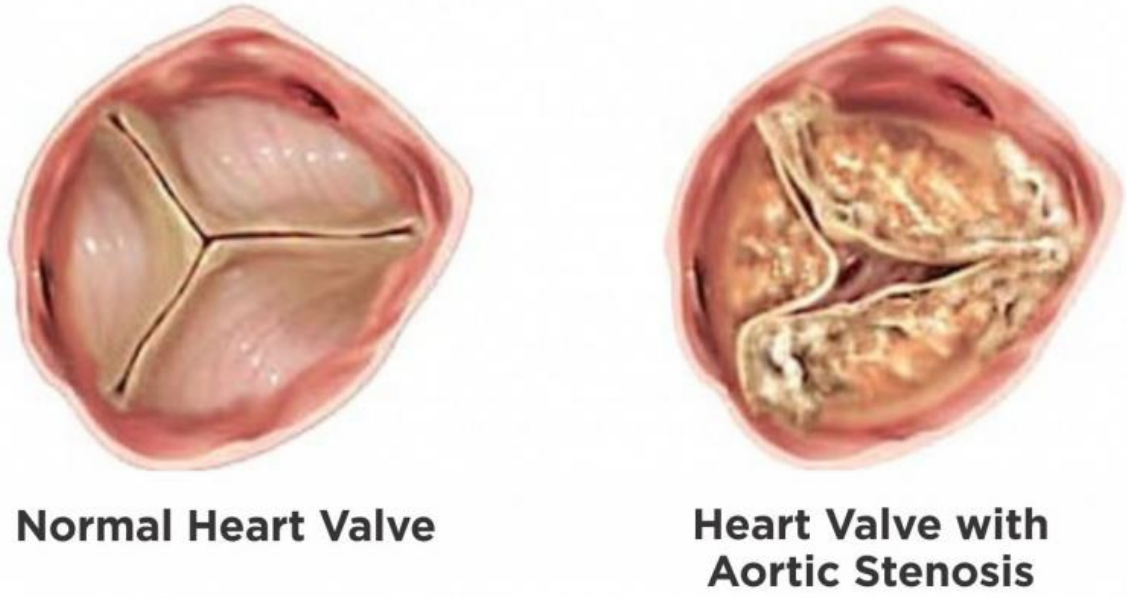
RANCHO SANTA FE BIO, INC.

A Clinical Stage Company Focusing on Calcification Disorders

Calcific Aortic Valve Stenosis

Calcific aortic valve stenosis:

- Affects 3% of adults over age 65
- Is characterized by massive deposition of calcium on the aortic valve
- Results in progressive impairment in valve opening
- If untreated, ultimately results in progression to heart failure and death



Normal Heart Valve

Heart Valve with Aortic Stenosis

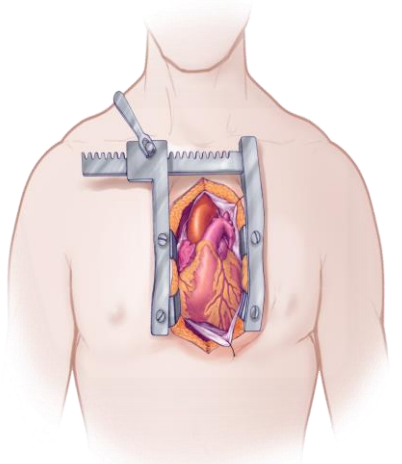
The Clinical Problem

Diagnosis of Moderate AVS

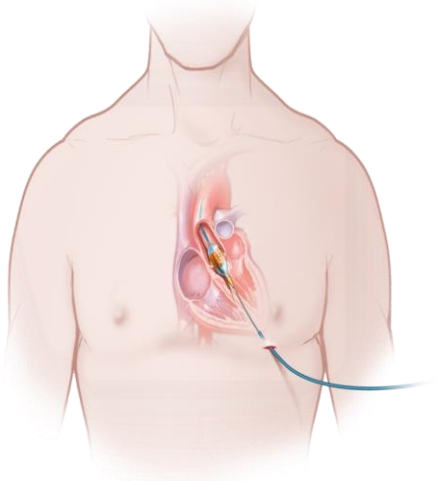
2 Million Patients Undergoing Watchful Waiting in U.S.

