Orchestra BioMed

Corporate
Presentation
Q2 2024

Forward-Looking Statements

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Certain statements included in this document that are not historical facts are forward-looking statements for purposes of the safe harbor provisions under the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements generally are accompanied by words such as “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “expect,” “should,” “would,” “plan,” “predict,” “potential,” “seem,” “seek,” “future,” “outlook” and similar expressions that predict or indicate future events or trends or that are not statements of historical matters. These forward-looking statements include, but are not limited to, statements relating to the potential safety and efficacy of our product candidates, the initiation and timing of our planned pivotal trials and reporting of top-line results, expected market sizes for our product candidates, the ability of our partnerships to accelerate clinical development, and our estimated future financial performance and financial position. These statements are based on various assumptions, whether or not identified in this document, and on the current expectations of the Company’s management and are not predictions of actual performance. These forward-looking statements are provided for illustrative purposes only and are not intended to serve as and must not be relied on as a guarantee, an assurance, a prediction, or a definitive statement of fact or probability. Actual events and circumstances are difficult or impossible to predict and may differ from assumptions. Many actual events and circumstances are beyond the control of the Company. These forward-looking statements are subject to a number of risks and uncertainties, including changes in domestic and foreign business, market, financial, political, and legal conditions; risks related to regulatory approval of the Company’s product candidates; the timing of, and the Company’s ability to achieve expected regulatory and business milestones; the impact of competitive products and product candidates; and the risk factors discussed under the heading “Item 1A. Risk Factors” in the Company’s annual report on Form 10-K filed with the U.S. Securities and Exchange Commission on March 27, 2024 as updated by any risk factors disclosed under the heading “Item 1A. Risk Factors” in the Company’s subsequently filed quarterly reports on Form 10-Q.

The Company operates in a very competitive and rapidly changing environment. New risks emerge from time to time. Given these risks and uncertainties, the Company cautions against placing undue reliance on these forward-looking statements, which only speak as of the date of this presentation. The Company does not plan and undertakes no obligation to update any of the forward-looking statements made herein, except as required by law.

Orchestra BioMed Executive Overview

Partnership-enabled business model designed to:

Accelerate innovation to patients & yield exceptional future profitability

Lead Program

BackBeat CNT™ (AVIM* therapy)

Targets >$10B annual hypertension markets

- Statistically significant double-blind, randomized pilot study efficacy results
- **BACKBEAT Global pivotal study now actively enrolling**

Strategic collaboration

Medtronic

Double-digit revenue share

Pipeline Program

Virtue® SAB

- **Targets >$4B** annual artery disease markets
- Strong 3-year multi-center pilot study safety and efficacy data
- Conditional IDE approved for coronary pivotal study

Strategic collaboration

TERUMO

Double-digit revenue share

Expected cash runway into 2H 2026

Major strategic & institutional investors

Medtronic rtw PERCEPTIVE ADVISORS TERUMO

*AVIM = atrioventricular interval modulation

Orchestra BioMed

Orchestra BioMed's Partnership-Enabled Model Benefits All

Orchestra BioMed
Development

- Secure substantial long-term royalties
- Outsource commercialization
- Multiple pipeline opportunities

Shared Benefits
Innovation

- Improve patient lives
- Accelerate development
- Leverage expertise & resources

Strategic Partners
Commercialization

- Enable new growth opportunities
- Outsource development
- Minimize P&L dilution

Advancing High-Impact Pipeline

Product Platforms	Target Indications	Preclinical	Clinical Feasibility	Clinical Pivotal	Partner	Study Sponsor
Lead Program						
BackBeat CNT™ (AVIM Therapy)	**Hypertension (HTN)** (pacing patients; HTN+P)	**BACKBEAT Global Pivotal Study Enrolling**			Medtronic	Orchestra BioMed
	High-Risk HTN[1] (non-pacing patients)				Medtronic ROFN	
CNT - HF	Heart Failure					
Pipeline Program						
Virtue® Sirolimus AngioInfusion™ Balloon (SAB)	**Coronary In-Stent Restenosis (ISR)**	**IDE Approved & FDA Breakthrough**[3]			TERUMO	Orchestra BioMed
	Coronary Small Vessel (SV)[2]	**FDA Breakthrough**[4]			TERUMO	TERUMO
	Below-the-Knee (BTK)[2]	**FDA Breakthrough**[5]			TERUMO	TERUMO
SirolimusEFR™ / Microporous Balloon	Ortho, oncology, urology, GI & other					

[1]Will seek to leverage data from HTN+P pilot and pivotal trials to support clinical and regulatory development for High-Risk HTN indication given that age and other demographic factors of the target population are expected to be similar, the type of hypertension treated will likely be isolated systolic hypertension which is predominant in the HTN+P population, and other co-morbidities are also expected to be common to both target populations. However, there have been no discussions with the FDA or a comparable foreign regulator in this regard. [2]Plan to leverage existing coronary ISR data to support potential Pivotal Study, although there have only been limited discussions with the FDA or a comparable foreign regulator in this regard. [3] In addition, in light of the recent FDA approval of Boston Scientific Corporation's AGENT™ paclitaxel-coated balloon for the treatment of coronary ISR, we and Terumo are reviewing the design for the Virtue ISR-US pivotal study and considering alternative clinical study designs with input from our clinical steering committee for Virtue SAB. Virtue SAB has received Breakthrough Device Designation for the balloon dilatation of the stenotic portion (up to 26 mm length) of a stented coronary artery (in-stent restenosis (ISR)) that is 2.25 to 4.0 mm in diameter, for the purpose of improving lumen diameter; [4]Virtue SAB has received Breakthrough Device Designation for the balloon dilatation of the de novo stenotic portion (up to 26mm in lesion length) of a native coronary artery of 2.0 mm to 2.5 mm in diameter (small coronary arteries), for the purpose of improving lumen diameter; [5]Virtue SAB has received Breakthrough Device Designation for the balloon dilatation of the stenotic portion (up to 18 mm length) of an infrapopliteal artery (P-3 segment or distal, below the knee, with reference vessel diameter (RVD) 2.25 - 4.0 mm), for the purpose of improving lumen diameter.

