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Pharmacogenetic Precision Medicine for Cardiovascular Diseases

Nasdaq: ABIO

November 2021

Safe Harbor Statement

This presentation contains "forward-looking statements" for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, the ability of ARCA's financial resources to support its operations, potential future development plans for rNAPc2 (AB201) and Gencaro, ARCA's ability to complete any clinical trials, the expected features and characteristics of rNAPc2 or Gencaro, including the potential for rNAPc2 to treat COVID-19, the potential for genetic variations to predict individual patient response to Gencaro, Gencaro's potential to treat atrial fibrillation (AF), future vaccines and/or treatment options for patients with COVID-19, future treatment options for patients with AF, and the potential for Gencaro to be the first genetically targeted AF prevention treatment, the likelihood for PRECISION-AF results to satisfy the requirements of the U.S. FDA Special Protocol Assessment (SPA) agreement, ARCA's ability to raise sufficient capital to fund the PRECSION-AF trial and its other operations and the potential market opportunity for rNAPc2 and Gencaro, should they receive regulatory approval. Such statements are based on management's current expectations and involve risks and uncertainties. Actual results and performance could differ materially from those projected in the forward-looking statements as a result of many factors, including, without limitation, the risks and uncertainties associated with: ARCA's financial resources and whether they will be sufficient to meet its business objectives and operational requirements; ARCA may not be able to raise sufficient capital on acceptable terms, or at all, to continue development of rNAPc2 or Gencaro or to otherwise continue operations in the future; an FDA SPA agreement does not guarantee approval of Gencaro or any other particular outcome from regulatory review; results of earlier clinical trials may not be confirmed in future trials; the protection and market exclusivity provided by ARCA's intellectual property; risks related to the drug discovery and the regulatory approval process; and, the impact of competitive products and technological changes. These and other factors are identified and described in more detail in ARCA's filings with the Securities and Exchange Commission, including without limitation ARCA's annual report on Form 10-K for the year ended December 31, 2020, and subsequent filings. ARCA disclaims any intent or obligation to update these forward-looking statements.

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Investment Highlights

rNAPc2 (AB201) – Treatment for Severe COVID-19

- Potential treatment for life-threatening condition (not a vaccine)
- Safety data in 700+ patients through Phase 2 from prior development in other indications
- Potent inhibitor of tissue factor, a key driver of viral pathology
- Combination of anticoagulation, anti-inflammatory and antiviral activity
- FDA Fast Track Designation Nov 2020
- ASPEN-COVID-19 Phase 2b currently enrolling | Topline clinical trial data anticipated 1Q 2022

Gencaro™ – Genetically-targeted prevention of AF in HF

- Significant treatment benefits identified in previous Phase 2 trial (GENETIC-AF)
- SPA agreement with FDA for a single pivotal Phase 3 trial (PRECISION-AF)
- Phase 3 initiation delayed due to COVID-19 pandemic
- FDA Fast Track Designation expedites regulatory interactions and potential NDA review
- Substantial unmet medical need with no FDA approved treatments
- Potential annual sales of $400M – $900M in U.S. | Significant markets in EU & Asia