3 Million Patients Undergoing Watchful Waiting in Europe

Unabated Progression to intervention

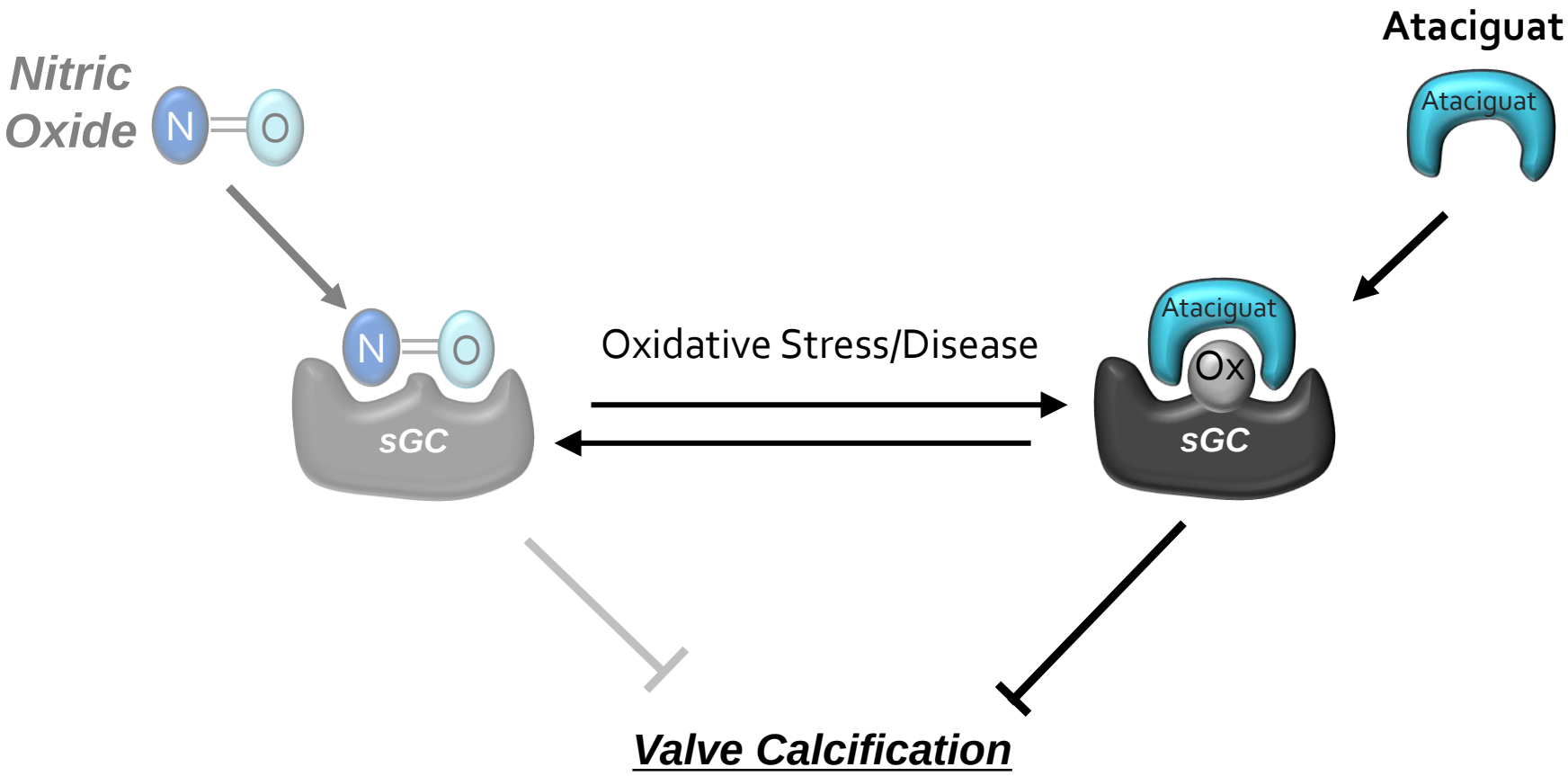


Valve Replacement



Transcatheter Approaches

Ataciguat will be a first-to-market activator of oxidized sGC



Development of Ataciguat for treatment of AVS

SANOFI

Preclinical development
and robust safety data
RSF secured worldwide exclusive license 6/21

NATIONAL INSTITUTES OF HEALTH

New Therapeutic Uses Program
Through NCATS

MAYO CLINIC

$4.5M grant from NCATS to study AVS

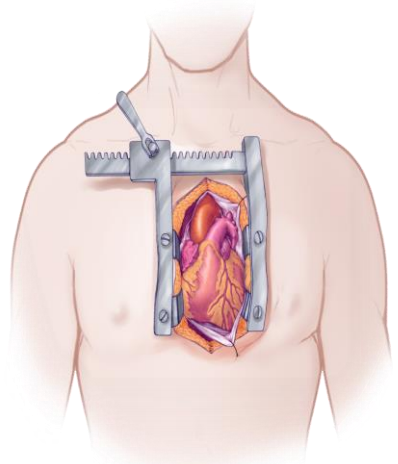
- Preclinical
- Phase Ib
- Phase IIb

The Ataciguat Solution

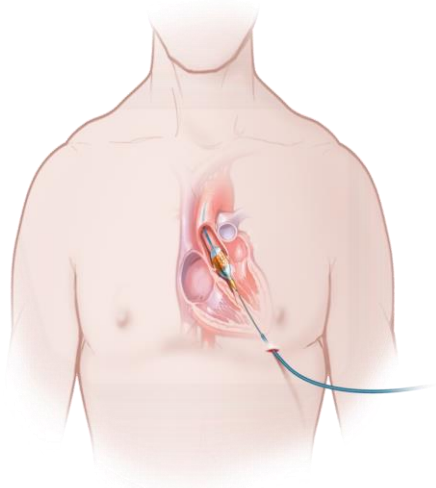
Diagnosis of Moderate AVS

Treatment With Ataciguat

Delay or Halt Progression to intervention



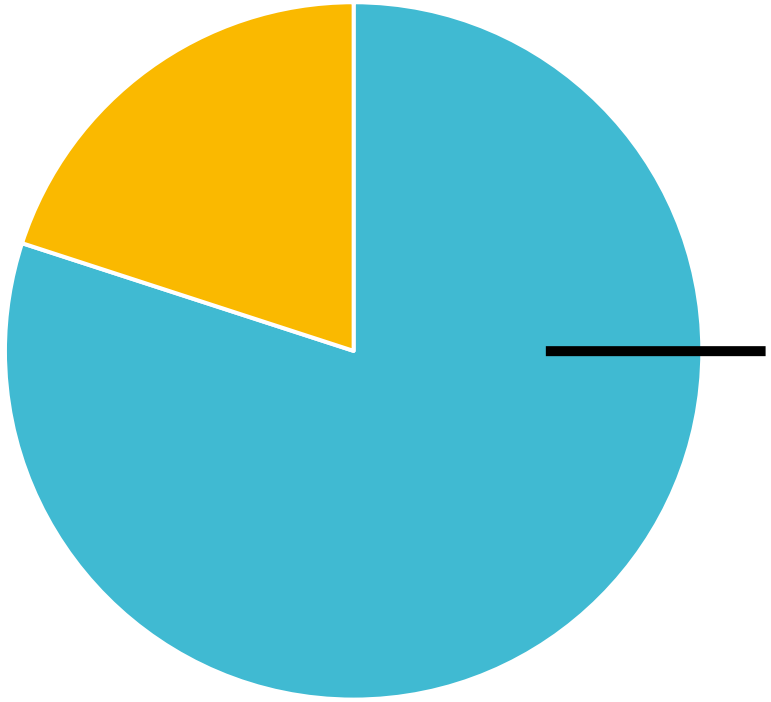
Valve Replacement



Transcatheter Approaches

Independent Validation of the Unmet Clinical Need

- **In the Fall of 2020, The Stratis Group conducted independent market research and found that 100% of cardiac care physicians managed patients with watchful waiting**



80% of cardiac care physicians would recommend treatment with a drug that slows progression of valve disease

