GenVara
BIOPHARMA

Tom Keuer, MS
President and CEO
tom@genvarabio.com

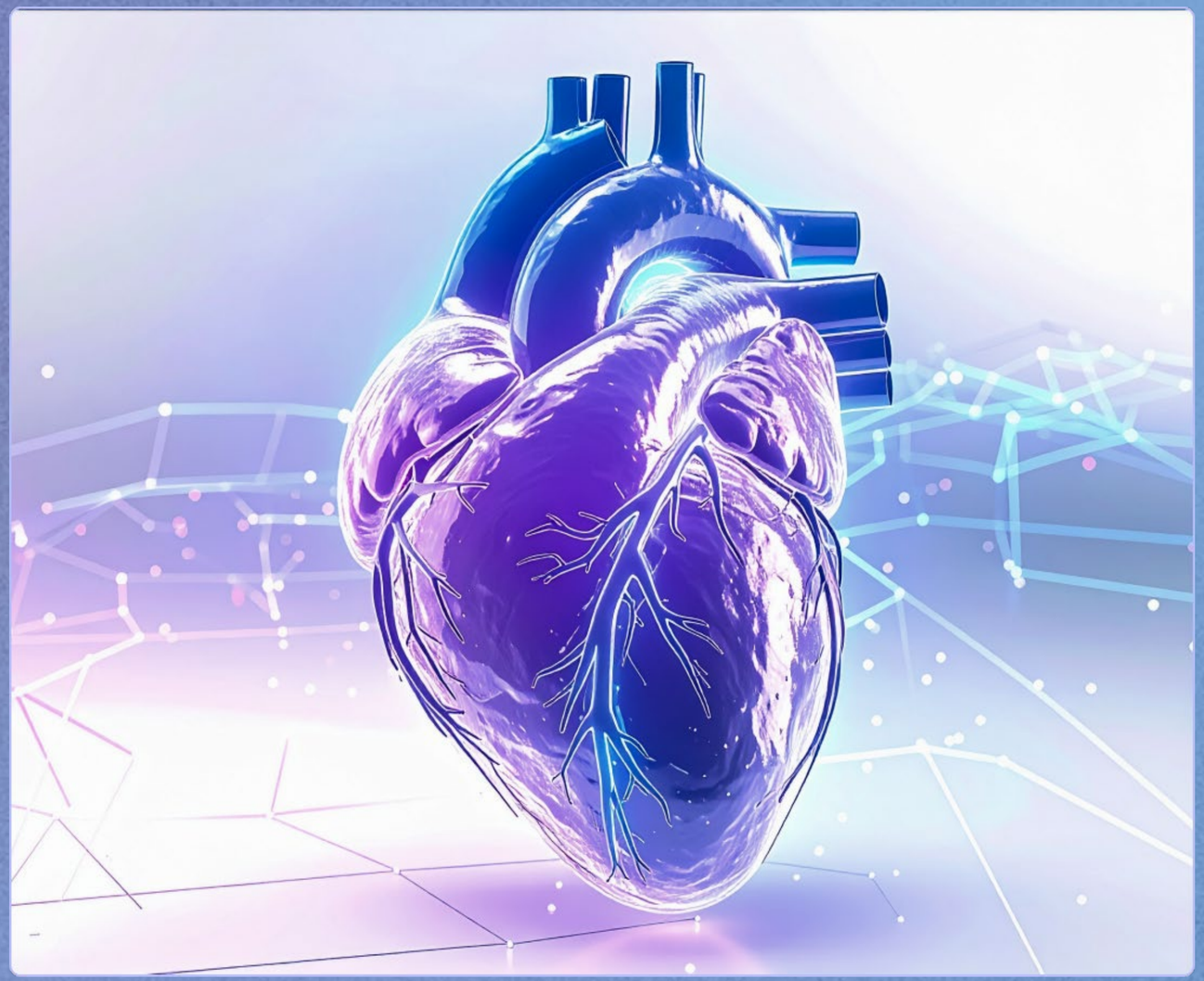
Michael Bristow, MD/PhD
Chief Science and Medical Officer
michael.bristow@genvarabio.com

The decoding and targeting of genetic variation for treating cardiovascular disease

Developing a Phase 3-Ready, Genetically-Targeted Therapy to Treat Atrial Fibrillation in Patients with Heart Failure

GenVara

There are currently no approved drug treatments that are both safe and effective for managing Atrial Fibrillation (AF) in patients with Heart Failure (HF)



GenVara

Transforming the Treatment of Atrial Fibrillation in Heart Failure

De-Risked Cardiovascular Opportunity with High Value Exit Potential

GENCARO™ (bucindolol) small molecule, oral therapy for genetically-defined patients with HF and AF

Robust IP protection expected through 2045

$1B+

Commercial opportunity in large growing market

First genetically-targeted drug to treat HF and AF

First haplotype-targeted small molecule for any indication

De-risked Phase 3 clinical trial with FDA guidance in place

High value exit potential due to unmet demand for differentiated CV products

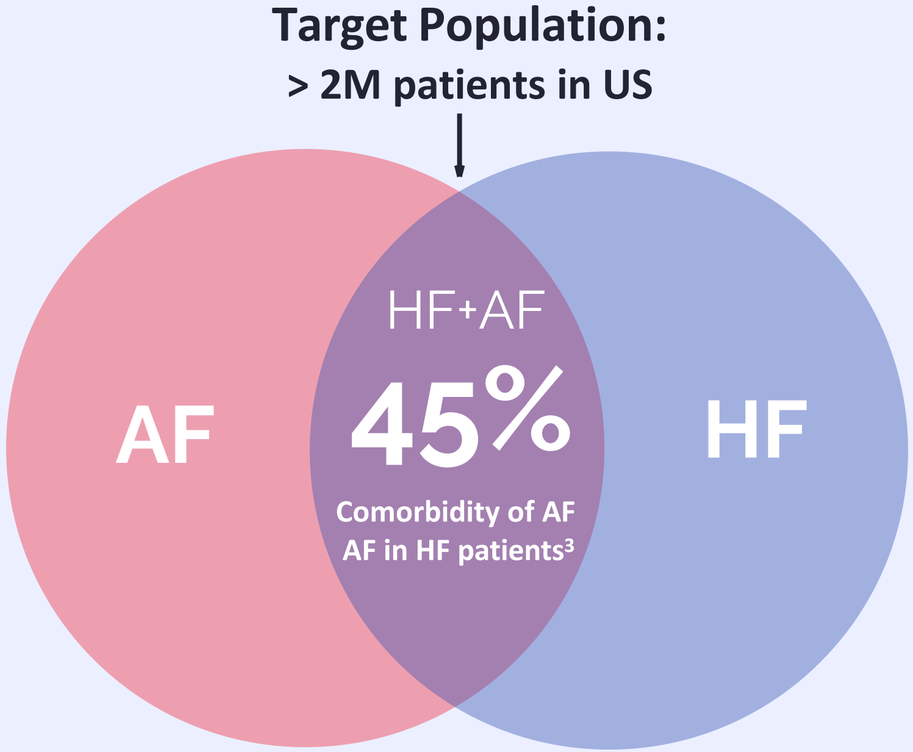
$65M funds 3 years of company operations and Ph 3 trial costs to FDA submission

Proven leadership team with multiple exits

GenVara

Crossroads of AF and HF is a Dangerous Place

Disabling Symptoms and Poor Quality of Life



Concomitant AF+HF is common and associated with increased hospitalization rates, morbidity, and mortality

55-60% 5-year survival (HF);[1] worsened by AF

1 in 4
People will develop HF in their lifetime[2]
1 in 3 for AF

6.7M U.S. HF Patients + (60M worldwide)[3]
increasing prevalence
10M U.S. AF patients, increasing prevalence

ZERO
approved, effective, or safe therapeutics
for concomitant AF and HF

[1]Jones et al, Eur J Heart Fail; 16;21(11)::1306-25, 2019

[2]Bozkurt et al, J Cardiac Fail; 31:66-116, 2025

[3]Diaz et al, ESC Heart Fail; 9(6): 4230-39, 2022

GenVara

GENCARO™ - First Pharmacogenetic Targeted Treatment

01

PHASE 3-READY ASSET
FAST TRACK DESIGNATION

Cost-effective, expedited Phase 3 trial design

De-risked by Phase 2 insights and FDA interactions

Robust IP coverage through 2045

02

HIGH UNMET NEED
NO APPROVED DRUGS FOR AF+HF

Immediate clinical need

No direct competitors

Independent market research shows doctors will prescribe GENCARO

03

UNIQUE LABEL

NEED + DIFFERENTIATION

First in-indication for concomitant HF+AF

Superior to off-label standard of care[4]

Guideline inclusion expected

04

PRECISION MEDICINE
INNOVATIVE + LEADING EDGE

Pharmacogenetically-targeted to 65% of patient population

First ever haplotype-targeted small molecule for any indication

Unique triple mechanism of action: rhythm, rate and remodeling

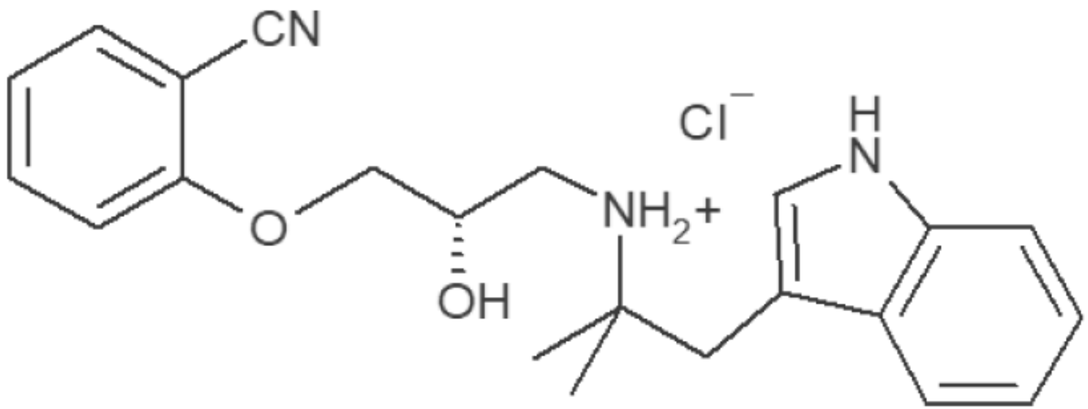
[4]Current regimen: Generic beta-blockers metoprolol and carvedilol are used off-label; both are approved for HF with LVEF ≤35% but not for higher LVEF HF and neither are effective for AF prevention or treatment. Metoprolol use is more prevalent than carvedilol for AF in HF.