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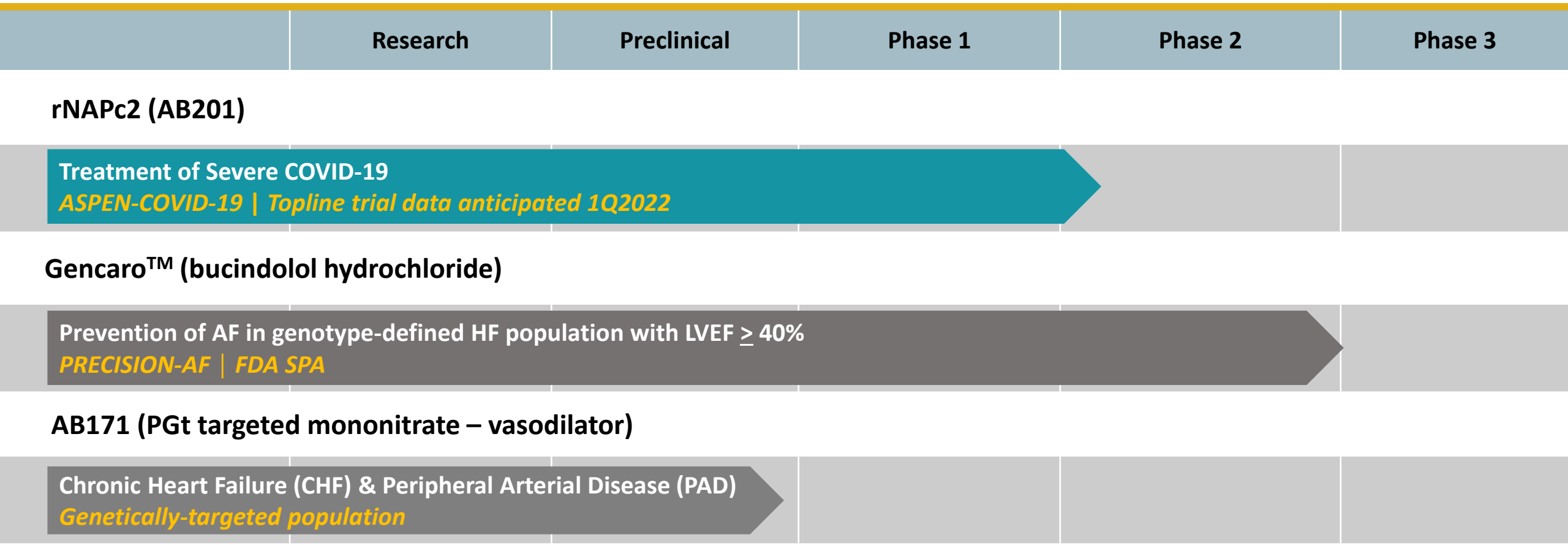
Late-Stage Pipeline



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rNAPc2

Potential treatment for patients hospitalized with COVID-19

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RNA Virus Associated Disease

- RNA viruses are a major threat to human health
  - Several RNA viruses are pandemic and infect hundreds of millions around the world leading to the death of millions of people every year
  - No vaccine or specific treatment is available for many of these viruses and some of the available vaccines & treatments are not highly effective
- 200+ known human-infective RNA virus species
  - Common cold, Influenza, Hepatitis C, Rabies, Polio, Measles
- RNA viruses are very prominent among emerging infectious diseases
  - Ebola virus disease, SARS, MERS, COVID-19
- RNA virus infections often lead to blood clotting disorders, hospitalization and death
- rNAPc2 may have broad spectrum potential for other coronaviruses & other RNA viruses

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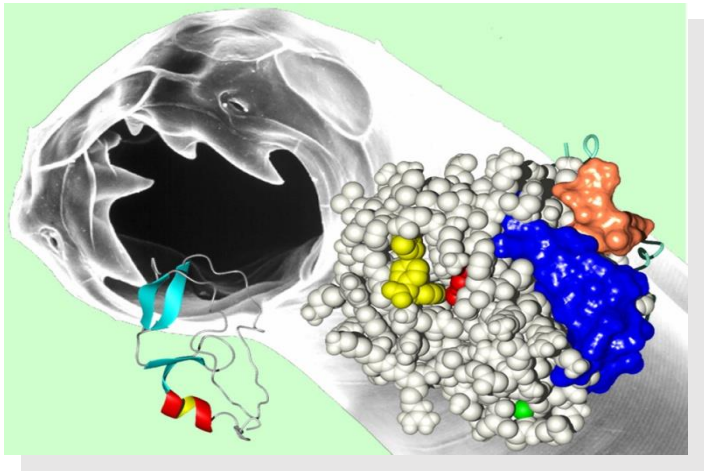
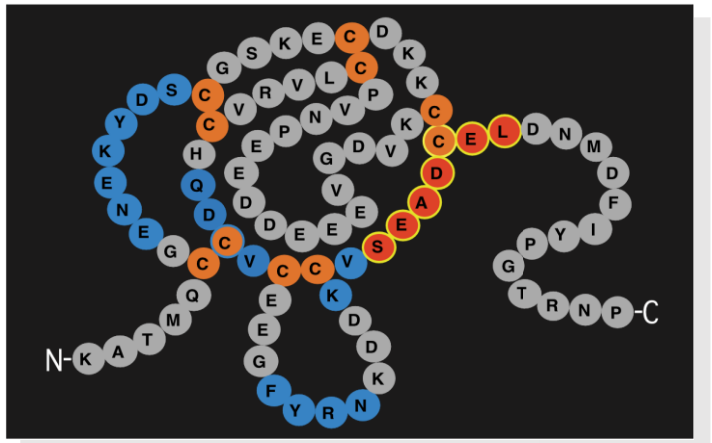
COVID-19

