ad5FGF-4

   The adenovirus containing the FGF-4 human growth factor gene (Ad5FGF-4) binds to CAR receptors and transfects the ischemic cardiac myocytes.

Fechner et al., Circulation 107, 876-882 (2003); Shi et al., Human Gene Therapy Methods 23:204-212 (June 2012)
PROTOCOL DESIGN INSIGHTS FOR AFFIRM STUDY

Transient Ischemia Drives Cardiac Uptake (Transfection)

Preclinical Data Confirming Transfection Efficacy Finding for Double Balloon Occlusion Procedure

Shi et al., Hum Gene Ther Methods 2012; 23(3):204-12
PROTOCOL DESIGN INSIGHTS FOR AFFIRM STUDY
Changes in AFFIRM Protocol Relative to AGENT-3

Increase in enrollment age from 35-75 to 55-75 years
Reduction in CCS Class range from II-IV to III-IV
Average of two baseline ETT times measured against final time
NTG administered with Ad5FGF-4
Transient ischemia induced with double occlusion procedure
Increase in viral particles administered to $6 \times 10^9$

Placebo Control

Transfection Increase
U.S. FDA-CLEARED PHASE 3 AFFIRM CLINICAL STUDY

Ad5FGF-4 In Patients with Refractory Angina due to Myocardial Ischemia

**Method:**
- Randomized
- double-blind
- placebo-controlled
- multicenter

**Endpoints:**
- safety
- definitive efficacy

**Indications:**
- stress-induced refractory angina
- myocardial ischemia

---

**Design**

**Patient Population**

- Refractory Angina
- CCS angina Class III or IV
- Age 55 - 75
- Evidence of Ischemia
- Modified Bruce Exercise Treadmill (Baseline ETT= 3-7 min)
- Average five angina attacks weekly

**6 Months Endpoint**

- **Primary:**
  - Functional ETT Improvement

- **Secondary:**
  - Change in CCS angina class,
  - Change in weekly angina attacks,
  - Change in weekly nitrate usage
  - Change in quality of life (SAQ)

**Statistical Methods**

- 320 enrolled patients
  - randomized 1:1 to placebo to Ad5FGF-4
  - Efficacy evaluated using analysis of covariance model
  - Powered at 90% to detect a 30 second difference between placebo and Ad5FGF-4
  - Two-sided test at the 5% level of significance
Phase 3 Clinical Design

The FDA-cleared Phase 3 AFFIRM study will include only CCS Classes 3 & 4 and ages 55-75, uses a sample size of 320 patients, and is expected to be powered at 90% (5% significance) to detect a difference of 30 seconds between Generx and Placebo in the change from baseline to Month 6.
<table>
<thead>
<tr>
<th>FACTOR</th>
<th>Generx</th>
<th>Ranexa (ranolazine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Status</td>
<td>FDA-Cleared Phase 3</td>
<td>FDA Approval: 2007</td>
</tr>
<tr>
<td>Medical Indication</td>
<td>Refractory Angina</td>
<td>Chronic Angina</td>
</tr>
<tr>
<td>Class of Therapy</td>
<td>Gene Therapy</td>
<td>Small Molecule</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Angiogenesis &amp; Arteriogenesis</td>
<td>Metabolic Modulation</td>
</tr>
<tr>
<td>Modality</td>
<td>Regenerative Medicine: Increases Cardiac Blood Supply</td>
<td>Symptom Relief: Reduces Cardiac Oxygen Demand</td>
</tr>
<tr>
<td>Comparable Therapies</td>
<td>Percutaneous Coronary Intervention (Stents) Coronary Artery Bypass Surgery</td>
<td>Beta Blockers Calcium Channel Blockers</td>
</tr>
<tr>
<td>Treatment Regimen</td>
<td>One-Time Delivery via Cardiac Catheter</td>
<td>Twice Daily Oral Tablet</td>
</tr>
<tr>
<td>Developer / Marketing &amp; Sales</td>
<td>Angionetics Inc.</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Annual Revenues (Patients / Penetration)</td>
<td>Pending Phase 3 Clinical Study and BLA</td>
<td>$680 Million (200,000 patients / 11.1%)</td>
</tr>
</tbody>
</table>
Change from Baseline at Week 12

<table>
<thead>
<tr>
<th>Change in Exercise Duration (Seconds)</th>
<th>91.7 Seconds</th>
<th>115.8 Seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (N=258)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranexa 1000 mg (N=261)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24 second Difference
P=0.03