Orchestra BioMed™

Highly Accomplished Executive Team & Board

David Hochman
Chairman, CEO, Founder

Darren R. Sherman
President, COO, Director, Founder

Andrew Taylor
Chief Financial Officer

Yuval Mika, Ph.D.
GM & CTO, Bioelectronic Therapies

George Papandreou, Ph.D.
GM & SVP, Focal Therapies

Hans-Peter Stoll, M.D., Ph.D.
Chief Clinical Officer

Bill Little
EVP, Corporate Development & Strategy

Avi Fischer, M.D.
SVP, Medical Affairs & Innovation

Bob Laughner
SVP, Regulatory & Quality

Ziv Belsky
VP, Research, Bioelectronic Therapies

Juan Lorenzo
SVP, Product Development, Focal Therapies

Lisa Daniels
VP, Human Resources

Executive Team: | >300 Years of Experience | >25 Avg Industry Years Each | >100 Product Approvals | >600 Authored Patents

Independent Board Members

Jason Aryeh

Pamela Connealy

Eric S. Fain, M.D.

Eric A. Rose, M.D.

David Pacitti

BackBeat CNT™

Atrioventricular interval modulation (AVIM) therapy

BackBeat CNT™ (AVIM Therapy) Overview

Collaboration with Medtronic

Risk of High Blood Pressure

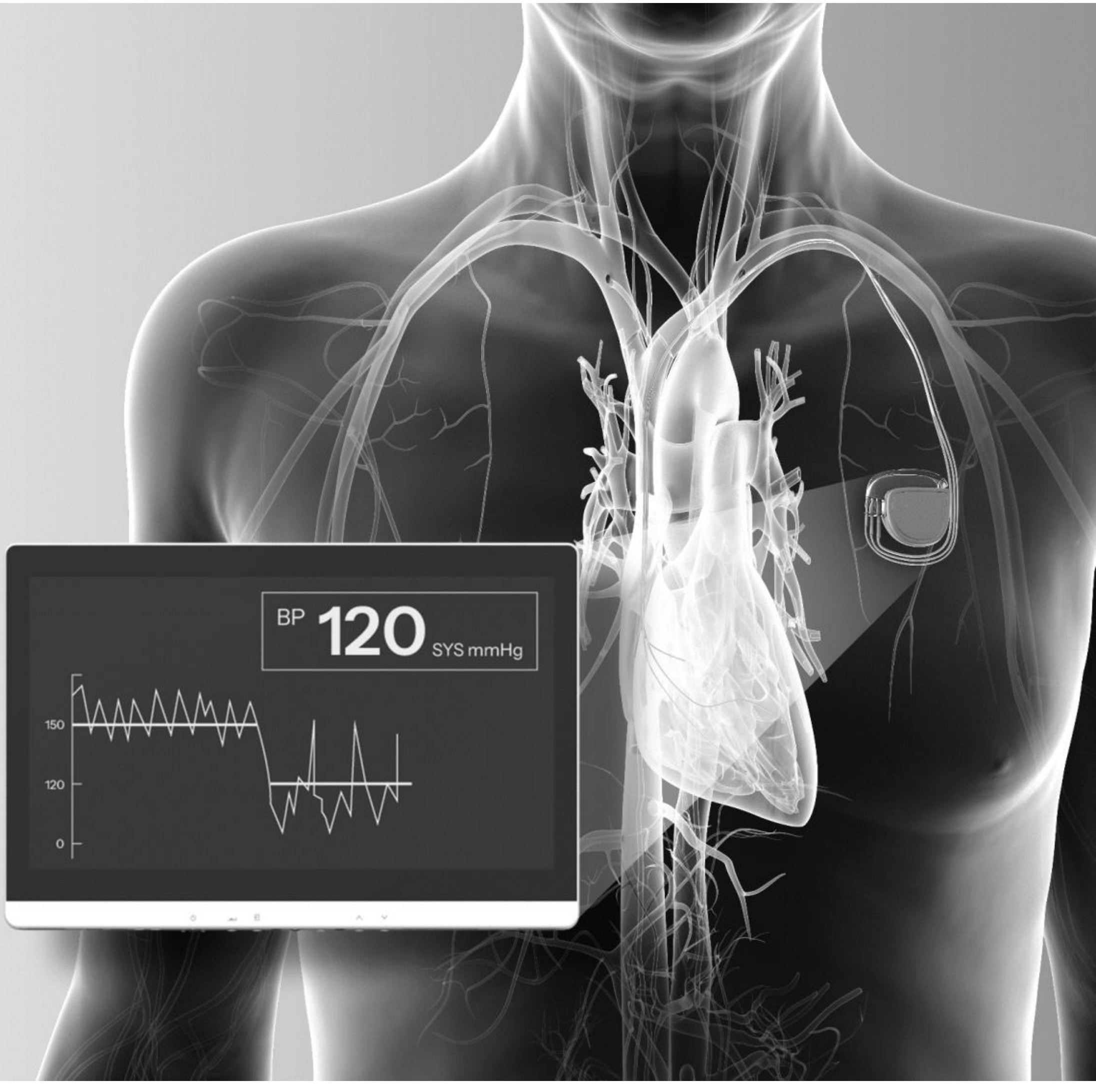
Hypertension is the **leading global risk factor for death,** particularly **older, higher risk patients** such as **the pacemaker population,** where it is **the #1 comorbidity**