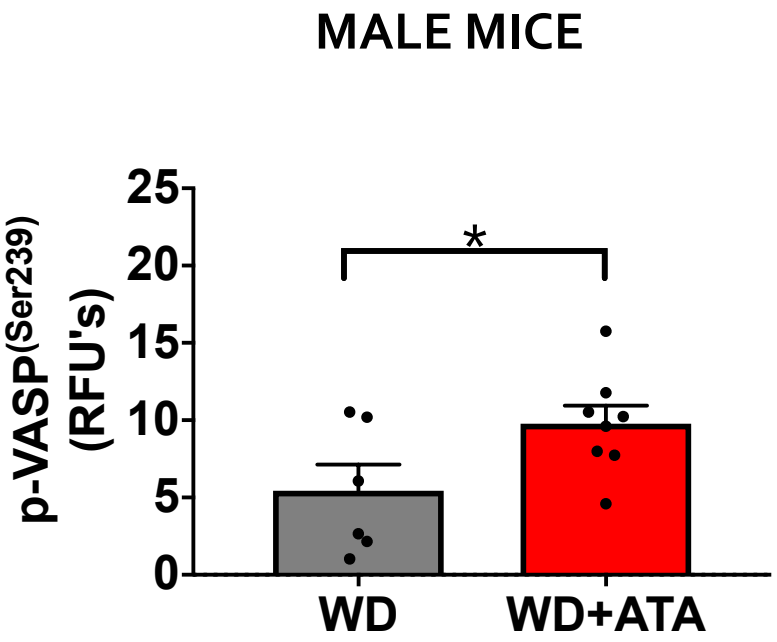
Preclinical Proof-of-Concept Studies

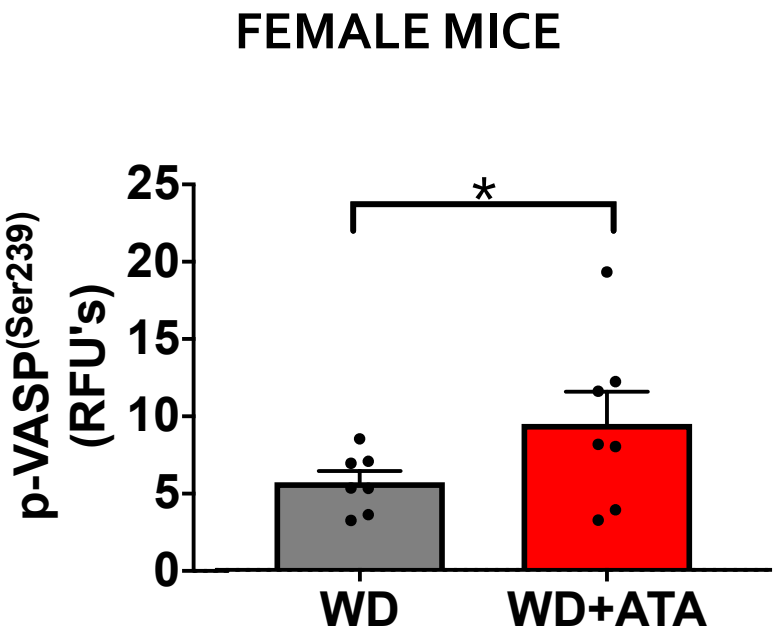
Preclinical Animal Studies of Ataciguat

In vivo studies focused on evaluating the efficacy of Ataciguat in reducing osteogenic signaling, calcification, and valvular stenosis in mice

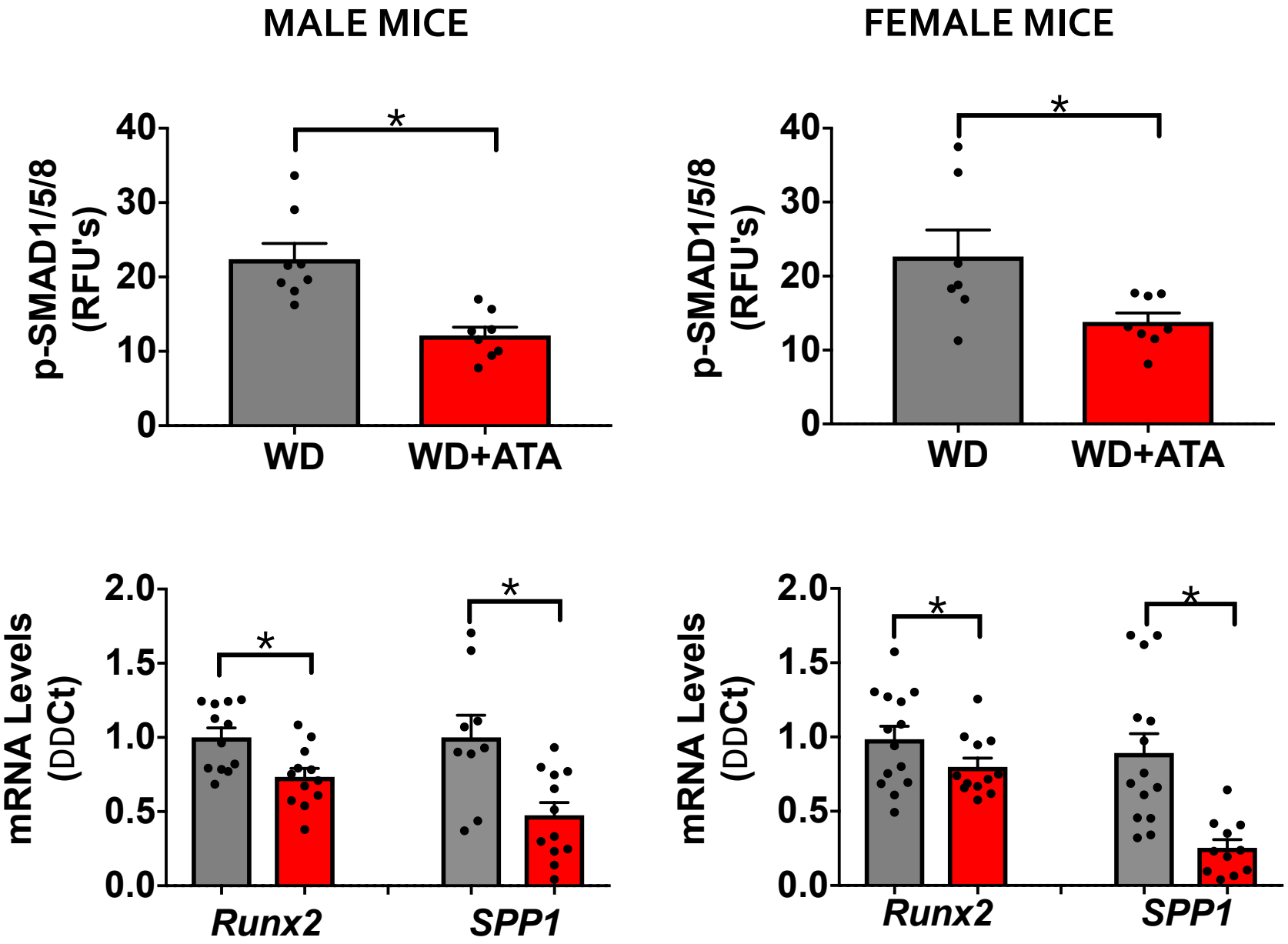
- Ldlr-deficient, ApoB100-only mice
  - Treatment initiated in established disease
- Determine whether Ataciguat attenuates
  - Osteogenic signaling
  - Calcification