- COVID-19 is a disease caused by SARS-CoV-2
- WHO declared the current outbreak of COVID-19 a global pandemic in March 2020

- COVID-19 is associated with a significant incidence of coagulation-related adverse events
  - Stroke, myocardial infarction (i.e., heart attack), pulmonary emboli, and disseminated intravascular coagulation (DIC)
  - 50% of hospitalized COVID-19 patients show evidence of coagulopathy
  - Coagulopathy is directly associated with adverse clinical outcomes

rNAPc2 (AB201)
Recombinant Nematode Anticoagulant Protein c2





- Small recombinant protein cloned from hookworm
- Potent, long-acting inhibitor of tissue factor via unique mechanism of action
- Anticoagulant activity, safety and PK established from clinical trials in 700+ patients
- GMP manufacturing well established in yeast
- Non-human primate (NHP) studies indicate potential to treat conditions associated with RNA virus infection
- Robust intellectual property protection

Vlasuk, G.V., Rote, W.E. Trends in Cardiovascular Medicine, (2002). Stanssens, P. et. al. Proc. Natl. Acad. Sci. (1997)

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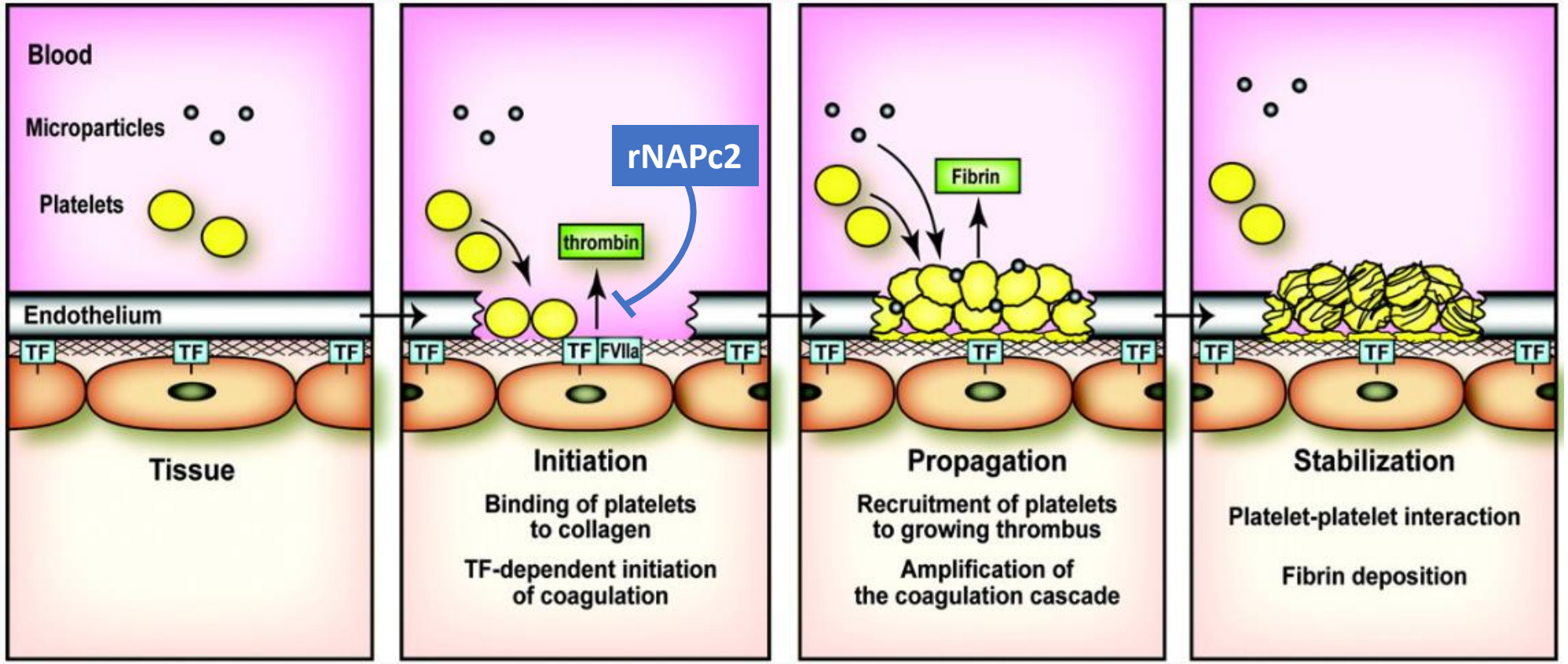
rNAPc2 Inhibits Coagulation at the Source



rNAPc2 inhibits Tissue Factor at the initiation phase of coagulation

N. Mackmanet al. Arterioscler Thromb Vasc Biol. 2007 Aug;27(8):1687-93

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rNAPc2 is a Potent and Specific Inhibitor of Tissue Factor