Weekly Angina Attacks

<table>
<thead>
<tr>
<th>Mean Number of Weekly Angina Attacks</th>
<th>3.3</th>
<th>2.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (N=258)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranexa 1000 mg (N=261)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.001

“*This is what clinical success looks like!*”

GENEREX COMPARATIVE VALUATION METRIC

CASE STUDY: GILEAD’S RANEXA®

1985  Syntex Corporation discovers Ranexa and initiates Phase 1 & 2 clinical studies

1994  Roche acquires Syntex and discontinues the clinical development of Ranexa

1996  CV Therapeutics acquires Ranexa and begins Phase 3, encounters setbacks from efficacy and safety issues, and refocuses development from classic to “chronic” angina

2006  Ranexa approved by FDA as second-line therapy for chronic angina

2009  CV Therapeutics is acquired by Gilead Sciences for $1.4 billion (14x annualized sales)

2017  After Phase 4, FDA approved Ranexa for front-line therapy, annualized revenues reach ~$600 million in U.S. ($3,000 per year [100x generic beta blocker price] @ 200,000 patients)

Generex Development Cycle Parallels Ranexa
CORPORATE DEVELOPMENT STRATEGY
“Value Unlock”

<table>
<thead>
<tr>
<th>Investor</th>
<th>Preferred Stock</th>
<th>Common Stock</th>
<th>Preferred Stock Fully-Converted into Common Stock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huapont Life Sciences Affiliate</td>
<td>600,000</td>
<td>-</td>
<td>3,400,000</td>
</tr>
<tr>
<td>Taxus Cardium</td>
<td>-</td>
<td>3,400,000</td>
<td>3,400,000</td>
</tr>
<tr>
<td>Total</td>
<td>600,000</td>
<td>3,400,000</td>
<td>4,000,000</td>
</tr>
</tbody>
</table>

*Adjusted for planned forward stock split
GENERX: CORPORATE DEVELOPMENT HISTORICAL PERSPECTIVE

(Collateral Therapeutics (NASDAQ)
University of California
San Diego

Discovery, Licensing and Initial Preclinical Studies

(Scherering (NYSE)
As Strategic Partner with Collateral Therapeutics
Schering Acquired Collateral in 2002 for $160 Million
Phase 1/2 to Phase 2b/3

(Cardium (NASDAQ)
Formed to Acquire Technology from Schering/Bayer
Phase 2b/3 & International Pilot Study

(Angionetics
Clinical & Commercial Development Activities, Cleared for Phase 3 Clinical Study
United States & China

$250 Million Invested in Preclinical Studies, Four FDA-Cleared Clinical Studies (Phase 1/2 thru 2b/3) and Product Commercialization
Angionetics’ gene therapy technology is primarily based on discoveries at Bayer, Schering AG, Collateral and Cardium Therapeutics.

Angionetics is a strategic partner of Huapont Life Sciences, the sublicensee of Generx in Mainland China.

Generx is available worldwide for license and/or partnership outside of Mainland China.
Comparative Cost Analysis
U.S. Medicine Reimbursement Procedure Codes

<table>
<thead>
<tr>
<th>Direct Cost Elements</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Angiographic Catheterization</td>
<td>$2,600(^{(2)})</td>
</tr>
<tr>
<td>Generx Biologic [Ad5FGF-4] (Range $2,000 - $5,000/ per Treatment)</td>
<td>$2,000 - $5,000(^{(3)})</td>
</tr>
<tr>
<td>Total Generx Angiogenic Gene Therapy</td>
<td>$4,600 - $7,600</td>
</tr>
</tbody>
</table>

Memo:
Coronary Artery By-Pass Surgery
Percutaneous Coronary Artery Intervention (to 4 stents)

$48,000\(^{(4)}\)
$17,800\(^{(5)}\)

(1) CPT code 78452
(2) ACP 2015 Medicare national average outpatient hospital payment
(3) Projected cost per single Generx Treatment (6x10\(^9\)) viral particles
(4) 2015 Medicare national average inpatient hospital payment for procedure total cost estimated at $75,000
(5) PCI procedure CPT code amount for up to 4 vessels/stents
## Gene Therapy
### Peer Group Comparative Valuations