GenVara

GENCARO™ has Unique and Clinically Proven Cardiac Benefits

GENCARO (bucindolol)

Small molecule "4th generation" β–Blocker



Extensive Clinical Data

Including Two Pharmacogenetic (PGt) Trials in Heart Failure

- 74% reduction in AF onset in 1040 patient study[5]
- 46% reduction in AF recurrence in 267 patient study[6,7]
- Favorable safety profile

Robust, Outcomes-Based Patent Portfolio

Genotype & haplotype PGt targeting, LVEF "HFmprEF"

- PGt patents issued or submitted provide coverage to 2045
- HFmprEF issued patents provided exclusivity to 2039

[5]Aleong et al, JACC Heart Fail; 1:338-44, 2013

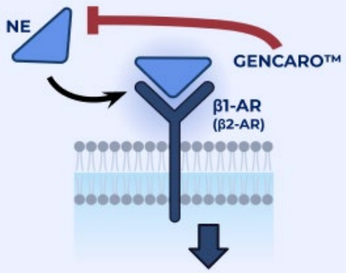
[6]Piccini JP et al. Circ AE 2021 Aug;14(8):e009591

[7]In predefined population (58% reduction in LVEF 40-55%)

GenVara

GENCARO™ Functions via a Differentiated

Triple Mechanism of Action

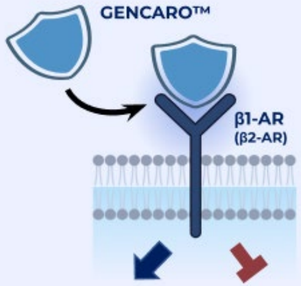


↑ SA/AV Conduction, Automaticity
↑ Contractility
Chamber pathologic remodeling

Sympatholysis

Regulates heart rate and rhythm by ↓ NE

– Potent inhibition of β1-AR activation

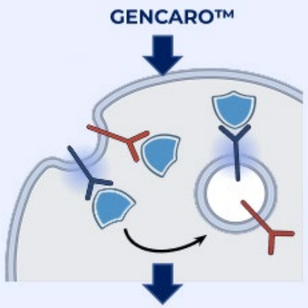


Reverse remodeling
- ↑ Contractility
- ↓ Hypertrophy

SA/AV Conduction, Automaticity

Receptor Blockade and β1-AR Inverse Agonism

– Blocks β1-, β2-ARs; Inactivates constituitively active Arg389 β1-ARs



Cardioprotection
Reverse remodeling

Biased Ligand Activity

Cardioprotection via Internalization of β1/β2-AR variants and activation of ERK1/2 signaling

NE: Norepinephrine; AR: Adrenergic Receptor; SA: sinoatrial node; AV: atrioventricular node

GenVara

Genvara Late-Stage Pipeline

Treating Serious Medical Disorders with High Unmet Need

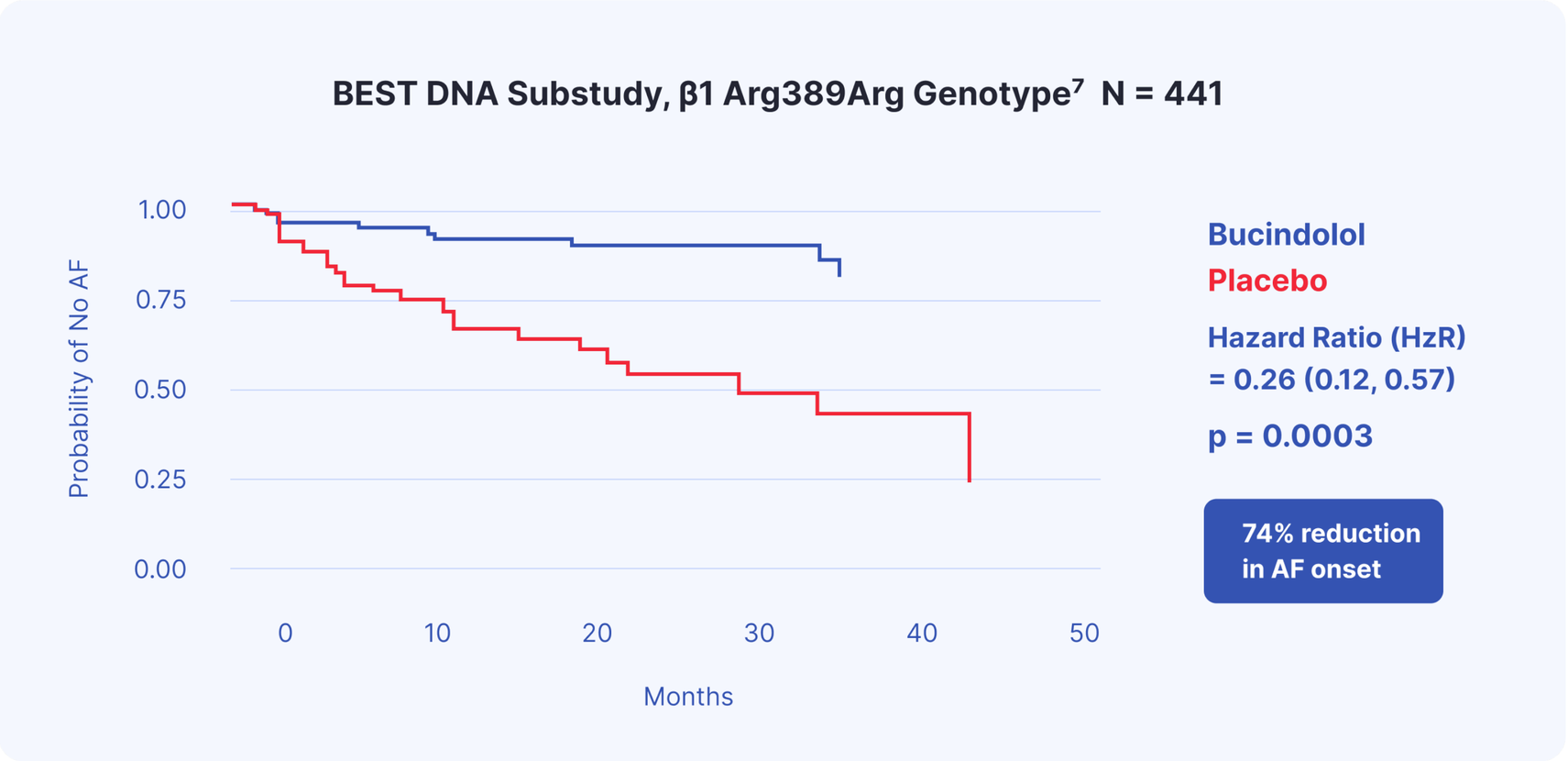
Indication	Research/ Preclinical	Phase 1	Phase 2	Phase 3
GENCARO (bucindolol hydrochloride)				
AF* in HFmprEF, Genotype Primary Indication			**PRECISION-AF Pivotal Trial - Efficacy Cohort (300 patients)** Genotype-defined population with mildly reduced to preserved LVEF (40 – 54%)	
AF* in HFpEF, Genotype Label Expansion			**PRECISION-AF Exploratory Cohort (50 patients) for Label Expansion** Genotype-defined population with preserved LVEF (55 - 64%)	
AF* in HFmprEF, Haplotype Label Expansion			**PRECISION –AF Adjunctive Cohort (75 patients) for Label Expansion - NIH Funded** Haplotype-defined population, LVEF 40 – 54%	
AF* in HFrEF, Genotype Label Expansion			**Expected Labeling if PRECISION-AF is Positive** Genotype-defined population, LVEF < 40%	
Treatment of HFrEF, PGt Label Expansion			**Expected Labeling if PRECISION-AF is Positive** Genotype-defined population, LVEF < 40%	
rNAPC2 (recombinant nematode anticoagulant protein C2, Anpocogin)				
Autoimmune Diseases (Orphan Indications)			**Treatment of Antiphospholipid Antibody Syndrome (APS) and/or Systemic Lupus Erythematosus (SLE) Flare**	

* Includes AF prevention and rate control

GenVara

GENCARO Proven Effective for AF Reduction in Two HF Trials

BEST Trial (vs. Placebo)