Ataciguat activates sGC signaling in diseased mouse valves *in vivo*

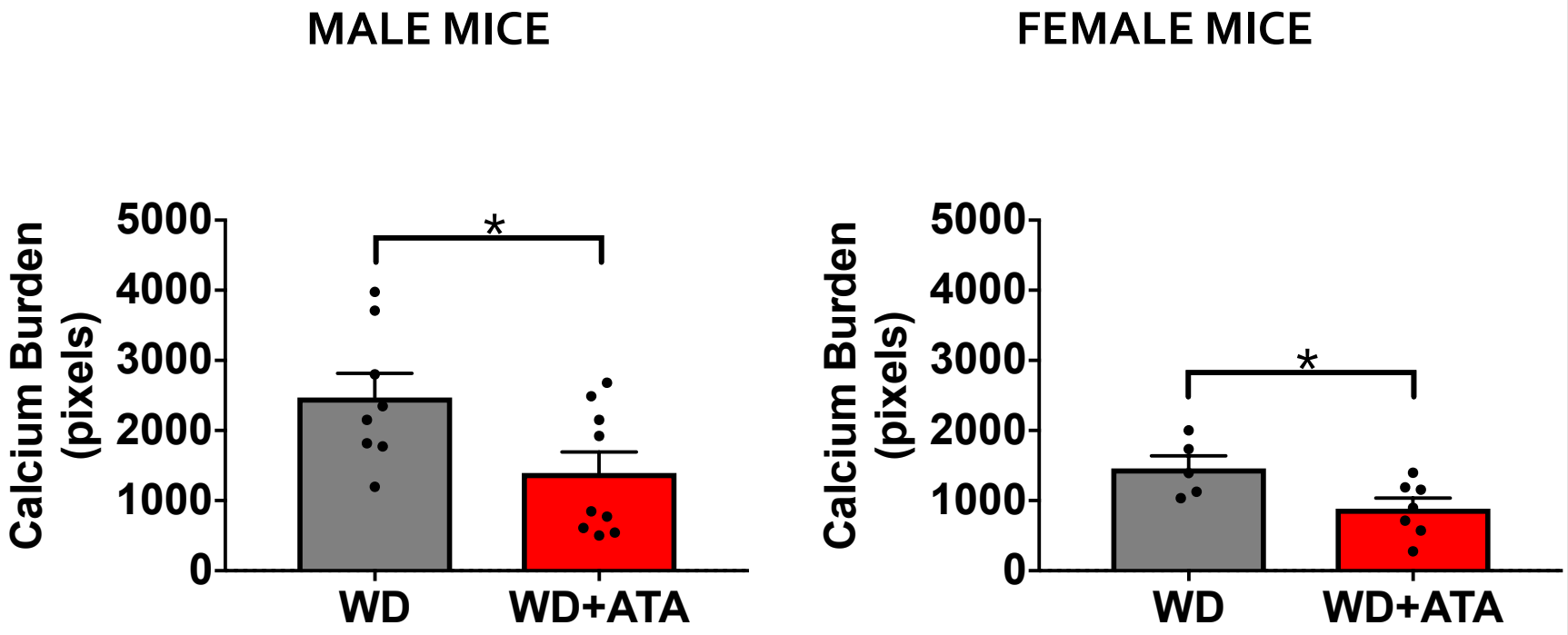




Ataciguat suppresses canonical BMP signaling and osteogenic gene expression in diseased mouse valves *in vivo*



Ataciguat reduces valvular calcification in diseased mouse valves *in vivo*



Preclinical Studies

SUMMARY OF PRECLINICAL EFFICACY STUDIES

Ataciguat

- Selectively attenuates canonical bone morphogenetic protein signaling, a known contributor to valve calcification
- Attenuates osteogenic gene expression
- Reduces valve calcification

Phase I Safety Study

Phase Ib Study of Ataciguat
A randomized, placebo, double-blinded study evaluating the safety of ataciguat in patients with moderate calcific aortic valve stenosis

- **ClinTrials Identifier:** NCT02049203
- **Start:** Jan 2014, **Finish:** March 2015
- **PI:** Dr. Jordan D. Miller, Mayo Clinic
- **14 consecutive days of oral treatment**
- **44 participants, 50 yrs or older**

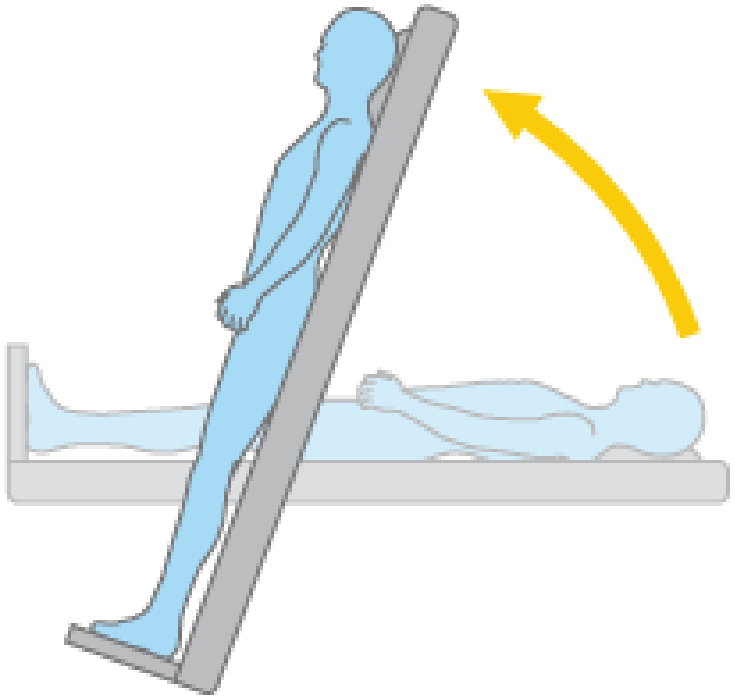
Primary Outcome Measures:
- Number of patients experiencing orthostatic hypotension
- Change in blood pressure (BP) from sitting to standing
- Change in BP following progressive head-up tilt
- Self reports of light-headedness/orthostatic intolerance