Novel Therapy

Pacemaker-delivered therapy designed to **immediately, substantially and persistently reduce blood pressure** while simultaneously modulating the autonomic nervous system

Immediate Unmet Patient Need

Over 750K patients globally per year
receiving pacemakers also have hypertension



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Large Global Opportunity for Treating Hypertension in Target Populations

HTN + Pacemaker

750,000 patients

~70% of pacemaker patients[1]

>$2 Billion*

- Same pacemaker patients, same device implant, and same treating physicians
- Leverageable existing reimbursement structures

High Risk HTN

2,400,000 patients

~0.2% of HTN patients

>$8 Billion*

- Older patients with uncontrolled hypertension and other significant comorbidities
- Similar demographic to pacemaker patients, high-risk, difficult-to-treat

*Total addressable market in 2025 based on company estimates; [1]Company estimates based on published sources, including National Inpatient Survey (NIS) and National Health and Nutrition Examination Survey (NHANES); Definition: Hypertension (HTN)

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Strategic Collaboration

Orchestra BioMed

- Developed BackBeat CNT (AVIM therapy) from concept stage; owns all related IP
- Conducted all prior development work including MODERATO I & II clinical studies
- Partnered with Medtronic for global regulatory approval and commercialization
- Sponsor for the BACKBEAT Global Pivotal Study
- **$500 - $1,600 revenue share** per AVIM-enabled device assuming existing reimbursement structures[1]

Medtronic

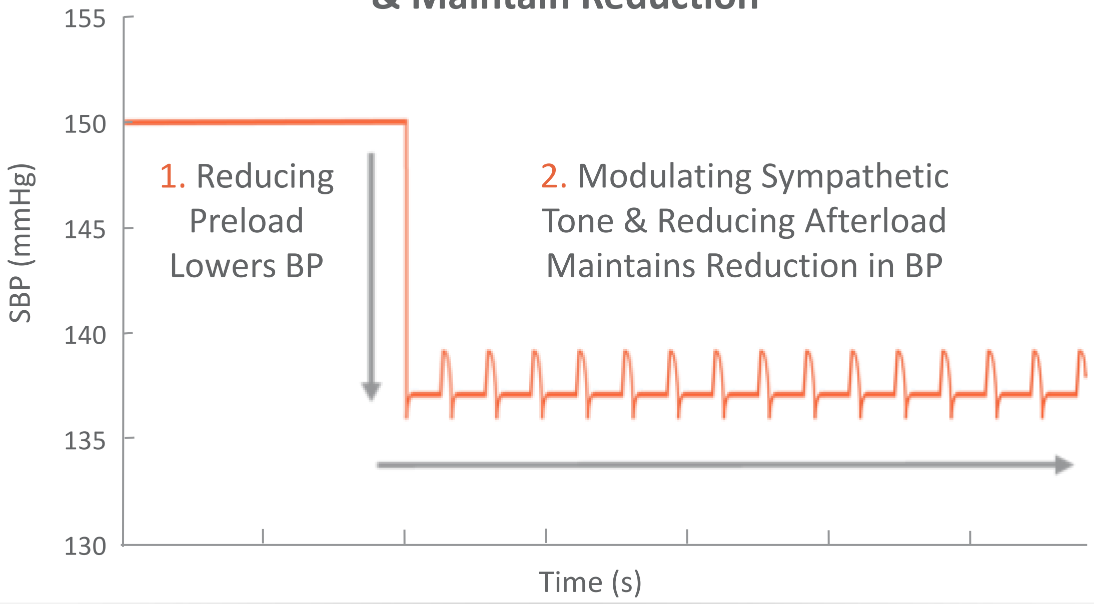
- Global market leader in cardiac pacing therapy: **>$1.5B** in annual revenues
- Providing leading device plus clinical & regulatory resources
- Exclusive global commercial rights for AVIM therapy in pacemaker-indicated patients
- Right of first negotiation to expand global rights for the treatment of non-pacemaker HTN patients
- **$50M equity investment** in Orchestra BioMed

[1] Amount is based on higher of (1) a fixed dollar amount per device (amount varies materially on a country-by-county basis) or (2) a percentage of sales.

Novel AVIM Therapy Mechanism of Action Designed to Substantially and Persistently Reduce Blood Pressure

- AVIM therapy uses a dual-chamber pacemaker to deliver programmed sequences of **short AV intervals** interspersed with **longer AV intervals** designed to to reduce blood pressure by:
  - Reducing cardiac preload
  - Modulating autonomic nervous system responses (sympathetic tone) and reducing afterload (TPR) to sustain blood pressure reduction
- Designed to utilize well characterized physiologic mechanisms, including Frank-Starling law, to **favorably impact circulatory hemodynamics:**
  - Reduced intra-cardiac volumes and pressures
  - Improved cardiovascular efficiency
  - No adverse impact on contractility
- Compatible with traditional pacing lead locations as well as emerging **conduction system pacing** lead placements

Designed to Substantially Lower Blood Pressure (BP) & Maintain Reduction



Definitions: TPR (Total Peripheral Resistance).

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Existing Body of Clinical Data Supporting Efficacy and Safety

2012

Feasibility Study in Canine HTN Model
Proof of concept in 5 dogs

Acute Feasibility Study in Subjects with HTN
18 patients

2016

MODERATO I - First In-Human Implant Study
Multi-center, Single-arm Study in 27 patients

TCT Innovation Shark Tank Award
Cardiovascular Research Foundation®

Best Abstract at ICI

2019

MODERATO II – Pilot Study
Prospective, multi-center, randomized, controlled, double-blind pilot study in 47 patients – 6-month primary endpoint data late-breaking presentation at TCT

Cardiovascular Research Foundation®

2021

MODERATO II Two-year and ISH results
Presented at TCT

Cardiovascular Research Foundation®

Peer-Reviewed Publication of MODERATO II Results
in the Journal of the American Heart Association

American Heart Association.