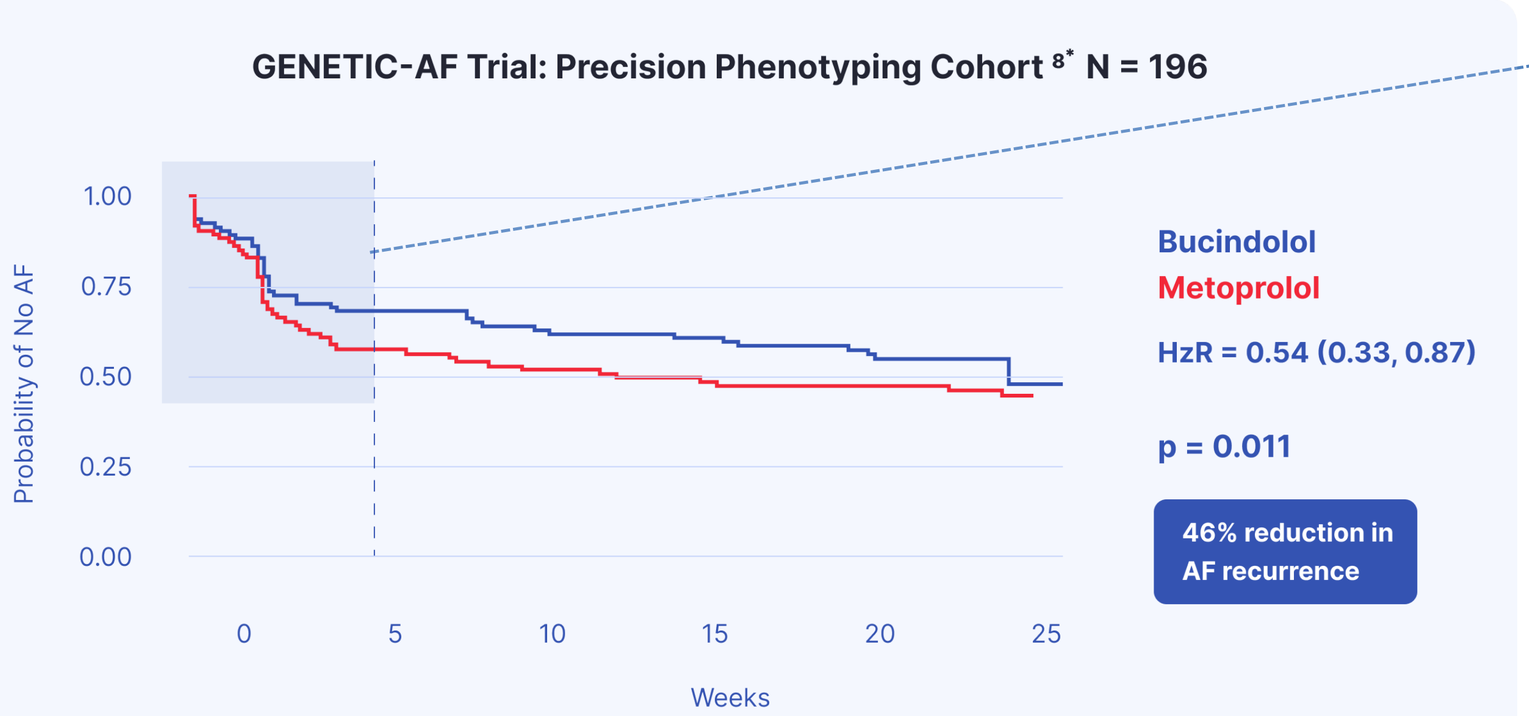
[7]Aleong et al, JACC Heart Fail; 1:338-44, 2013

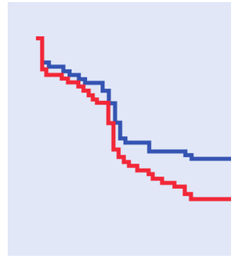
GenVara

GENCARO Proven Effective for AF Reduction in Two HF Trials

GENETIC-AF Trial vs. Metoprolol Succinate (TOPROL XL)*

*TOPROL XL is the most commonly used β-blocker to treat HF patients with concomitant AF





45% of Time to First Event (TTE) endpoints – limits usefulness as primary endpoint

*Eliminates patients with longstanding disease (predefined analysis) HF or AF diagnosis > 10 yrs, or AF onset preceding HF by > 2 yrs

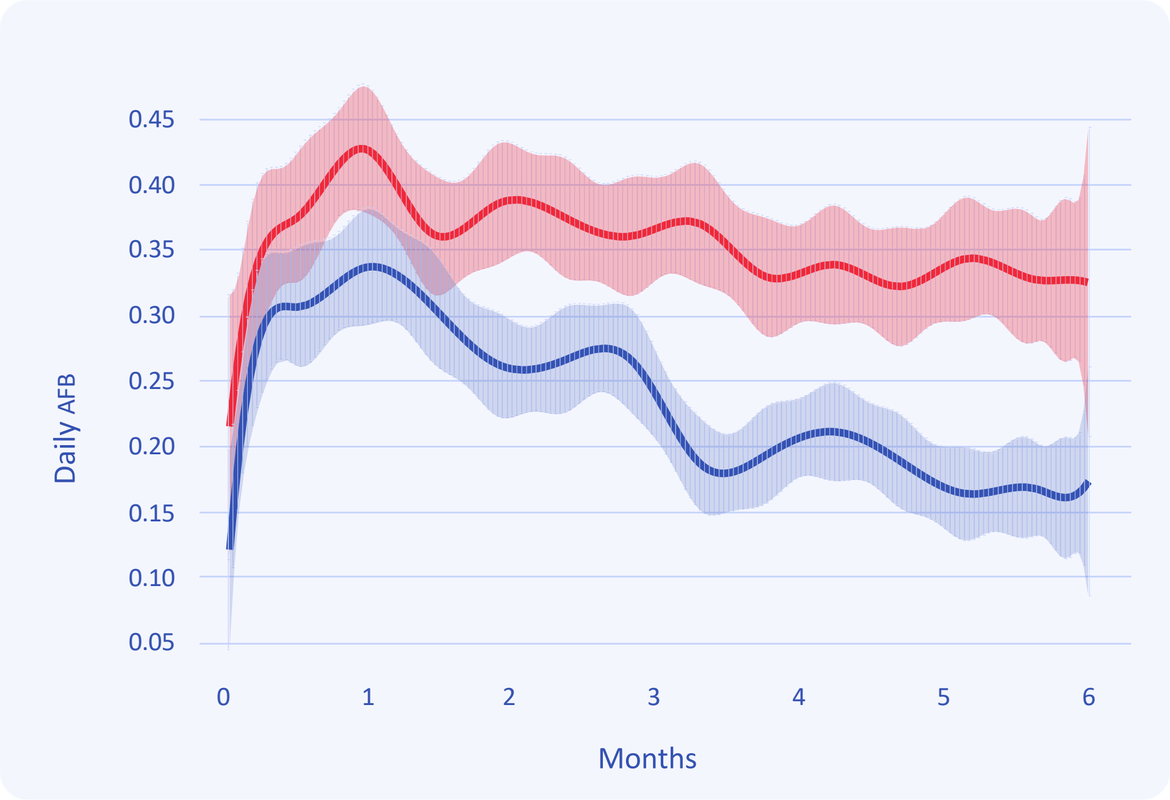
[8]Piccini JP et al. Circ AE 2021 Aug;14(8):e009591

GenVara

Demonstrated Reduction in AF Burden (AFB) vs. Toprol XL

In GENETIC-AF Substudy[9]

Continuous implanted device monitoring of AFB during 24 week follow-up



Group	Area Under Curve (AUC)	DAILY AFB Week 24	AFB HzR Week 24	AFB HzR AUC
Metoprolol	36.7%	34.7%	0.45 (0.39, 0.50)	0.64 (0.46, 0.86)
Bucindolol	24.4%	15.1%		
P value	–	–	<0.001	0.002

Metoprolol (N=32)

Bucindolol (N=35)

AFB= % time spent in AF over 24 hrs

[9]Piccini JP et al. Circ AE 2021 Aug;14(8):e009591

GenVara

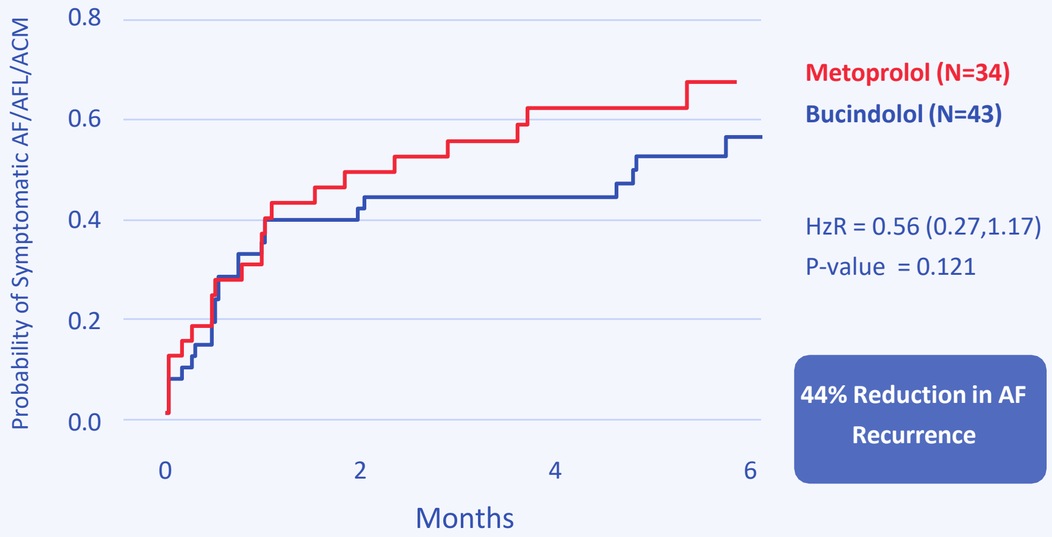
Development of an Improved Primary Endpoint to TTE:

Symptom Burden of AF (SxB_{AF})[10]

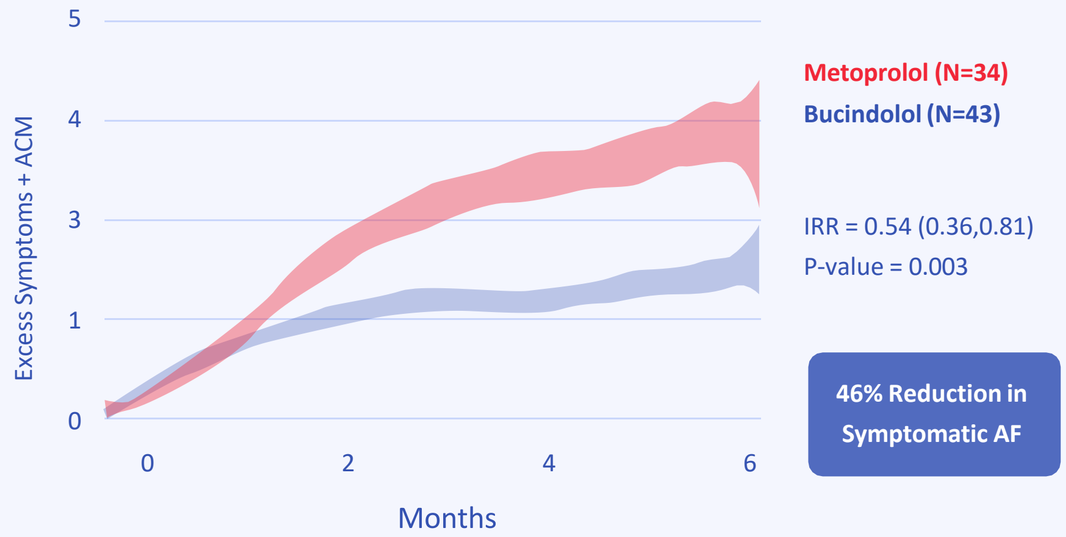
TTE = Time to First Symptomatic AF Event: Traditional FDA primary endpoint for AF therapies - Usefulness limited by high early event rates in both treatment groups due to electrical instability

Data from GENETIC-AF Precision Phenotyping Cohort, LVEF 40%-55%: Target Patient Population for Ph 3

TTE Endpoint: Probability of First Symptomatic AF Event



SxB_{AF} Endpoint: Freedom From Cumulative Symptomatic AF



[10]Carroll, IA JACC Heart Fail, published online 11/24/24

GenVara

Superior Efficacy vs Toprol XL Over Full Follow-Up (180d)

Multiple Endpoint Analysis for Full Study Cohort: Includes Patients with Longstanding Disease

GENETIC-AF Endpoint	GENCARO effect vs. Toprol XL (Hazard Ratio)	# of Patients (N), p-value
Time to 1st AF/AFL/ACM event (TTE)[11] (Primary Endpoint)	Neutral (1.01)	N = 267, p = 0.961
ECGs in Normal Sinus Rhythm[11]	**39% Improvement (1.39)**	N = 257, p < 0.001
AF Interventions[11] (ECVs, Ablations, & Class 3 AA Drugs)	**32% Reduction (0.68)**	N = 257, p = 0.009
Plasma NT-pro-BNP (HF Biomarker)[11]	**Two-fold Reduction**	N = 257, p = 0.011
Bradycardia Prevalence[12] (Ventricular Rate < 60 bpm)	**61% Reduction (0.39)**	N = 256, p = 0.001
Number of Bradycardia Adverse Events[12]	**Toprol XL: 11 (8.8% of Patients) GENCARO: 1 (0.076% of Patients)**	N = 256, p = 0.002

[11]Piccini JP et al. Circ AE 2021 Aug;14(8):e009591

[12]Abraham et al. Heart Rhythm O2; 3(1): 40-49, 2019

Recent Discovery:

Pharmacogenetic Targeting of Internalization-Resistant β- AR Haplotype Variants by GENCARO Results in Cardioprotective Signaling

First Ever Haplotype-Targeted Small Molecule

- Increases favorable genetically-targeted population to 65%
- ~30% increase in market

Mechanism Verified in Basic Science Experiments

- In human model systems
- Further differentiates GENCARO from other β-Blockers

Improves Efficacy

- >30% increase vs standard β-blockers in majority of overall population
- 60-70% increase in a 25% subset
- 90-100% increase in a 10% subset

Corroborated by Data Analyses of Multiple Clinical Trials

- With placebo and an active comparator

Extends IP Protection and Runway

- Provisional IP and PCT filed
- Expected expansion of patent coverage to 2045

Haplotype = A combination of DNA variants that are located close together on a single gene and are inherited together from one parent, encoding a protein haplotype

GenVara

Targeting of Haplotype Variants Improves HF Outcomes

BEST DNA Substudy - Primary Endpoint of All Cause Mortality/Transplantation (ACM/Tx)

Internalization-resistant Haplotypes:

ADRB1 Arg389Ser49 *ADRB1* Gly389Ser49
ADRB2 Gln27Gly16 *ADRB2* Glu27Gly16

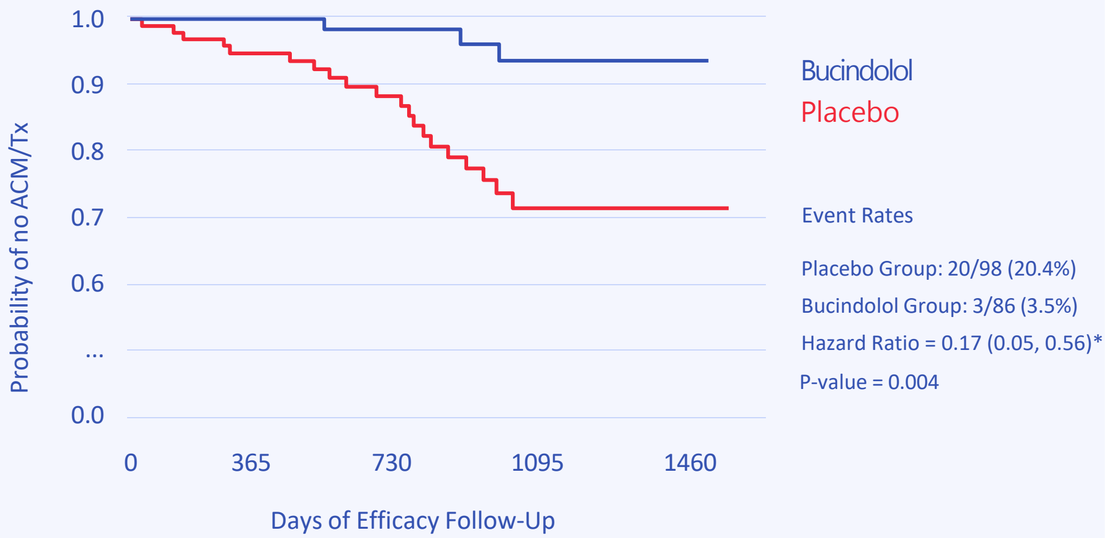
***83% Effect Size for ACM/Tx vs. Placebo**

Internalizing Haplotypes:

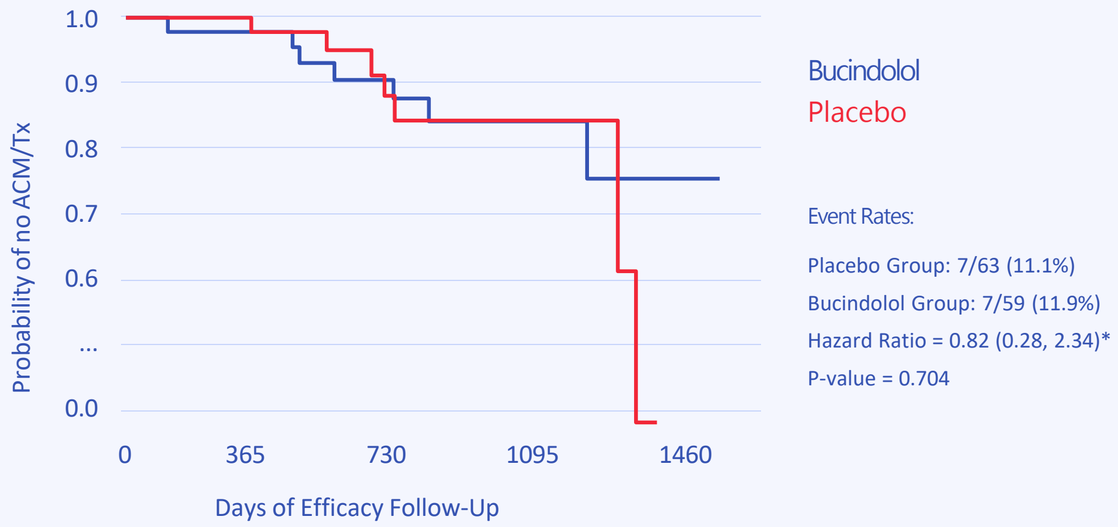
ADRB1 Arg389Gly49 *ADRB2* Gln27Arg16

Beneficial effect of Placebo = Bucindolol

Double Internalization-resistant β1, β2-AR Haplotypes (4 of 4, "4DIR")