Phase I Safety Study

Phase Ib

Protocol to Assess Orthostatic Tolerance

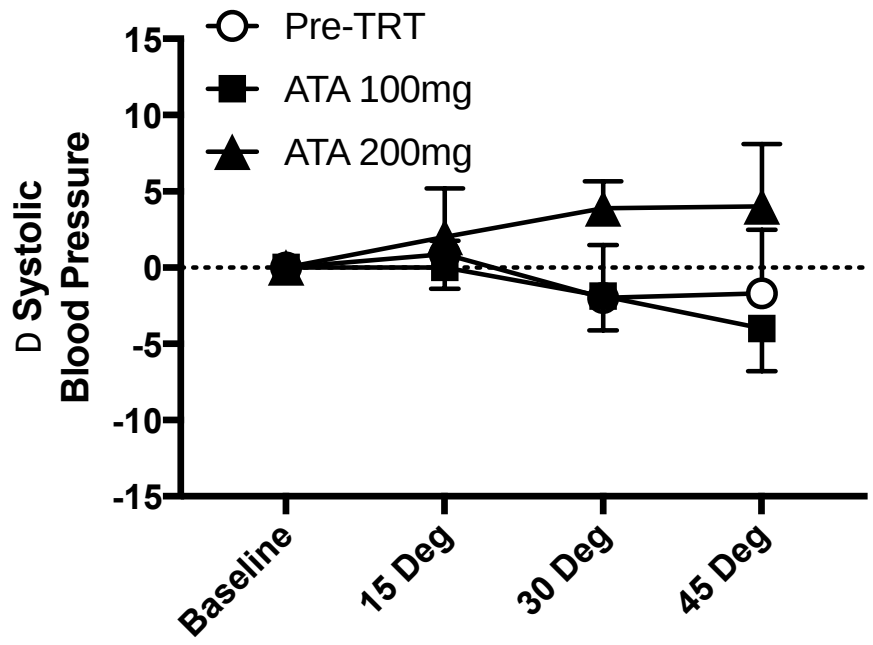
- Lie flat for 10 minutes
- Progressively tilt upright
- 15, 30, 45 degrees
- Return to flat
- Measure BP, HR throughout



Phase I Safety Study

Phase Ib

ATACIGUAT DOES NOT ALTER ORTHOSTATIC TOLERANCE



No other clinical or biochemical signs of poor tolerance or organ toxicity

Phase I Safety Study

SUMMARY OF PHASE Ib SAFETY STUDIES

Ataciguat

- Is well tolerated
- Does not induce hypotension
- Does not induce hepatotoxicity

Phase II Efficacy Study (6 months)

Phase IIb Study of Ataciguat

Title: A Phase II Randomized, Placebo-Controlled, Double-Blinded Study Evaluating the Effects of Ataciguat on Aortic Valve Calcification (CAVS) in Patients with Moderate Calcific Aortic Valve Stenosis

- 6-month oral treatment with Ataciguat, 35 participants

Primary Outcome Measure:

- Changes in aortic valve calcium levels measured by computed tomography

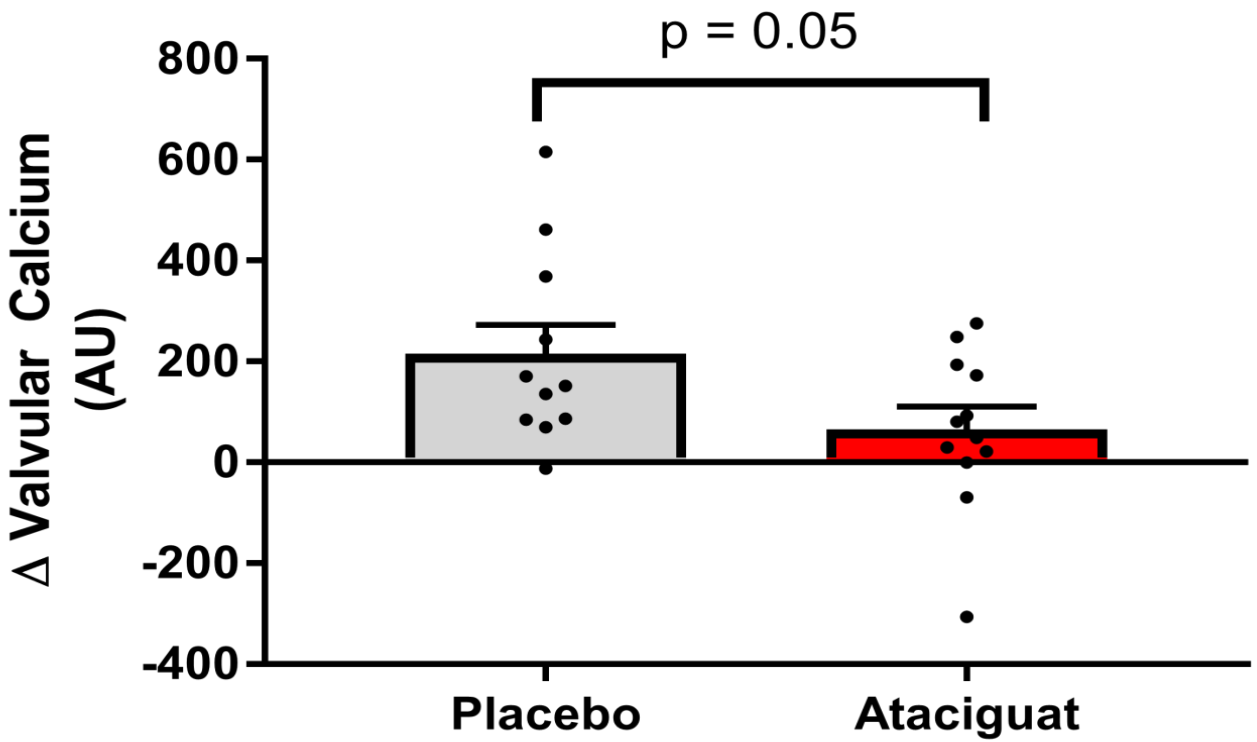
Secondary Outcome Measures:

- Changes in aortic valve function
- Changes in left ventricular function

Phase II Efficacy Study (6 months)