2022

Strategic partnership with Medtronic
for development and commercialization of AVIM therapy for hypertensive pacemaker patients

Medtronic

2023

Initiation of the BACKBEAT IDE Study
Prospective, multi-center, randomized, controlled, double-blind pilot study in approximately 500 patients at 80 sites

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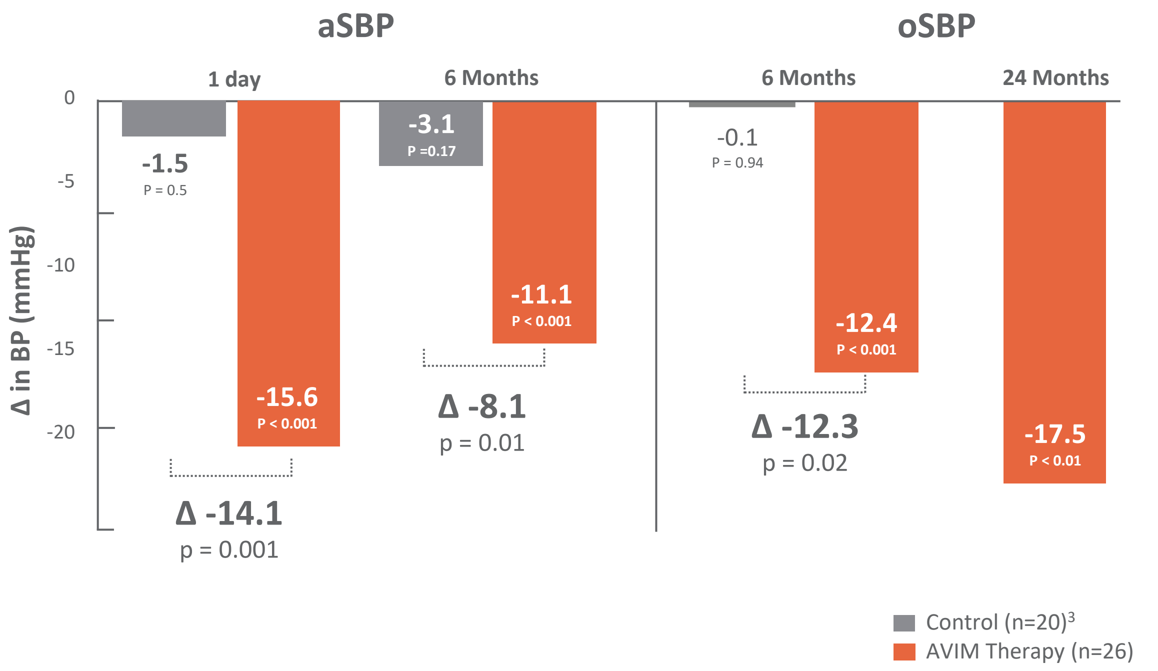
MODERATO II Randomized, Double-Blind Results

MODERATO II, a prospective, multi-center, randomized, controlled, double-blind, pilot study of pacemaker patients with persistent uncontrolled hypertension despite medical therapy (at least 1 drug; mean 3.3 drugs per patient)

Significant Reduction in 24-Hr aSBP and oSBP[1,2]



-11.1 mmHg
in 24-Hour aSBP at 6 months

0%
MACE vs. 14.3% in control group at 6 months[4]

-17.5 mmHg
in oSBP at 2 years

85%
of patients with reduction in aSBP at 6 months

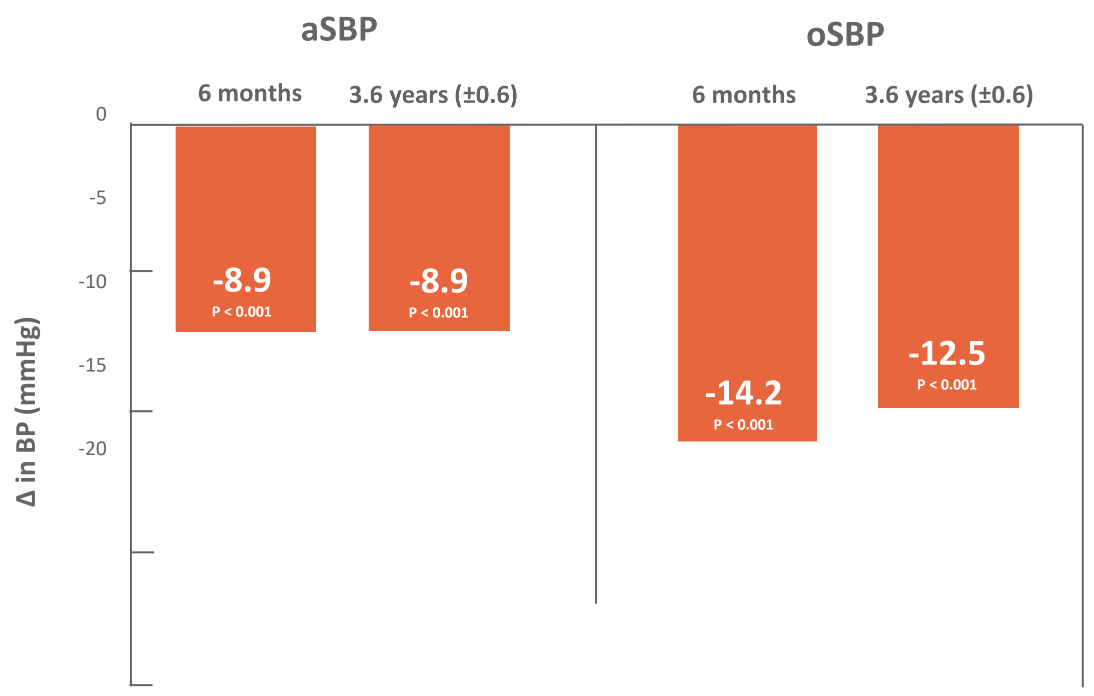
[1]Kalaras et al. Journal of the American Heart Association. 2021;10:e020492 ahajournals.org/doi/10.1161/JAHA.120.020492; [2]Burkhoff MODERATO II Study 2-Year Results TCT 2021; [3]24-Hr aSBP Control (n=19),1 control patient could not be measured despite repeat measurement (patient had extremely high blood pressure); [4]The formal final Data Safety Monitoring Board report for MODERATO II included a revised major adverse cardiac event rate in the control group from 9.5% to 14.3% to reflect another event of heart failure in a third control patient after publication of the study results. This report was provided to the FDA. **Definitions**: Major Adverse Cardiac Events (MACE) included death, heart failure, clinically significant arrhythmias (i.e., persistent or increased atrial fibrillation, serious ventricular arrhythmias), myocardial infarction, stroke and renal failure in treatment group calculated per patient. Office Systolic Blood Pressure (oSBP); Ambulatory Systolic Blood Pressure (aSBP)