<table>
<thead>
<tr>
<th>Company</th>
<th>Symbol</th>
<th>Clinical Phase</th>
<th>Cash</th>
<th>Market Cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverum</td>
<td>ADVM</td>
<td>1/2</td>
<td>$222 Mil</td>
<td>$114 Mil</td>
</tr>
<tr>
<td>Applied Genetic</td>
<td>AGTC</td>
<td>1/2</td>
<td>$99 Mil</td>
<td>$101 Mil</td>
</tr>
<tr>
<td>Audences</td>
<td>BOLD</td>
<td>1/2</td>
<td>$106 Mil</td>
<td>$312 Mil</td>
</tr>
<tr>
<td>Avexis</td>
<td>AVXS</td>
<td>1</td>
<td>$240 Mil</td>
<td>$2.2 Bil</td>
</tr>
<tr>
<td>Bluebird Bio</td>
<td>BLUE</td>
<td>2/3</td>
<td>$704 Mil</td>
<td>$3.4 Bil</td>
</tr>
<tr>
<td>Dimension</td>
<td>DMTX</td>
<td>1/2</td>
<td>$78 Mil</td>
<td>$36 Mil</td>
</tr>
<tr>
<td>Juno</td>
<td>JUNO</td>
<td>1/2</td>
<td>$733 Mil</td>
<td>$2.52 Bil</td>
</tr>
<tr>
<td>Regenxbio</td>
<td>RGNX</td>
<td>1/2</td>
<td>$89 Mil</td>
<td>$621 Mil</td>
</tr>
<tr>
<td>Spark</td>
<td>ONCE</td>
<td>3</td>
<td>$296 Mil</td>
<td>$1.6 Bil</td>
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<tr>
<td>Sangamo</td>
<td>SGMO</td>
<td>2</td>
<td>$143 Mil</td>
<td>$292 Mil</td>
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<tr>
<td>Tocagen</td>
<td>TOCA</td>
<td>2/3</td>
<td>$110 Mil</td>
<td>$243 Mil</td>
</tr>
<tr>
<td>uniQure</td>
<td>QURE</td>
<td>2/3</td>
<td>$132 Mil</td>
<td>$132 Mil</td>
</tr>
<tr>
<td>Voyager</td>
<td>VYGR</td>
<td>1b</td>
<td>$174 Mil</td>
<td>$278 Mil</td>
</tr>
</tbody>
</table>

**Average Market Cap**

$911 Mil
## Valuation Perspectives

### Angionetics - Current Valuation

| Lead product Generx, an angiogenic gene therapy with FDA-cleared Phase 3 clinical study with fast track status for refractory angina (1.0 million U.S. patients), based on a new mechanism of action (↑ cardiac O$_2$ supply). $250 million prior investment by Bayer / Schering A.G, and Collateral & Cardium Therapeutics | $35 Million To $50 Million |

### Gene Therapy Sector - Peer Group Analysis

- Includes 13 public companies (see attached schedule) focused on clinical development of gene-based therapeutics primarily for orphan disease indications

- Average Market Capitalization: $911 Million
- Company Value Range: $36 mil - $3.4 bil

### Tocagen - Most recent Gene Therapy Sector IPO

| Lead product Toca 511 is a Phase 3 gene therapy clinical study for treatment of recurrent high grade glioma brain cancer with limited treatment options (≈ 40,000 U.S. patients). IPO raised > $80 million | Current Market Capitalization: $243 Million 4/20/2017 |

### Ranexa - Competitive Product Acquisition Value

- Following a 20-year development cycle, in 2006, the FDA approved Ranexa, a small molecule drug for treatment of chronic angina, based on a new mechanism of action (↓ cardiac O$_2$ demand). In 2009, Ranexa (C.V. Therapeutics) was acquired by Gilead Sciences for $1.4 billion (14x annual revenues)

- Product Predicate Terminal Value $1.4 Billion
- Gilead Sciences Acquisition Price
### PRECLINICAL & CLINICAL RESEARCH FINDINGS (1 OF 3)