PHASE IIb EFFICACY STUDY

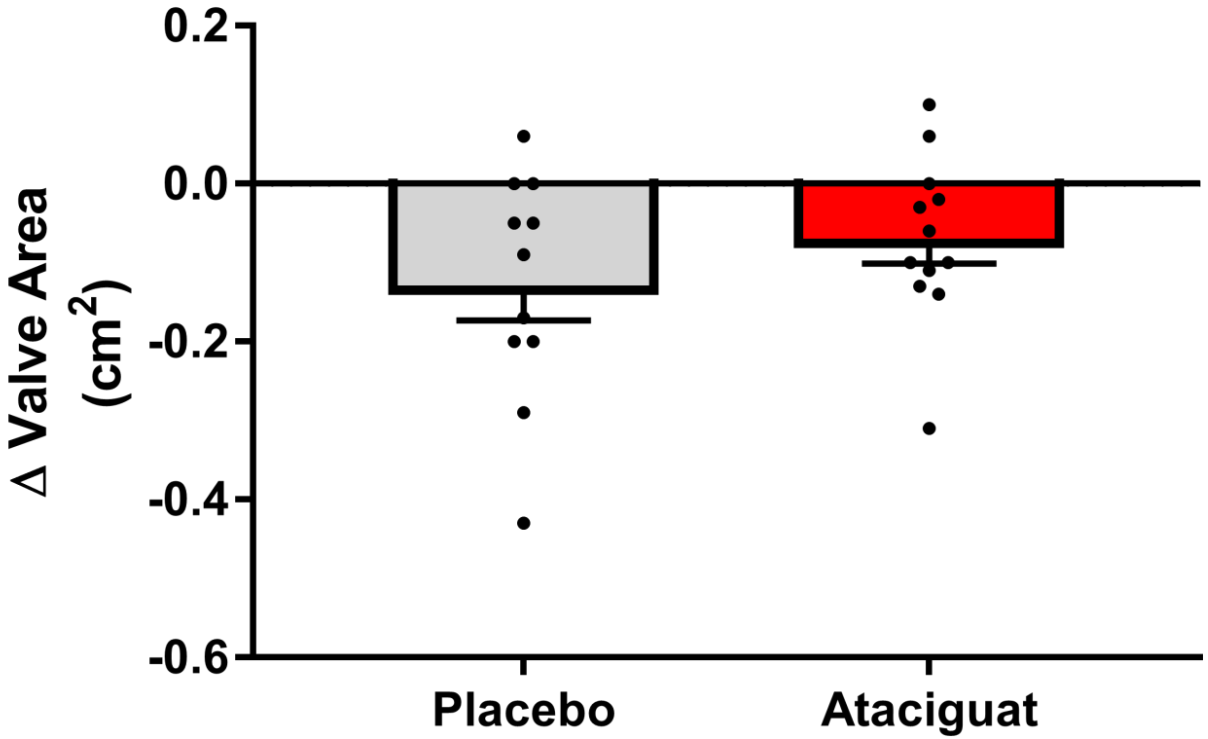
Ataciguat significantly PREVENTS PROGRESSION OF VALVE CALCIFICATION by **70%** at six months

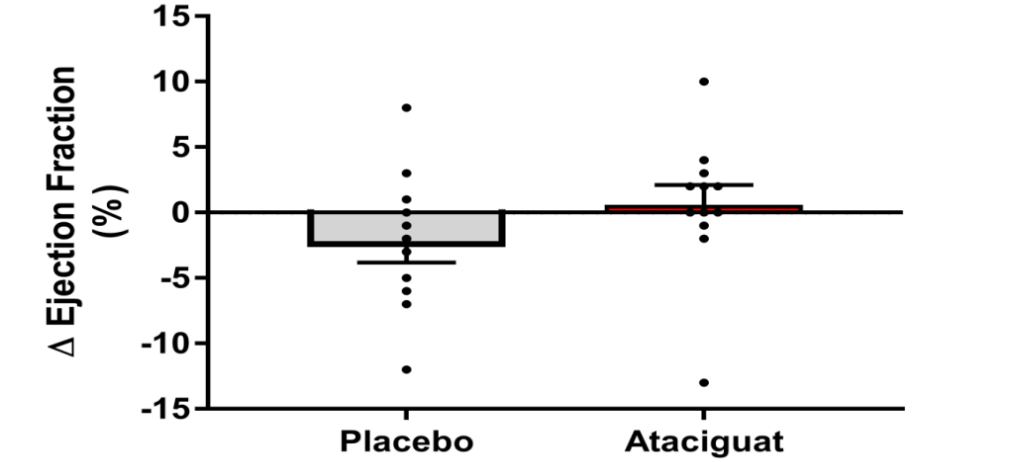


Phase II Efficacy Study (6 months)

PHASE IIb EFFICACY STUDY

Ataciguat TENDS TO SLOW VALVULAR DYSFUNCTION by **50%** at six months





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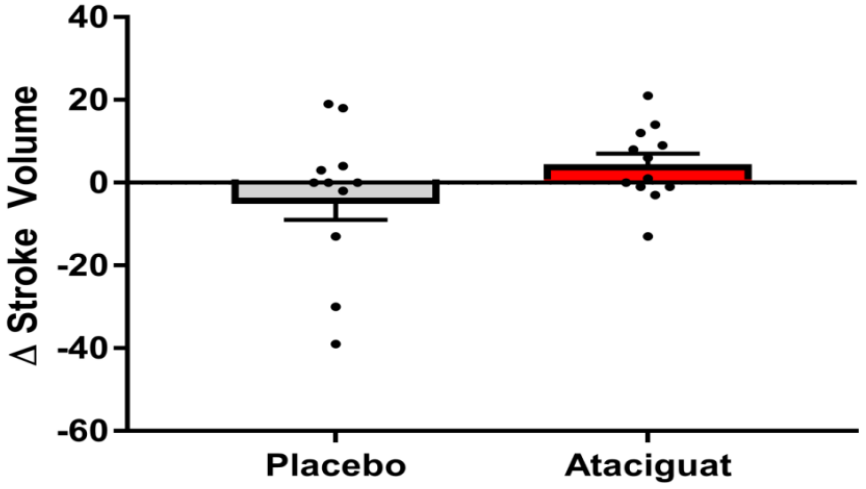

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PHASE IIb EFFICACY STUDY

ATACIGUAT MITIGATES DECLINE IN LV FUNCTION

Phase II Efficacy Study (6 months)