Long-Term Blood Pressure Reduction with AVIM Therapy

Long-term blood pressure from a follow-up study* of 16 patients from MODERATO II

- 8 AVIM therapy & 8 control patients who crossed-over to AVIM therapy at the end of the 6-month double-blind phase of Moderato II and agreed to be followed long-term
- Each patient had aSBP and oSBP measured at an average of 3.6 years (±0.6) following initiation of AVIM therapy

Significant Reduction in 24-Hr aSBP and oSBP



P value between 6 months and 3.6 years (±0.6) = ns

-8.9 mmHg in 24-Hour aSBP from baseline at 3.6 years (±0.6)

-12.5 mmHg in oSBP at 3.6 years (±0.6)

100% of patients with reduction in aSBP at 3.6 years (±0.6)

* Patients were re-consented for long-term follow-up

Data on File. **Definitions:** Office Systolic Blood Pressure (oSBP); Ambulatory Systolic Blood Pressure (aSBP)

BACKBEAT Study Summary

Enrollment underway of prospective, multi-center, double-blind study investigating the efficacy and safety of AVIM therapy in patients indicated for a dual-chamber pacemaker who also have uncontrolled hypertension (HTN) despite the use of antihypertensive medications

Randomizing approximately **500 patients across ~80 study sites** globally

Inclusion and exclusion criteria apply learnings from MODERATO II and other recent HTN clinical studies

Study endpoints:

- **Primary Efficacy endpoint:** Difference in the **change of mean 24-hour aSBP at 3 months** post randomization
- **Primary Safety endpoint:** Rate of **unanticipated serious adverse device events at 3 months** post randomization
- **Secondary/additional endpoints**: Double-blind follow-up will continue **through 12 months** to enable collection of additional clinical results and secondary endpoints

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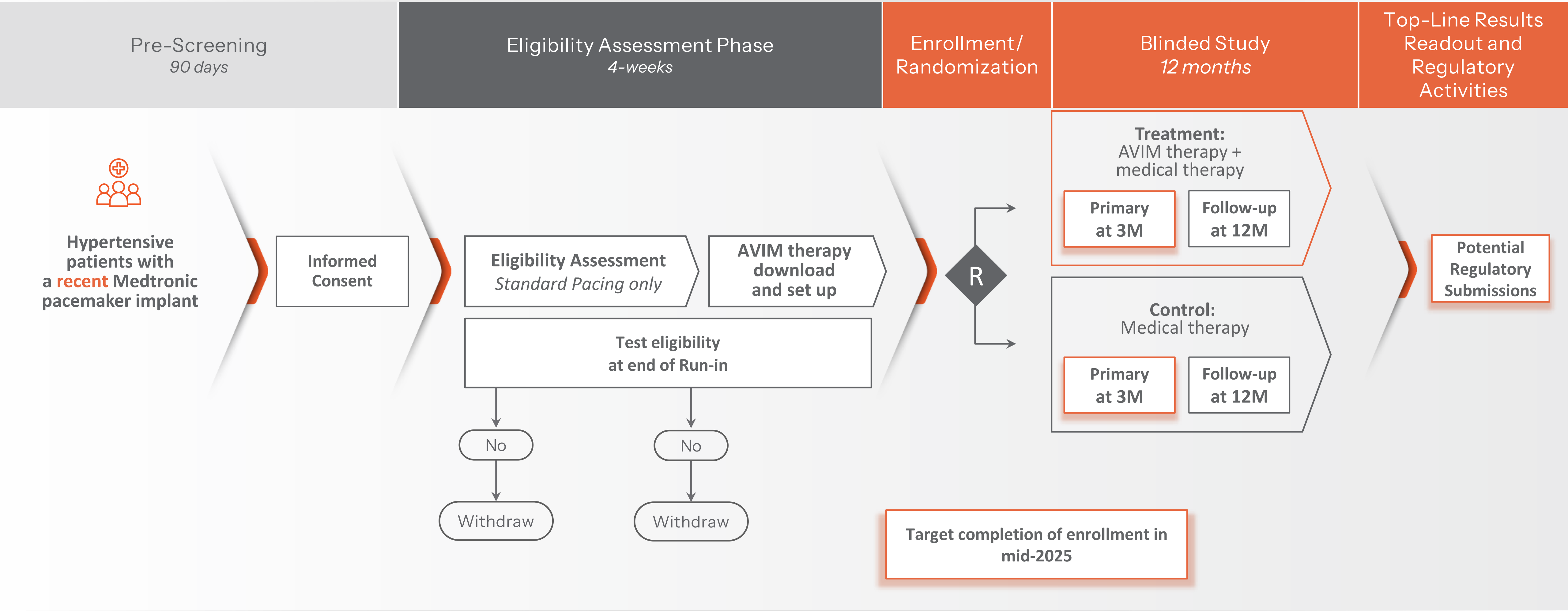
BACKBEAT Study Design



*Implant is decoupled from study outcomes & endpoints.