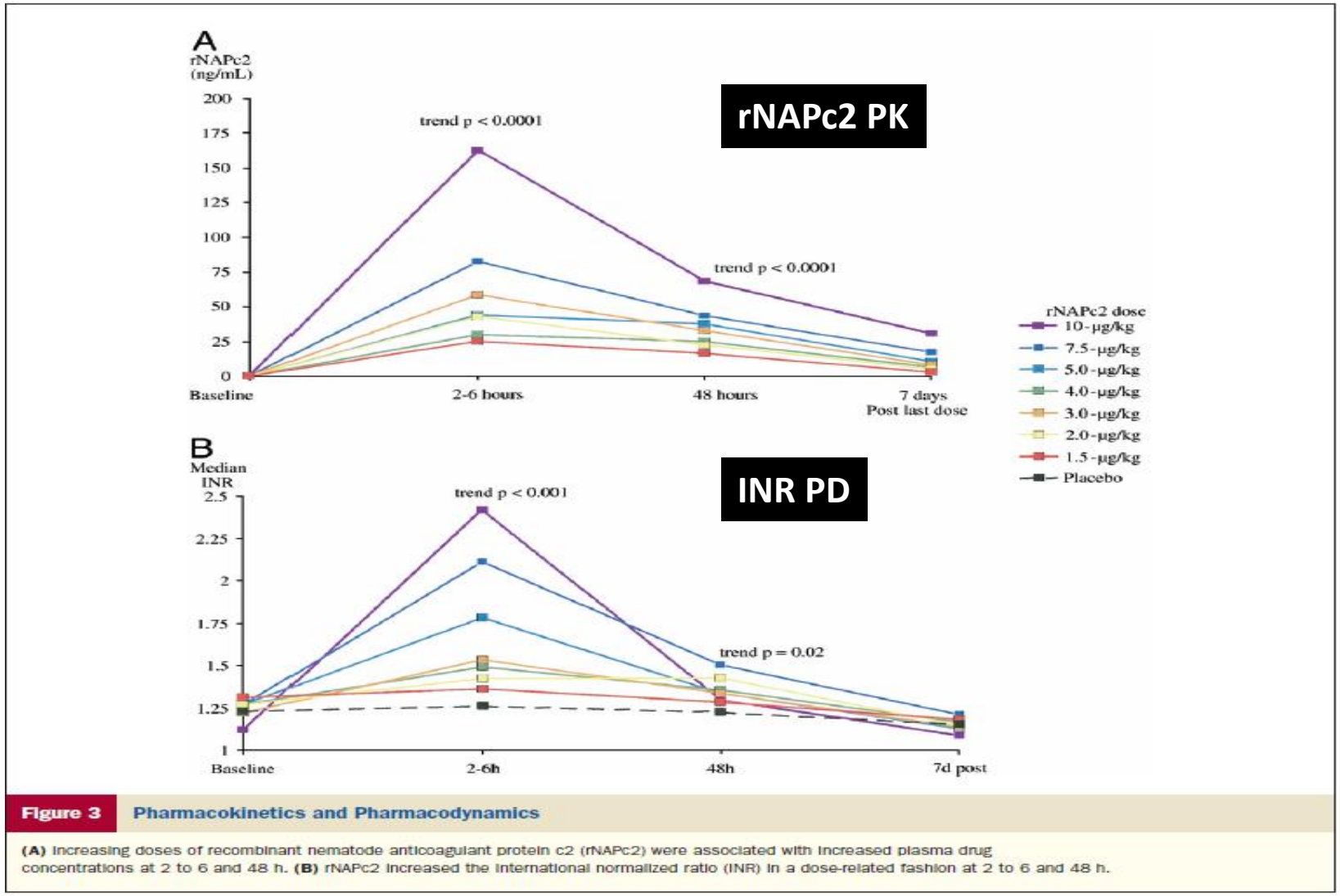
Tissue Factor (TF)