Internalizing β1, β2-AR Haplotypes (≥1 of 2 for β1 and β2, "≥2DI")

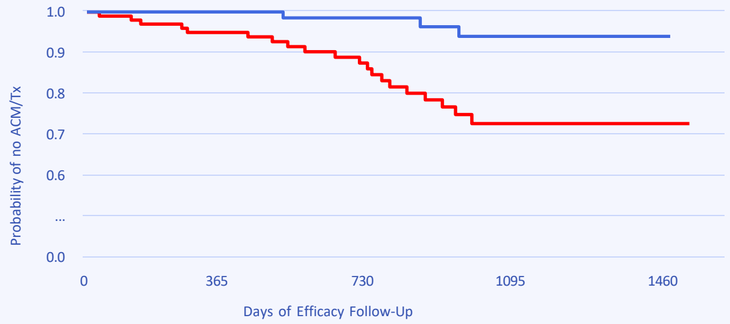


GenVara

Haplotype Targeting: Efficacy Benefit Consistent Across All Endpoints

BEST PGx Substudy

ACM/Tx, Double Internalization-Resistant

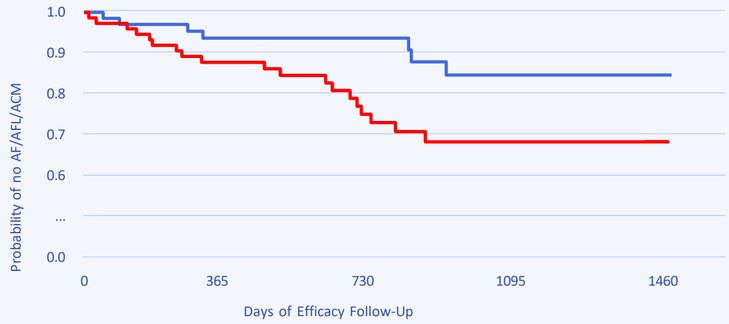


Bucindolol
Placebo

Event Rates:
Bucindolol Group: 3/86 (3.5%)
Placebo Group: 20/98 (20.4%)
Hazard Ratio = 0.17 (0.05,0.56)
P-value = 0.004

83% Effect Size

AF/AFL/ACM, Double Internalization-Resistant

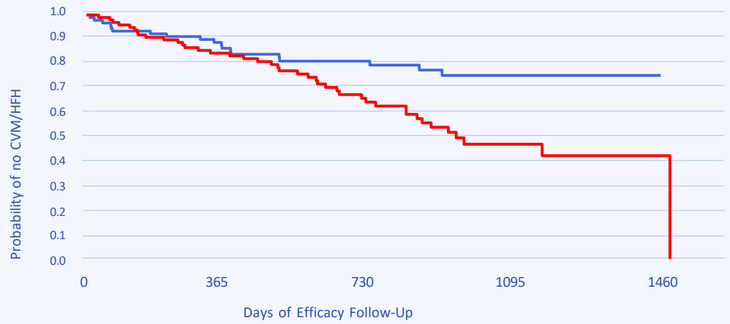


Bucindolol
Placebo

Event Rates:
Bucindolol Group: 7/67 (10.4%)
Placebo Group: 19/76 (25%)
Hazard Ratio = 0.41 (0.17,0.97)
P-value = 0.042

59% Effect Size

CVM/HFH, Double Internalization-Resistant

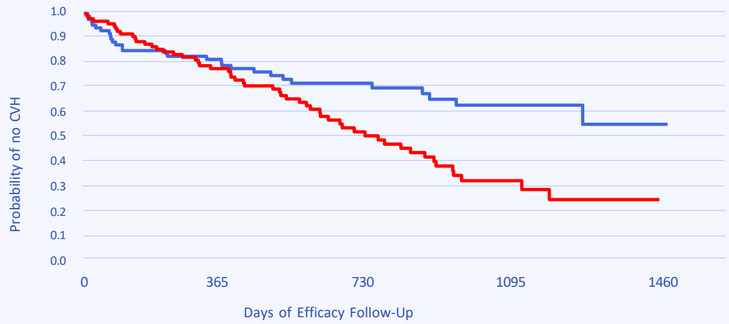


Bucindolol
Placebo

Event Rates:
Bucindolol Group: 19/86 (22.1%)
Placebo Group: 41/98 (41.8%)
Hazard Ratio = 0.49 (0.28,0.85)
P-value = 0.011

51% Effect Size

CVH, Double Internalization-Resistant



Bucindolol
Placebo

Event Rates:
Bucindolol Group: 28/86 (32.6%)
Placebo Group: 53/98 (54.1%)
Hazard Ratio = 0.53 (0.33,0.84)
P-value = 0.007

47% Effect Size

AFL: AF flutter; CVM: cardiovascular mortality; HFH: heart failure hospitalization; CVH: cardiovascular hospitalization

GenVara

The Benefit of GENCARO's Extensive Development History

- Paved the way in converting a contraindicated drug class to a pillar of heart failure therapy.
- Each clinical trial used a novel design ultimately adopted by others; each pharmacogenetic discovery was unanticipated and ultimately confirmed.
- As discoveries were continuously made the next stage was de-risked and opportunities were enhanced, resulting in the current opportunity.

Bristow, Bouvier Labs — **Preclinical:** Nonselective high affinity β1/β2 blocker with vasodilator activity, biased ligand with no ISA in human heart.

Bristow Lab, BMS — **Phase II (HF):** Well tolerated, improves remodeling & contractility at 3 months, no ISA in vivo, lowers norepinephrine.

NIH; Eichhorn, Bristow Labs; Intercardia — **BEST Ph 3 Trial:** First HF mortality trial with β-Blocker, First HF DNA Bank.

Liggett, Bristow Labs — **New Discoveries:** PGt of β1-ARs, Enhanced bucindolol response with β1 389 Arg/Arg genotype in human heart, inverse agonism.

ARCA biopharma — **GENETIC-AF Ph 2B Trial:** First PGt-targeted AF/HF trial.

PRECISION-AF: Planned Ph 3 Pivotal Trial.

GenVara

Latest Discovery — Bucindolol PGt of β1, β2-AR Internalization haplotypes (Bristow, Liggett Labs; IP licensed to Genvara 9/2024)

Acquired by GENVARA in 2024 as part of a reverse merger involving ARCA biopharma (prior sponsor)

Proven in > 3000 HF patients - Favorable safety and efficacy profile, outperforming other β-blockers

GENCARO: 20+ years of scientific leadership

First β-blocker tested in novel indications, study designs and patient populations

Key Opinion Leaders consistently support continued development

GenVara

GENCARO™ Clinical Development Insights

De-risk the PRECISION-AF Pivotal Trial Design

01

Ensure targeted patients are stable and optimized for response (from BEST and GENETIC-AF)

- Exclude unstable Class III/IV HF with fluid overload
- Exclude long-duration HF/AF (disease >10 yrs, AF >2 yrs pre-HF)
- Target HF with mildly reduced/preserved LVEF—highest unmet need and best efficacy

02

Pharmacogenetic Insights from BEST Adrenergic Receptor Pharmacogenomic Substudy

- Gencaro therapeutic effects markedly better in *ADRB1* Arg389Arg genotype patients
- Avoid racial imbalance: Blacks have lower responsive genotype (32% vs. 50%)
- Target internalization-resistant β-AR haplotype variants to expand patient population and optimize response

03

Gencaro effect on preventing AF extends into HFmrEF and lower LVEF range of HFpEF (from GENETIC-AF)

04

Improved efficacy endpoint More precise, sensitive, and relevant than time to first event (from GENETIC-AF)

- Symptom Burden of AF (SxB_{AF})
- Atrial Fibrillation Burden (secondary endpoint)

Plus — **multiple productive FDA interactions align the pathway to approval**

GenVara

PRECISION-AF

An FDA Approved Pivotal Trial with a Clear Path to Approval

1. **Enriched Patient Population: Precision Phenotyping Cohort**
   - Eliminates non-responsive patients with longstanding AF

2. **Improved Primary Endpoint: Symptom Burden of AF (SxB_{AF})**
   - Evaluates treatment effect over entire dosing period
   - Reviewed extensively and approved by FDA's Division of Cardiology and Nephrology and Division of Clinical Outcome Assessment

3. **Focus on HF with LVEF $\geq$ 40%**
   - Highest AF prevalence and best efficacy demonstrated in GENETIC-AF: Reduced trial size
   - Highest unmet medical need with greatest differentiation: No approved therapies

4. **Incorporates PGt Targeting of Haplotypes**
   - Expansion of favorable patient population to 65%

GenVara

Key Advisors for PRECISION-AF Phase 3 Trial Design

Genvara Consultants:

- *Jon Piccini, MD* (Assoc Professor of Medicine & Director of Cardiac EP, Duke Heart Center; PI of GENETIC-AF)
- *David DeMets, PhD* (Max Halperin Emeritus Professor and former Department Chairman of Biostatistics, U. Wisconsin)
- *Norman Stockbridge, MD, PhD* (former Director, Division of Cardiology and Nephrology, CDER/FDA)



Independent KOLs:

- *Christopher O'Connor, MD (President, Inova Fairfax Heart and Vascular Institute)*
- *John Camm, MD* (Electrophysiology Expert; Professor of Clinical Cardiology at St George's, University of London, UK)


GenVara

PRECISION-AF

Cost Efficient Pivotal Phase 3 Cardiovascular Trial with High Probability of Success

350 patients, **100** sites

Estimated Trial Cost ~ **$50M**

Timeline to Top Line data ~ 27 months from trial start
with interim analysis at 50% of primary events