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Virtue® Sirolimus AngioInfusion™ Balloon (SAB)

Virtue® SAB Overview

Collaboration with TERUMO

Paradigm Shift in Treatment of Artery Disease

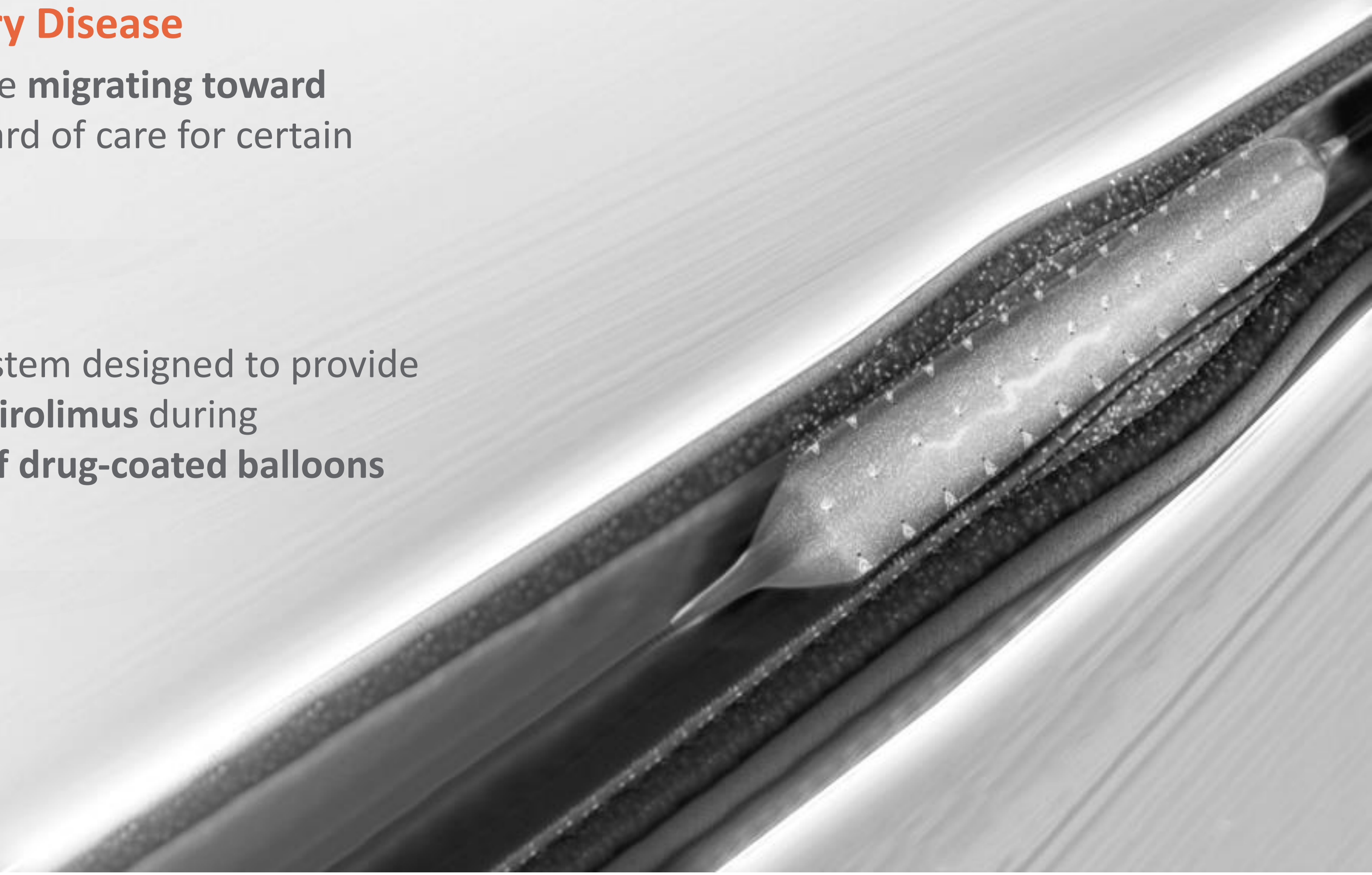
Interventional treatment of artery disease **migrating toward paclitaxel-coated balloons** as new standard of care for certain key indications

Highly Differentiated Solution

Non-coated drug/device combination system designed to provide **protected delivery of extended release sirolimus** during angioplasty and **overcomes limitations of drug-coated balloons**

Large Market Opportunity

Over 3M* targeted annual procedures globally; strategic partnership provides double-digit revenue share



*Total addressable market in 2025 based on company estimates

Large Breakthrough Designation Opportunity for Virtue SAB

Coronary

~2,000,000 patients

ISR, SV De Novo

>$2.4 Billion

Peripheral

~1,250,000 patients

BTK

>$1.6 Billion

>$4 Billion
Annual Global Market for FDA Breakthrough Indications (Coronary ISR, SV, BTK)

>3.2M
Annual Global Addressable Procedures for FDA Breakthrough Indications

Large mature market with suboptimal treatments for coronary ISR, coronary SV de novo and BTK

Multibillion dollar established market for additional potential vascular indications

Designed to leverage existing treatment paradigm & established technologies: sirolimus and balloon angioplasty

*Total addressable market in 2025 based on company estimates; Definitions: Coronary Artery Disease (CAD), Peripheral Artery Disease (PAD), In-stent Restenosis (ISR), Small Vessel (SV, ≤2.5mm), High bleeding Risk De Novo (>2.5mm), Below-the-Knee (BTK, Rutherford 3-6, w/out severe comorbidities).