Summary of Efficacy Data

SUMMARY OF PHASE IIb PRELIMINARY EFFICACY STUDY

Ataciguat:

- **70%** Reduction of the progression of valve calcification
- **50%** Reduction of progression of aortic valve dysfunction
- Tends to prevent declines in left ventricular function
- No negative impact on bone formation
- Similar results seen over 12 month period

Phase III Ready Asset

ATACIGUAT'S UNIQUE HISTORY SYNERGIZES WITH OUR EFFICACY DATA

- Preclinical data suggest that Ataciguat should have negligible or even beneficial effects on non-target tissues
  - bone mineral density, GI side effects, etc…
  - largely supported by its selective mechanism of action on oxidized sGC
- Consistent with preclinical studies, Ataciguat has a robust safety and tolerance history from studies at Sanofi and Mayo Clinic
  - More than 1,000 patients have received chronic treatment with Ataciguat for up to 12 months
    - Stable angina
    - Peripheral arterial disease (ACEELA)
    - Neuropathic pain (SERENEATI)
    - Aortic valve stenosis (RSF Bio)

Phase III Ready Asset

ATACIGUAT'S UNIQUE HISTORY SYNERGIZES WITH OUR EFFICACY DATA

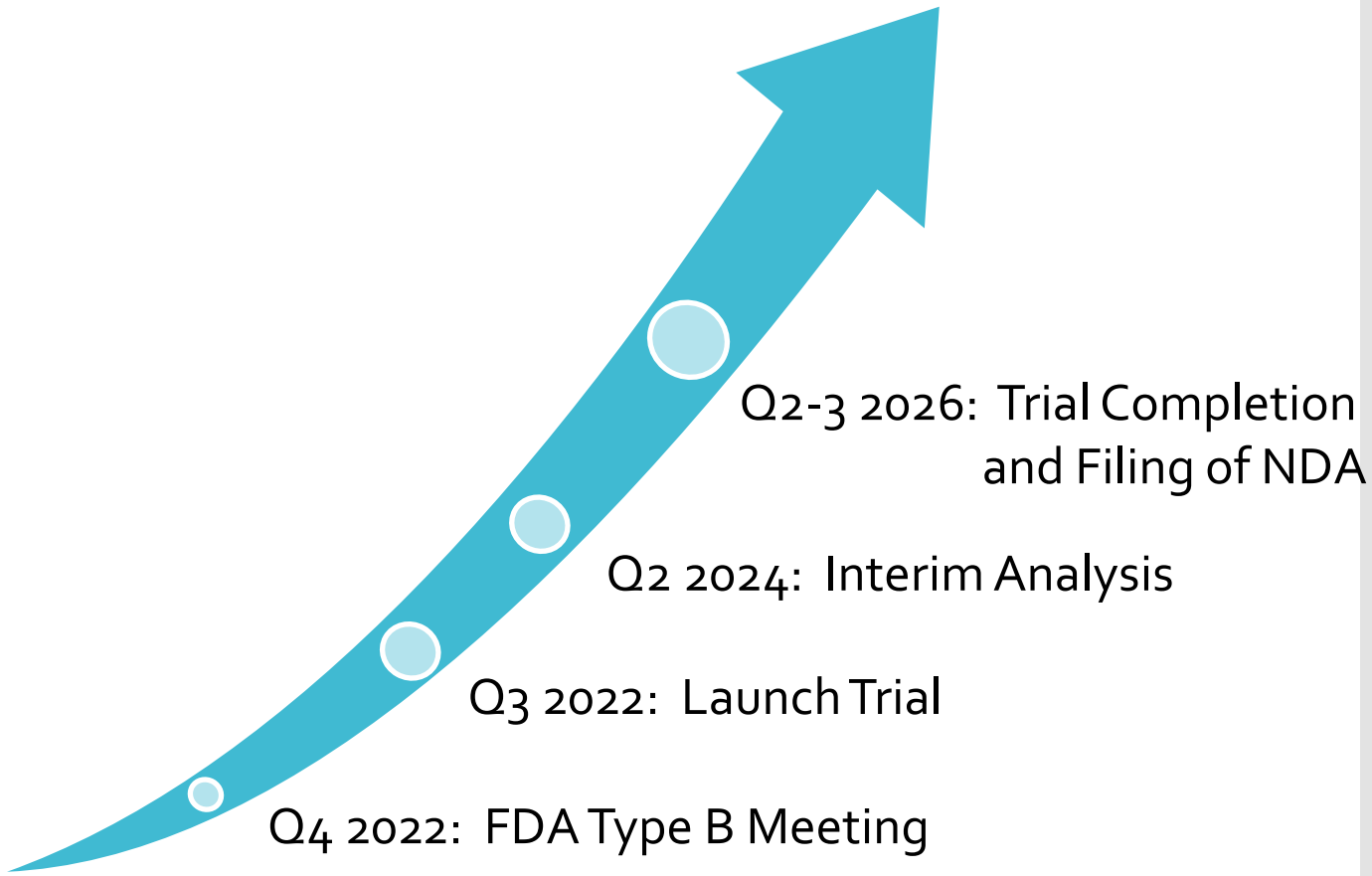
- Our Phase II data suggest that long-term treatment with Ataciguat could yield clinically meaningful benefits
  - Reducing progression of aortic valve dysfunction by 50% could double event-free survival
  - Lower levels of valve calcium are predictive of event-free survival
  - Preventing deterioration of left ventricular function will preserve functional capacity, independence, and quality of life

FDA-Endorsed, Streamlined Pathway for a First-in-Class Treatment for AVS

Phase III Study Endorsed by FDA

- **Outcomes from our Type C meeting on August 2nd, 2021**
  - **Single pivotal trial supporting registration**
  - **Number of Patients:** 800 to 1,000 total participants
    - Based on the following conservative assumptions
      - Effect size of 30% for changes in valve area
      - Declines in valve area of 0.1 cm^2/yr
  - **Length of treatment:** 36 months
  - **Sole Primary Endpoint:** changes in valve function by echocardiography
    - ***FDA's first endorsement of a surrogate endpoint in AVS to accelerate approval***
  - **Composite Secondary Endpoints Requiring only directional changes/trends:** (a) AVA less than 1.0 cm2, (b) cardiovascular death, (c) time to TAVR or SAVR and (d) Cardiovascular hospitalization.