Similar in Scope to Phase 2B GENETIC-AF

- Ensures efficient trial execution

Upside potential for HF with reduced LVEF labeling

- With a positive outcome

GenVara

Roadmap to Approval of a Transformative Blockbuster Therapy for AF/HF

$65M Funds Pivotal Trial, Operations through FDA Submission

	$1.6 Million Founder Seed	$65 MILLION Series A Round Q3 2025-Q3 2028					
	2025		2026		2027		2028	
	Q1-2	Q3-4	Q1-2	Q3-4	Q1-2	Q3-4	Q1-2	Q3-4
Team	Finalize Team							
Clinical Trial Prep	Clinical Trial Prep				Interim Analysis		Top Line Data	
Clinical-Precision-AF (350 pts)			Clinical – Phase 3 PRECISION-AF					
Clinical-Haplotype (75 pts)				PRECISION-AF Adjunctive Haplotype Trial, Grant-Funded				
Business Development		Establish Corporate Partnership						

GenVara

GENCARO Outperforms all Existing Treatment Options Across Key Metrics

Attribute	Antiarrhythmic (AA) Drugs	Ablation (Procedure)	Beta-Blockers	GENCARO
Manages Heart Rate	✗	✓	✓	✓ ✓
Manages Heart Rhythm	✓	✓	✗	✓
Effective for AF Prevention in Low Ejection Fraction HF (LVEF < 35%)	✗ Not durably effective	✓ Reduced effectiveness in advanced HF	✗	✓
Indicated for Mildly Reduced and Preserved HF	✗	✓	✗	✓
Safe in HF Patients	✗ Many contraindicated	✓ ✗ Invasive procedure	✓	✓
Simple Administration	✗ Requires careful monitoring	✗ Complex invasive procedure Operator dependant	✓ Oral	✓ Oral
Cost Effectiveness	✓ ✗ Moderate	✓ ✗ Often repeated[13]	✓	✓ Targeted to responsive patients

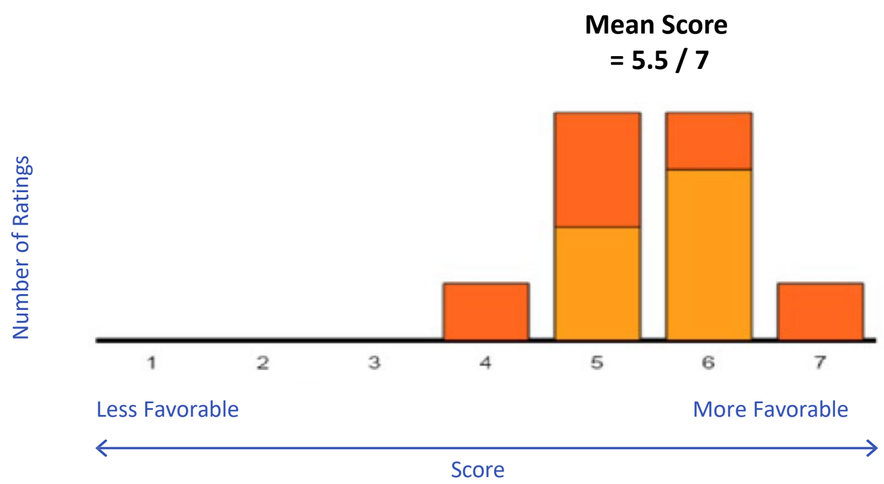
[13]High AF recurrence rate of 35-50% often requiring repeat procedures

GenVara

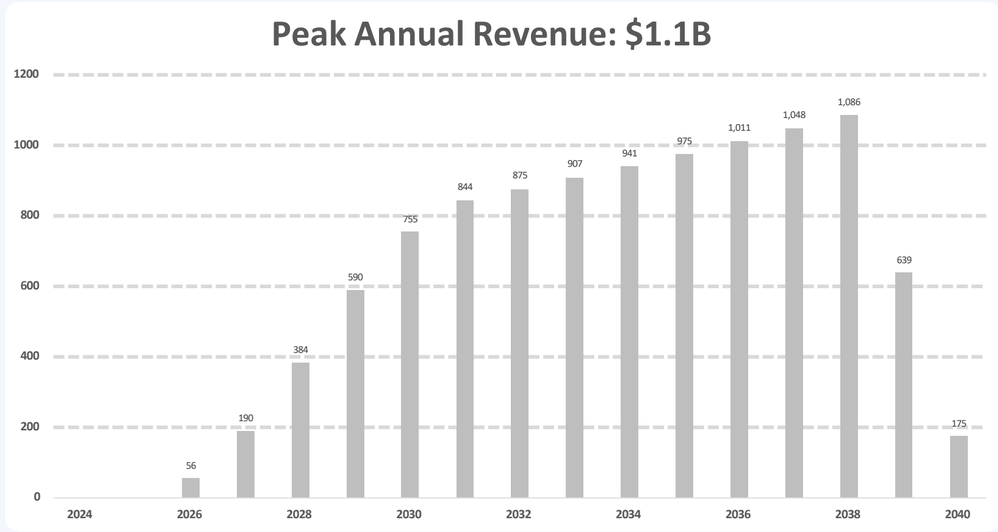
Primary Market Research Confirms >$1B Annual Revenue Potential

100+ Stakeholders (Physicians, Payers) surveyed by Syneos Health

Physician Scores for Gencaro TPP



Gencaro Revenue Forecast



Majority of Physicians intend to prescribe GENCARO

- Targeting patients with poor beta blocker tolerability or response
- Interest expressed in expanded patient population; e.g. permanent/persistent AF & reduced ejection fraction HF (HFrEF)

Payers indicate GENCARO be priced as branded cardiovascular drug (e.g. Entresto) ≈ $900 monthly

- Genotyping increases assurance of appropriate patients being treated – supports efficient prior authorization process
- Tier 2 or 3 formulary positioning likely

GenVara

High Value Exit Potential

Cardiovascular Biopharma Focus Remains Significant

Bristol Myers Squibb
MYOKARDIA
CAMZYOS™ (mavacamten) capsules

$13.1B

October 2020

Positive Phase 3 prior to FDA Approval for Hypertrophic Cardiomyopathy Therapy

AstraZeneca
CINCOR

$1.8B

January 2023

Baxdrostat - oral inhibitor for treatment-resistant hypertension entering phase 3 development

novo nordisk®
Cardior

$1.1B

March 2024

Phase 2 RNA based therapies in Heart Failure

NOVARTIS
ANTHOS
A Novartis Company

$2.15B

February 2025

Abelacimab in Phase 3 development, with the lead indication for prevention of stroke and systemic embolism in patients with atrial fibrillation

GenVara

Robust Patent Portfolio for Lead Indications with Protection to 2045

Treatment based on β1 Arg389 genotype IP extends to at least 2039

- Issued in US, Australia, China, Europe, Israel, Mexico, Japan
- Pending in US, Brazil, China, Europe, Mexico, Canada, South Africa

Treatment based on non-internalizing β1, β2 receptor haplotypes IP extends to at least 2045

- Pending International patent application with opportunity to file in major pharma markets

IP Strategy follows playbook for other successful products based on generic off patent drugs

- Viagra (sildenafil)
- Auvelity (dextromethorphan-bupropion) - withstood challenge by Teva in Q1 2025
- KarXT (xanomeline-trospium)

Gencaro™ Exclusivities

Patent Related Market Exclusivity

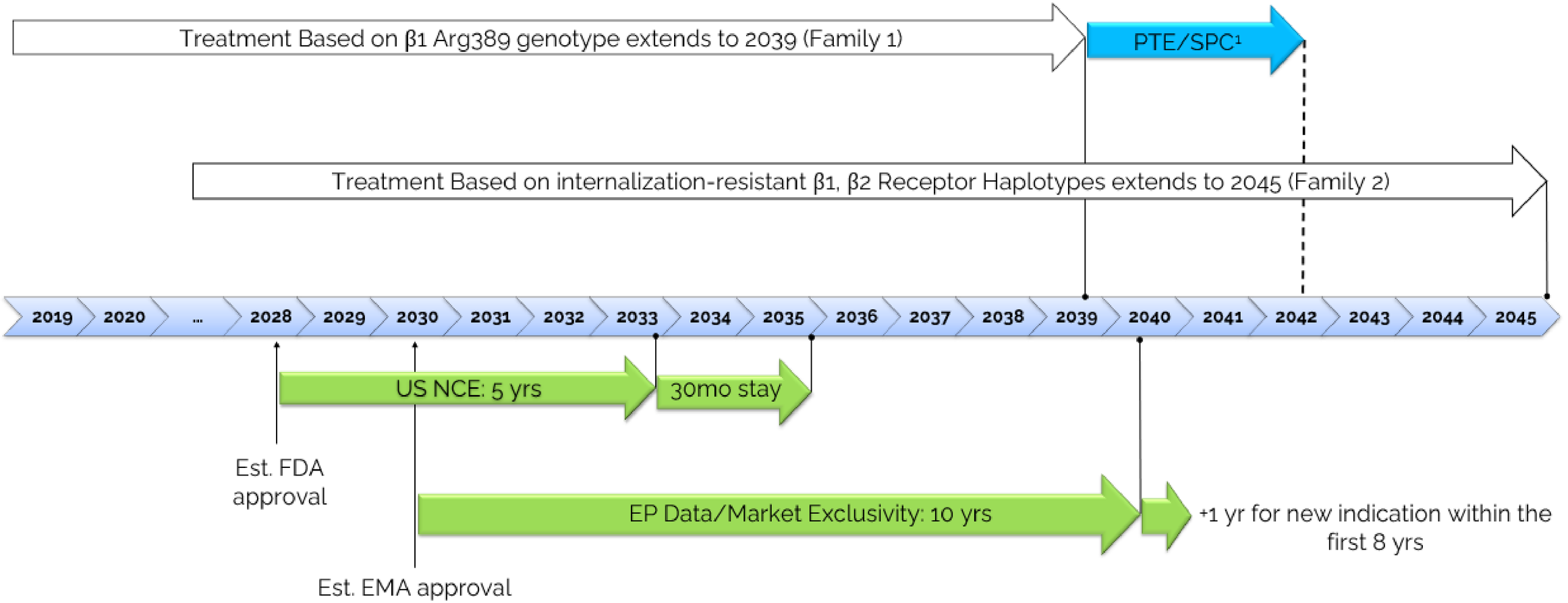
- **Issued patent protection for methods of using bucindolol extend to at least 2039**
- **For Orange Book (OB) Listable Patents**
  - US Patent Term Extension (PTE) (up to 5 years) available for any patent listed in OB
  - Life of patent + PTE cannot exceed 14 years post approval
- **In EU, Supplemental Patent Certificates (SPCs) are available (similar to US PTE)**