<table>
<thead>
<tr>
<th>Research Topic</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Gene Transfer**               | In porcine model of stress-induced myocardial ischemia, intracoronary delivery of Ad5FGF-4 demonstrated FGF-4 protein expression in the heart (but not in other tissues) for ~3 weeks, and improved regional myocardial function and perfusion for up to 12 weeks. [Gao et al., Hum Gene Ther. 15:574-87 (2004)]  
  Sponsored preclinical study at Emory University demonstrated >100 fold increase in gene expression with catheter-based Ad5 delivery during consecutive, 3 min balloon inflations to induce transient ischemia and upregulation of Ad5 CAR receptors, and with co-administration of nitroglycerin to increase vascular permeability. [Shi et al., Hum Gene Ther. 23:1-9 (2012)]  
  Safety of Ad5FGF-4 delivery during transient ischemia confirmed in Phase 2b ASPIRE study, as assessed by post-treatment serial measurement of cardiac troponin levels. |
| **Biodistribution & Vector Safety** | In porcine model of stress-induced myocardial ischemia, no adverse histologic effects on the heart or other organs were observed following intracoronary delivery of Ad5FGF-4. FGF-4 protein was detected in the hearts of treated animals, but not in extracardiac tissues.  
  No detectable circulating FGF-4 protein was detected in plasma of treated animals.  
  Limited, dose-dependent DNA biodistribution was detected by PCR, but no FGF-4 mRNA was detected. [Gao et al., Hum Gene Ther. 15:574-87 (2004)]  
  87% first-pass uptake of Ad5FGF-4 across human coronary circulation in AGENT-1 clinical study [Grines et al., Circ. 105:1291-97 (2002)]. |
<table>
<thead>
<tr>
<th>Research Topic</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunologic Response</strong></td>
<td>Preclinical studies in the porcine model of myocardial ischemia found no effect of preexisting serum antibodies to Ad5 or repeat dosing on Ad5FGF-4 efficacy. The intracoronary route of administration limits systemic exposure and immune response. [Roth et al., Hum Gene Ther. 17:230-8 (2006)]</td>
</tr>
<tr>
<td></td>
<td>In Phase 2b AGENT-2 SPECT imaging study, perfusion improvements in Ad5FGF-4-treated patients were not affected by the presence or absence of baseline neutralizing adenoviral antibodies. [Grines et al. JACC 42:1339-47 (2003)]</td>
</tr>
<tr>
<td><strong>Risk of Germline Transmission</strong></td>
<td>Sponsored study by Dr. Robert Braun (U. Washington) found no evidence of germ-line transfection following intracoronary administration of Ad5 at a dose level more than 2-logs greater than the Phase 3 AFFIRM study dose.</td>
</tr>
<tr>
<td></td>
<td>Semen samples collected at 8 weeks after treatment in the Phase 1/2 AGENT-1 study were negative for Ad5FGF-4 DNA by PCR. [Grines et al., Circ. 105:1291-97 (2002)]</td>
</tr>
<tr>
<td><strong>Risk of Restenosis</strong></td>
<td>Sponsored preclinical study in a pig model of mild atherosclerosis and hypercholesterolemia, conducted at Maastricht University (Dr. Mark Post), found extremely low transgene expression and no augmentation of neointima formation in stented (bare metal or drug-eluting) arteries following administration of Ad5FGF-4.</td>
</tr>
</tbody>
</table>
### Research Topic

<table>
<thead>
<tr>
<th><strong>Patient Safety</strong></th>
<th><strong>Results</strong></th>
</tr>
</thead>
</table>
| Phase 1/2 and Phase 2/3 dose-ranging studies (9x10^7 vp to 9x10^9 vp) completed with no findings of dose-related toxicity. [Grines et al., Circ. 105:1291-97 (2002); Henry et al. JACC 50:1038-46 (2007)] | AFFIRM Phase 3 study dose level of 6x10^9 vp/mL confirmed safe in Phase 2b ASPIRE study.  
7% of treated patients experience transient mild fever, resolved with anti-pyretics.  
87% first pass extraction across coronary circulation in AGENT-1 clinical study [Grines et al., Circ. 105:1291-97 (2002)].  
Human blood erythrocytes bind to and inactivate Ad5, limiting potential systemic exposure.  
Long-term safety database includes 450-Generx-treated patients, > 2,500 patient years of safety data, with no findings of treatment-related adverse events. |

<table>
<thead>
<tr>
<th><strong>Perfusion Mechanism of Action</strong></th>
<th><strong>Results</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>ETT &amp; Angina Outcomes</strong></th>
<th><strong>Results</strong></th>
</tr>
</thead>
</table>
| Significant improvement in ETT vs. placebo in patients with more advanced CAD (limited ETT exercise capacity and CCS angina class 3&4). [Grines et al., Circ. 105:1291-97 (2002); Henry et al. JACC 50:1038-46 (2007)] Improvement in CCS class, angina frequency and nitroglycerin use also observed. [Grines et al., JACC 42:1339-47 (2003)] | Age- and CCS class-adjusted subgroup analysis of AGENT-3 data identify durable biological response across multiple covariant strata, with age and ETT time inversely correlated.  
Significant ETT response in patients ages >55 years and with baseline ETT ≤300 seconds confirm age and level of ischemia hypothesis, and form basis for Phase 3 AFFIRM study protocol design. |
Developing New Therapeutics for a Global Market

PRODUCT CANDIDATE

Generx
[Ad5FGF-4]

angionetics
MICROVASCULAR GENE THERAPY