Key Milestones and Value Inflection Points



- *Key Licenses Executed for Global Rights*
- *Manufacturing started*

Seeking FDA Regulatory Breakthrough Status

- No other technologies (that are non-invasive) and products currently on market that treat this unmet need
- Initial discussions with outside regulatory groups to file for expedited regulatory status ("breakthrough" classification)
- Current intent is to seek similar status in the EU

Independent Market Analysis by *Stratis Group*: Confirmation of Yearly Revenue Forecast

NOTE: Based off the current Medicare rules, the maximum price that will not incur co-insurance is $670/mo or **$8,040/year**

Projected yearly revenue forecasts for Ataciguat in US based on independent market assessments and prescriber feedback.					
Yearly Cost	Year 1	Year 2	Year 3	Year 4	Year 5
$8,400/yr with 4 year market capture	$2.8 B	$5.8 B	$7.9 B	$10.1 B	$10.4 B

Building a platform and long-term pipeline of solutions to address unmet needs

Ataciguat for Aortic Valve Stenosis

Phase 3 Trial in United States EU, UK, Canada

Ataciguat for other soft-tissue calcification disorders

"Straight to Phase 2" ready asset for multiple new indications

Novel sGC agonists for broad use

10 novel chemical entities for treatment of multiple conditions

Biomarkers to predict clinical response to treatment

Asset to enable earlier treatment and response to Tx

*Composition of Matter

Intellectual Property

Methods and Materials for Treating Calcific Aortic Valve Stenosis

- US Patents 9,789,126, 10,238,669, 10,568,895
- US Patent Application 2020/0230158 (Allowed)
  - Additional applications to be filed
- EP Patent 2938343 (DE, ES, FR, GB)
- EP Patent 3470070 (DE, ES, FR, GB, IT)

Methods and Materials for Gender-Dependent Treatment of Cardiovascular Dysfunction

- WO 2020/210707
  - National stage filings in progress

Methods and Materials for Treating Calcification Disorders

- 2 patent applications in progress

Intellectual Property

Methods and Materials for Treating Calcific Aortic Valve Stenosis

United States

9,789,126 (issued) 10,238,669 (issued) 10,568,895 (issued)	12/2033	Hatch-Waxman Extension	12/2036-12/2038
2020/0230158 (Allowed)	12/2033	Hatch-Waxman Extension	12/2036-12/2038

Europe (DE, ES, FR, GB)

2938343	12/2033	Supplemental Protections Certificate	12/2036-12/2038

Europe (DE, ES, FR, GB, IT)

3470070	12/2033	Supplemental Protections Certificate	12/2036-12/2038

Methods and Materials for Gender-Dependent Treatment of Cardiovascular Dysfunction

United States (National filings in progress)

WO 2020/210707	12/2020	Hatch-Waxman & Supplemental Protections Cert.	12/2040-12/2045

Leadership Team

- **Randy Berholtz, MBA/JD**

  Chairman and Chief Executive Officer: Randy is a biotech executive with over 20 years experience with public and private companies such as Nanogen, Inc., the ACON Group of Chinese and US life science companies, Apricus Bio, Inc. and Innovus Pharmaceuticals, Inc (acquired by Aytu Biosciences, Inc.) He also is a Senior Advisor to Mesa Verde Venture Partners and is Chairman of the Boards of Ambulero, Inc. and Abbreos, Inc. He has a BA from Cornell, an M.Litt. Form Oxford (Rhodes Scholar), a JD from Yale and an MBA from the University of San Diego.

- **Inder Anand MD/D.Phil**

  Chief Medical Officer, Dr. Anand is a Clinical Cardiologist, and D.Phil. in Cardiovascular Physiology from Oxford University, England, where he was a Rhodes Scholar. Dr. Anand brings a wealth of global knowledge to designing and conducting clinical trials, authoring 450+ peer-reviewed scientific publications, 600+ abstracts, and 31,760+ citations. Founder of Heart Failure Society of America (HFSA), in-depth analyses on the prognostic role of several biomarkers in over 5,000 patients with heart failure.

- **Leonard Miller, Ph.D.**

  Chief Scientific Officer: Dr. Miller has over 20 years of biotech experience with San Diego-based companies such as Gensia Pharma, Inc., Metabasis, Inc. as Sr Scientific Investigator and Targazyme, Inc.as VP Research. Prior to Industry he had over 17 years of academic science experience with 65 peer-reviewed publications and primary editor on three books.

- **Laura Lewerentz-Juziuk, MSN**

  Chief Operating Officer: Laura is a clinical catalyst with over 20 years of corporate and scientific leadership. Delivering a synergistic blend of clinical, compliance, and commercialization acumen. Optimizing clinical substructures, augmenting productivity in fast-paced clinical environments, and mitigating operational risk for optimal progression and corporate profitability. Laura has built a clinical consortium, maintains military base access and privileges, and received her MSN from the University of California, Los Angeles.

Advisory Board

- **Jordan Miller, Ph.D.,** Dr. Miller was the Principal Investigator on the studies with Ataciguat at Mayo Clinic, and holds multiple leadership roles including Vice Chair for Research in the Department of Cardiovascular Surgery and Director of the Cardiovascular Disease and Aging Program in the Kogod Center on Aging at Mayo Clinic, Rochester, Minn.
- **Daniel Bloomfield, MD, D.Phil., FACC, FAHA.** Dr. Bloomfield is an Interventional Cardiologist, Chief Medical Officer for Anthos Therapeutics, Inc. and former Senior VP, Global Chemical Development at Merck.
- **Howard Dittrich, MD.** Dr. Dittrich is the Chief Medical Officer for Cirius Therapeutics, Inc.
- **Hartzell Schaff, MD.** Dr. Schaff is a cardiac surgeon at Mayo Clinic, Rochester, Minn, past president of the American Association of Thoracic Surgeons, and founding member of the Heart Valve Society.
- **Jaime Gerber, MD, FACC**, Dr. Gerber is a Cardiologist and Associate Professor of Clinical Medicine at the Yale University School of Medicine
- **Hector Michelena, MD,** Dr. Michelena is a cardiologist with internationally-recognized clinical expertise in aortic valve stenosis and echocardiographic methods to assess heart valve disease at Mayo Clinic, Rochester, Minn.

Series A Financing

- We are currently raising funds for our Series A round of between $40 to $50 million
- Use of funds are to execute our Phase III trial of Ataciguat for moderate AVS and for preclinical work on additional indications

Contact Information

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Chairman and Chief Executive Officer

Rancho Santa Fe Bio, Inc.

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rberholtz@rsfbio.com