Non-Patent Statutory Data and Marketing Exclusivity

- **Bucindolol is a New Chemical Entity (NCE)**
  - US NCE exclusivity = 5 Years on approval
  - Generic cannot be placed on the market
- **30-month regulatory stay of approval added to the 5-year NCE period if patents are listed in OB**
- **European 10-year Market Protection on approval**
  - Generic cannot be placed on the market

GenVara

Patent and Exclusivity Timeline Overview for Gencaro™



[1] Maximum of 5 yrs
(can't extend patent beyond 14 yrs from approval)

GenVara

Leadership with Proven Cardiovascular Drug Development Expertise

History of Successful Drug Approvals and Company Exits

Tom Keuer, MS
President & CEO

- Over 40 years leadership experience in pharma and biotech
- Former President/COO of ARCA, SVP Operations for Insmed, VP Engineering for Baxter
- Successful development, approval and launch of multiple products

ARCA biopharma
Baxter
Insmed

Michael Bristow, MD/PhD
Chairman, Chief Science & MO

- Pioneer in development of β-Blockers to treat Heart Failure, with numerous National and International Awards
- Professor of Medicine (Cardiology, Pharmacogenomics), CU
- Founder of multiple biotech companies including Myogen, acquired by Gilead in 2006 for $2.3B

ARCA biopharma
miRagen
Myogen

Jeff Dekker
Chief Financial Officer

- Over 30 years financial leadership experience, 20 in biotech
- Former CFO of ARCA, President of GlobeImmune
- Led acquisition of GlobeImmune by ImmunityBio

ARCA biopharma
WEBROOT
GlobeImmune

Richard Clark
Chief Business Officer

- Over 30 years experience in biopharma & medical devices
- Co-founded three companies with two successful exits
- Extensive cardiovascular disease commercialization experience

Medtronic
BIOGENERATOR VENTURES
seal CardioVascular
Genentech
CIRCLE NEUROVASCULAR IMAGING
Altos Therapeutics

GenVara

A Genetically-Targeted Therapy to Transform Treatment of AF in HF

Precision Medicine for an Underserved Cardiovascular Patient Population

01

Scientific & Clinical Innovation

- First pharmacogenetically developed CV drug to treat AF and HF
- First haplotype-targeted small molecule drug for any indication
- Development program based on top tier science, preclinical and clinical data – all data published

02

Market and Medical Uniqueness

- Not previously introduced in any market
- First drug to treat AF in HF – no other drugs are approved, indicated or effective
- Substantial commercial potential – independently validated

03

Program Readiness and De-Risking

- Program significantly de-risked through key learning in clinical trials
- Extensive history and interactions with FDA de-risk the program and provide a clear development pathway
- One small pivotal trial away from FDA approval

04

Strategic Advantages

- Extensive KOL support
- Long IP runway – Exclusivity to 2045 expected

Most importantly, GENCARO has the potential to favorably alter the natural history of a serious and common disorder

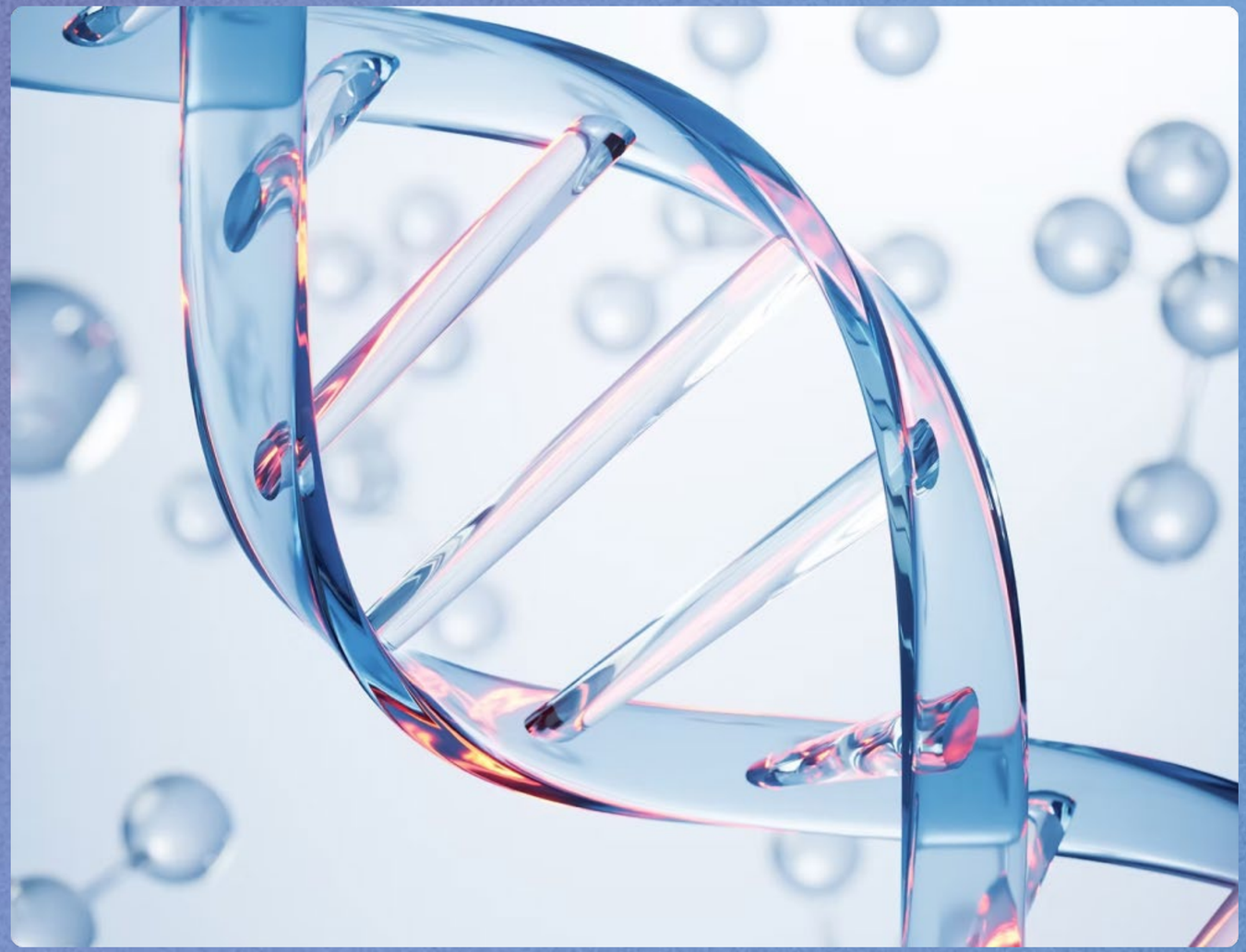
GenVara

Tom Keuer, MS
President and CEO
tom@genvarabio.com

Michael Bristow, MD/PhD
Chief Science and Medical Officer
michael.bristow@genvarabio.com