Strategic Collaboration

- Developed Virtue SAB from concept stage; owns all related IP (SirolimusEFR, AngioInfusion balloon, etc.)
- Conducted all prior development work including SABRE study in coronary ISR
- Partnered with Terumo for global regulatory approval and commercialization in vascular indications
- Sponsor for the Virtue ISR-US pivotal study (conditional IDE granted)
- **10-15% royalty on net sales PLUS per unit payments** for SirolimusEFR
- Orchestra retains rights for all non-vascular indications

- Global leader in interventional cardiology accessory devices: **>$2.4B in annual revenues**[1]
- **$30M upfront payment** to and $5M equity investment in Orchestra BioMed
- **Orchestra BioMed was initially eligible for $65M in milestone payments**; ***currently being renegotiated***
- Responsible for clinical and regulatory expenses, excluding Virtue ISR-US study, as well as device supply chain and commercialization
- Virtue SAB has potential to become **Terumo's flagship therapeutic offering**

[1]Based on Terumo's consolidated financial results for the fiscal year ended March 31, 2023; Initiation of Virtue ISR-US pivotal study of Virtue SAB for the treatment of coronary ISR, as well as submissions to Japanese PMDA in coronary ISR and small vessel disease are pending ongoing operational and financial plan calibration with Terumo, currently anticipated to conclude in the second half of 2024.

Benefits of Sirolimus Compared with Paclitaxel

- Paclitaxel-coated balloons (PCB) are **widely used in EU and Japan** to treat coronary ISR and coronary SV
- **AGENT™ PCB** for coronary ISR US commercial launch **Q2 2024**

Boston Scientific Receives FDA Approval for the AGENT™ Drug-Coated Balloon

Boston Scientific
Advancing science for life™

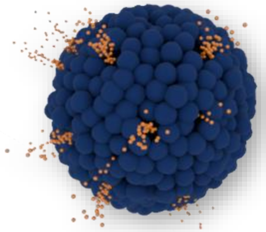
- **Sirolimus has demonstrated clear superiority to paclitaxel** in drug-eluting stents
- **Extended release required to achieve full benefits of sirolimus** with balloon delivery[1]

Head-to-Head Comparison of Sirolimus-Eluting Stents versus Paclitaxel-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention: A Meta-Analysis of 76 Studies

Xinlin Zhang, Jun Xie, Guannan Li, Qinhua Chen, Biao Xu*

Department of Cardiology, Affiliated Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China

- **A novel solution is required to realize advantages of sirolimus** during balloon angioplasty without a permanent stent implant



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Angioplasty with Protected Delivery of Extended Release Sirolimus

[1]Xinlin Zhang, et. al. PLOS ONE 2014 May 20;9(5):e97934.

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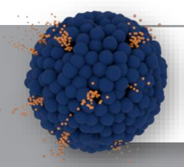
Virtue® SAB – A True Sirolimus-Eluting Balloon



SirolimusEFR™

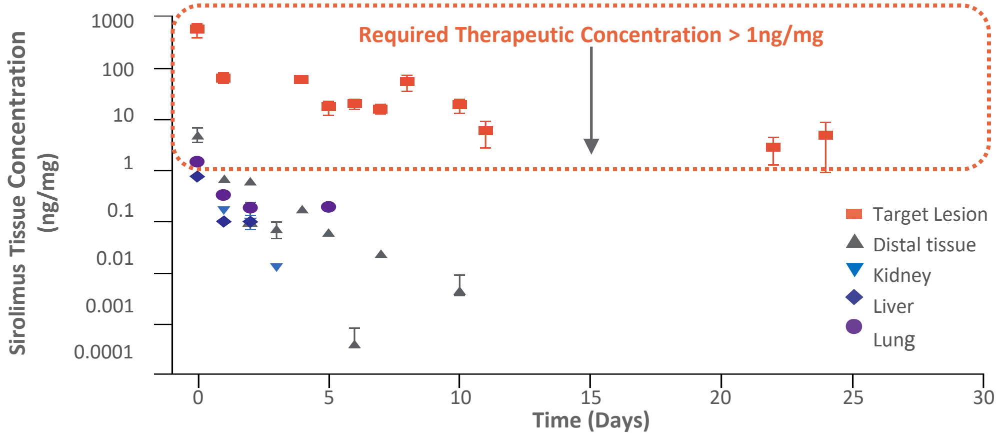
Angioplasty with Protected Delivery of Extended Release Sirolimus

Microporous AngioInfusion™ Balloon

Enabled by Sostenocel™ technology
developed by **Orchestra BioMed**

Proprietary technology
developed by **Orchestra BioMed**

Published Animal Data Demonstrates Therapeutic Sirolimus Tissue Concentration Through Critical Healing Period



N = 753 porcine coronary artery segments

Lung, liver & kidney below level of assay quantification (0.1 ng/mg) in <1 week

Precise dose loaded inside balloon system

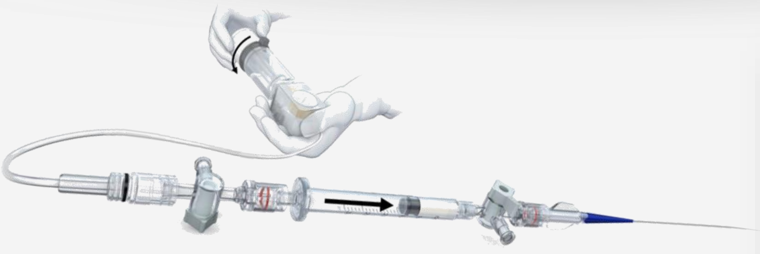
***No coating* = no drug loss in transit**

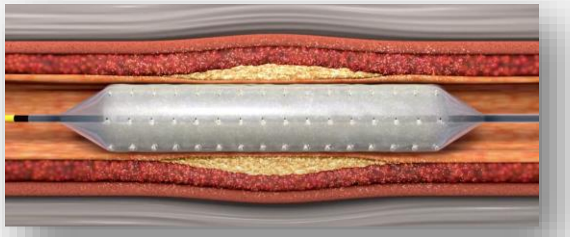
Standard navigation to lesion

***No coating* = no rush to deliver**

Intended dose delivered through balloon micropores

***No coating* = no large particulate**





[1]Granada et al. EuroIntervention 2016;12:740-747

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Compelling SABRE Trial Results in Coronary ISR Patients

Virtue® SAB demonstrated **encouraging safety and efficacy results in patients with first time coronary in-stent restenosis** (ISR) in prospective, multi-center SABRE Trial[1]

2.8%
Target Lesion Failure at 1 year

0%
New TLR between 1-3 years

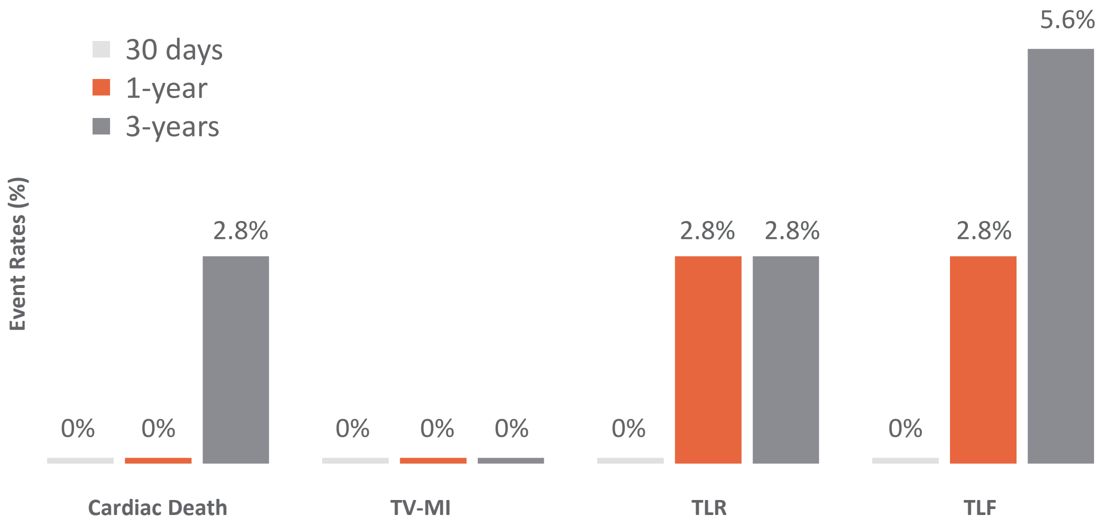
0.12mm
LLL at 6-months

Primary Efficacy Results: 2.8% TLF at 1 Year

	Per Protocol+
n	36
Reference Vessel Diameter (RVD) mm++	2.52 ± 0.32
Minimum Lumen Diameter (MLD) mm	1.96 ± 0.32
% Diameter Stenosis	22.3 ± 9.4
Change in % Diameter Stenosis	5.2 ± 11.4
Late Lumen Loss (LLL) mm+++	0.12 ± 0.33
Binary Restenosis++++	2.8%

+Data includes all patients that met revised per protocol population criteria; ++RVD reported using Internormal values; +++Trial primary performance endpoint; ++++Trial secondary performance endpoint (binary restenosis = >50% lumen diameter stenosis).

Low Safety Event Rates Out to 3 Years[2]



[1]Verheye et al. JACC Cardiovasc Interv 2017 Oct 23;10(20):2029-2037. DOI: 10.1016/j.jcin.2017.06.021. [2]Granada 3-Year Clinical Results TCT 2018. 3-Year SABRE Trial Clinical Report on file. ***Definitions:*** Target lesion failure (TLF), late lumen loss (LLL), target lesion revascularization (TLR) and Myocardial Infarction (MI).

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Key Takeaways and Strategic Priorities

- **Global pivotal study actively enrolling** for lead program, **BackBeat CNT (AVIM therapy)** with **market-leading strategic partner**
  - 70% of pacemaker patients also have hypertension, equating to an addressable annual market opportunity of **approximately 750,000 patients worldwide valued at over $2 billion**
  - **Medtronic** is the ideal partner as the **global leader in cardiac pacing therapies**
  - Orchestra BioMed has a substantial royalty-based revenue sharing interest in future commercial sales and is expected to receive between **$500-1600 for each AVIM-enabled pacemaker sold**
  - **Significant follow-on market opportunity** in other targeted high-risk populations
- Pipeline program, **Virtue SAB** represents a **highly differentiated solution for a significant established market**, with **strong strategic partner** and an **approved IDE** for pivotal study in lead coronary indication
- **Novel business model** provides pathway for pipeline expansion and additional strategic collaborations
- **Expected cash runway into 2H 2026**, beyond target reporting of top-line data readout for BACKBEAT study

Bringing Medical Innovations to Life Through Partnerships