Thank You

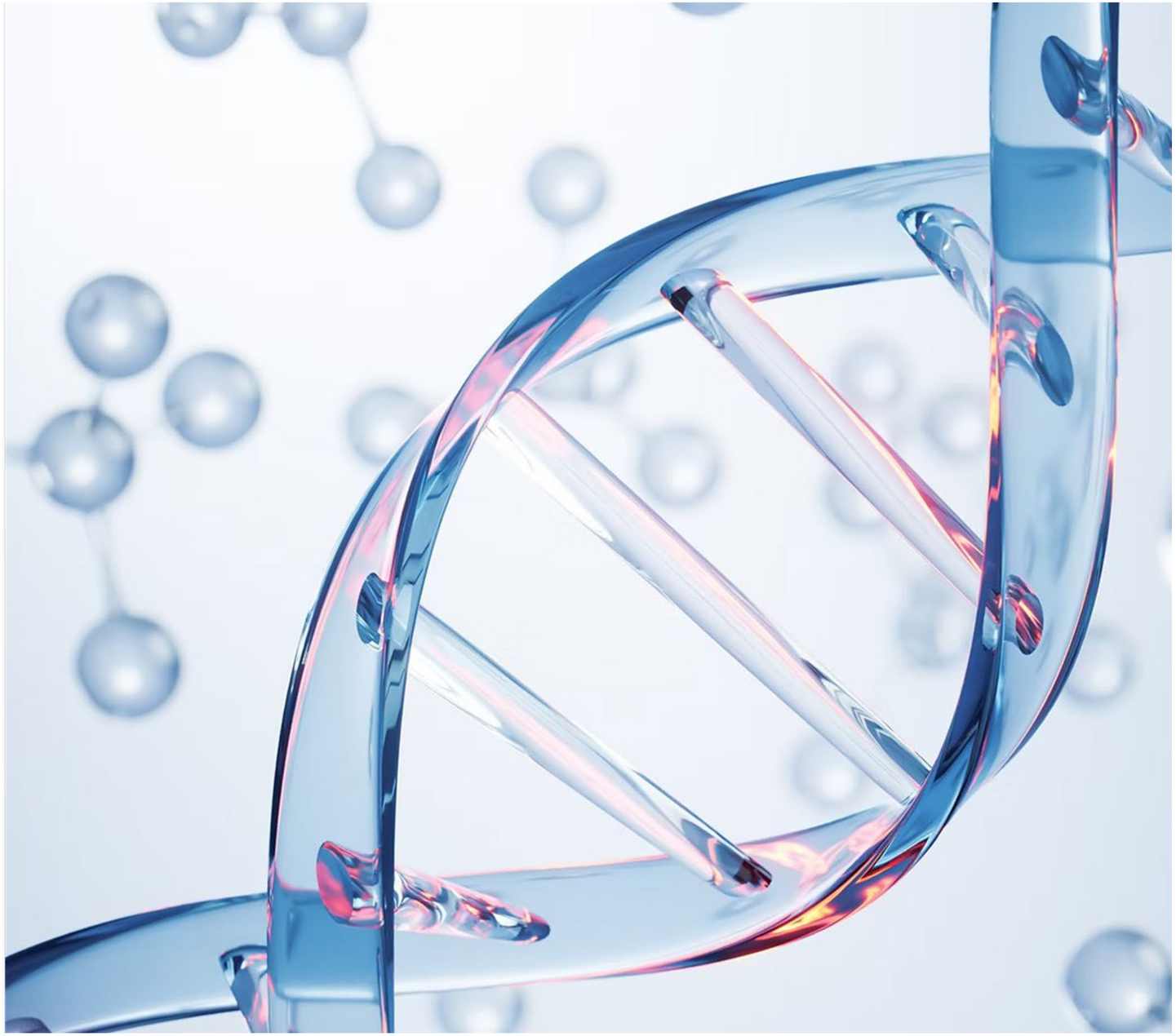
$65M Series A raise for completion of a pivotal cardiovascular trial



www.genvarabiopharma.com

GenVara

Appendix



Genvara

Genvara FAQs:

The new endpoint proposed for the PRECISION-AF trial, Symptom Burden of AF (SxB_{AF}), is novel and has never been used for a drug approval by FDA. What are the risks of using this type of endpoint that relies on patient reported outcomes (PROs)?

- **The historic primary endpoint used by FDA to approve AF prevention drugs, TTE, or time to the first symptomatic AF event, has significant shortcomings as demonstrated in the GENETIC-AF trial**
  - There is a high early AF event rate caused by electrical instability after cardioversion and transition of medications.
  - Bucindolol works through reverse cardiac monitoring, a time-dependent biologic mechanism of action that requires at least 4 weeks to take effect.
  - Aside from TTE, every other endpoint in GENETIC-AF trial monitored efficacy over the entire treatment and follow-up period, and all of these endpoints demonstrated a statistically-significant superiority of bucindolol over metoprolol. In addition, the efficacy improved over time in favor of bucindolol.
- **The FDA approved the use of (SxB_{AF}) after a rigorous review that spanned over 14 months**
  - FDA clearly understands the need for an alternate endpoint to TTE for a drug with a MOA like bucindolol.
  - Both the Cardiorenal Division and the Division of Clinical Outcome Assessment (DCOA) were involved in the review.
  - (SxB_{AF}) is not a PRO, but rather a clinical outcomes assessment consisting of a PRO linked/anchored to a clinician-reported outcome (ClinRO), namely AF as determined by a cardiologist-read ECG.
  - Rationale for this new endpoint is strong and supported by data from GENETIC-AF, as detailed in our recent publication: *https://www.jacc.org/doi/abs/10.1016/j.jchf.2024.08.02*
  - Dr. Norman Stockbridge, former Director of the Division of Cardiology and Nephrology at FDA and now a Genvara consultant, has clearly stated that based on the rigorous review and acceptance by DCOA, which is a very high bar to clear, there should be no concern regarding the acceptability of this endpoint by FDA.

GenVara

Genvara FAQs:

Bucindolol is in a drug class that has been around for decades. What is novel or exciting about development of another beta blocker?

- **While it is true that beta blockers have been around for many years, they remain a cornerstone of heart failure treatment and are recommended in current guidelines as a first line therapy for HFrEF.**
  - In HFrEF (about 50% of all HF), beta blockers produce the largest reduction of mortality of any therapy, an effect that is enhanced when they are administered in combination with other therapies such as ACE inhibitors and ARNIs.
  - Beta blockers are here to stay, and their treatment effects can be substantially improved by pharmacogenetic targeting, as we have demonstrated for bucindolol.
- **Bucindolol is unique among beta blockers in several ways**
  - It is better tolerated than other beta blockers, as demonstrated in the GENETIC-AF trial with an improved achievement of target dose and a significantly reduced incidence of bradycardia vs. metoprolol.
  - Bucindolol is the only beta blocker that has shown an enhanced efficacy response by means of genetic targeting.
  - By studying higher LVEF heart failure (>40%) in our pivotal trial design, bucindolol will be the only beta blocker approved for AF/HF and HF in the LVEF 40 – 55% range.
- **As a 4th generation beta blocker, bucindolol has the potential to be the first pharmacogenetically-targeted cardiovascular drug and the first small molecule haplotype-targeted drug for any indication**
- **The commercial potential of GENCARO has been evaluated in a primary market research study by Syneos**
  - Study involved feedback from over 100 stakeholders, including physicians and payers.
  - The majority of physicians intend to prescribe GENCARO for their HF patients with AF. Interest was expressed to expand the population to persistent/permanent AF and also HFrEF.
  - Payers indicated that GENCARO should be priced similar to branded cardiovascular drugs such as Entresto.
  - Commercial opportunity is in the range of $1B in the US alone.

GenVara

Genvara FAQs:

Isn't the basis for the genetic targeting with bucindolol, including the enhanced efficacy observed with the drug and identification of responsive patient populations, based on a post-hoc analysis?

- **According to Webster, the definition of post hoc is "formulated after the fact." Everything we are doing at Genvara is based on pre-established hypotheses, not developed or formulated after an event, and therefore nothing is post hoc**
- **The primary pharmacogenetic discovery is based on the original hypothesis that beta receptor polymorphisms discovered by Steve Liggett (Genvara Co-founder) affect the therapeutic response to bucindolol**
  - This hypothesis was tested as part of the N=1040 BEST trial adrenergic receptor polymorphism substudy that was submitted for NIH review, accepted by the BEST Trial Substudies and DNA Oversight Committees in 1999, and completed in 2002.
  - Data from this substudy and from NIH grants awarded to Liggett and Michael Bristow, Genvara Founder and CSMO, led to the discovery that bucindolol had selective and enhanced efficacy in the $ß_1$AR Arg 389 genotype.
  - This is the discovery that launched ARCA biopharma in 2005.
- **The second, more-recent pharmacogenetic mechanism discovery, effects on internalization-resistant $ß_1$ and $ß_2$ ARs, is also based on data from the same NIH grant submission in 1999 but completed only after the technology for efficiently resolving haplotypes from double heterozygote genotypes became available in 2021**
  - Long-read sequencing allowed the identification of the enhanced effect of bucindolol in internalization-resistant receptor haplotypes.
- **The existence of an AF patient phenotype that is resistant to bucindolol's therapeutic effects in the first few weeks of treatment was not known until results from the GENETIC-AF trial were received. However, detection of this phenotype was based on a pre-established, multivariate analysis that was incorporated in the trial statistical analysis plan long before the study was completed and unblinded**

Genvara

Genvara FAQs:

The composition of matter (COM) patents for bucindolol are expired. How will the IP and market exclusivity be protected from generic competition?

- **As outlined in the main deck, Genvara has a robust portfolio of method of use (MOU) patents based on the genetically-influenced mechanisms of action, the heart failure phenotype and the genetically-targeted patient populations that can benefit from bucindolol. These patents are expected to provide global patent protection until at least 2045**
- **Genvara's IP strategy follows a similar playbook for many other successful products based on drugs that no longer have COM protection, including Viagra, Auvelity, and KarXT**
- **Pharmacogenetic MOU patents offer several advantages over COM, and IP protection generally extends beyond the typical term of COM patents**
  - On average, the remaining life of COM patents for drug therapies is only 7 - 8 years from date of NDA approval.
  - IP protection offered by Hatch Waxman for any approved drug upon NDA approval is 5 years.
  - In addition, if a drug has a method of use approved by FDA the applicant is entitled to an automatic litigation stay, extending protection to a minimum of 7.5 years, which already matches the typical COM term.
  - Pharmacogenetic MOU patents are filed based on data generated from clinical trials, which occurs much later in the development cycle, and extends the exclusivity beyond what can be offered by COM. In the case of the Genvara PGt use patent families filed most recently, this is expected to extend well beyond the protection offered by Hatch Waxman.
- **Pharmacogenetic use patents are strong and enforceable as long as the patent claims are consistent with the drug indication and labeling**
  - Genvara's PRECISION-AF trial, if successful, will result in a drug label that is covered by the claims in our MOU patents