- A major activator of the coagulation cascade during viral infection
- Plays a central role in inflammatory signaling and dysregulated immunity related to viral infections
- Enhances viral dissemination
- Incorporation into viral envelope may lead to dysregulation of coagulation cascade

rNAPc2 Clinical Findings

- Predictable dose-dependent pharmacokinetic (PK) profile
  - Plasma half-life of ~72 hours with repeat subcutaneous administration
- Potent dose-dependent anticoagulant effects
  - Effects are reversible with administration of commercially available therapy (factor VIIa)
- Safe & well-tolerated at all doses studied (max: 10 ug/kg)
  - Similar to doses used in NHP virus studies
- Phase 2 studies showed evidence of efficacy in each cardiovascular indication studied (venous and arterial thrombosis)
- Previous development stopped by prior sponsor due to financial/commercial factors
  - Not due to issues with safety or efficacy

Phase 2: Increasing rNAPc2 Dose Associated with Increased Anticoagulation



rNAPc2 PK

INR PD

Figure 3 **Pharmacokinetics and Pharmacodynamics**

(A) Increasing doses of recombinant nematode anticoagulant protein c2 (rNAPc2) were associated with increased plasma drug concentrations at 2 to 6 and 48 h. **(B)** rNAPc2 increased the international normalized ratio (INR) in a dose-related fashion at 2 to 6 and 48 h.

Giugliano RP et al. JACC 49:2398-2407, 2007

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rNAPc2 as a Potential Viral Therapeutic in Non-human Primate (NHP) Models

- rNAPc2 has been tested in vitro and in vivo in NHP challenge models of Ebola
  - rNAPc2 demonstrated a 33% survival of 100% lethal challenged
  - Significant increase in survival time for all rNAPc2-treated animals
  - rNAPc2 attenuated coagulation activation and inflammation
  - No significant safety concerns observed for repeat dosing of up to 14 days
- rNAPc2 also demonstrated evidence of efficacy against a lethal challenge of the Marburg-Angola hemorrhagic fever virus in NHPs
- No additional supportive care was provided in either the Ebola or Marburg study
- FDA granted rNAPc2 Orphan Drug Designation status for treatment of viral hemorrhagic fever post-exposure to Ebola virus in 2014

rNAPc2 Development for COVID-19

- rNAPc2 is being developed as a potential treatment for diseases associated with RNA viral infection, initially for COVID-19 infection severe enough to require hospitalization
- U.S. FDA: IND approval Oct 2020; Fast Track Designation Nov 2020
- On-going Phase 2b clinical trial began evaluating rNAPc2 as treatment for patients hospitalized with COVID-19
  - Currently enrolling patients at investigative sites in U.S., Argentina and Brazil
- Phase 2b topline clinical trial data anticipated Q1 2022

ASPEN-COVID-19: Phase 2b Clinical Trial

Inclusion Criteria: SARS-CoV-2 positive; D-dimer > ULN

Enrollment target n= ~160
Randomization - 1:1:2

rNAPc2 Lower Dose (n = ~40)	rNAPc2 Upper Dose (n = ~40)	Heparin SOC (n = ~80)

30-day follow up

Primary Endpoint:
D-dimer change from baseline at Day 8

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rNAPc2 Intellectual Property

- Data exclusivity and potential patents provide strong commercial protection
- Data protection for rNAPc2 as a biologic is robust:
  - New molecular entity (NME) status; rNAPc2 never submitted/approved in any jurisdiction
  - 12 years from approval in US; 10 years from approval in EU
- New patent IP has potential to broaden protection
  - rNAPc2 to treat COVID-19 and other viral infections
  - Application filed 2020; based on new research on tissue factor pathway
  - Supplements data protection
  - Patent advantageous for some ROW territories (China) where data protection less recognized

GENCARO

Potentially the first genetically-targeted atrial fibrillation treatment for patients with heart failure

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Precision Medicine Applied to Drug Development and Therapy

Tailoring of medical treatment[1,2]:

- to the individual genetic characteristics of each patient ("*personalized*")
- in order to classify individuals into subpopulations ("*precision*") that differ in their susceptibility to a particular disease or their response to a specific treatment

Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Our Approach:

- ***Pharmacogenetic drug development*** by targeting therapy to a functionally different genetic variant in the primary or secondary drug target
  - ➢ Candidate gene variant approach to pharmacogenetic targeting
    - Start with a known and characterized genetic variant, in a drug target or something that may affect drug response
    - *Test hypothesis* that drug response in patients with the candidate variant is different than in the counterpart variant
- ***Biomarker selected patient populations likely to possess activation of a drug's target***
  - ➢ D-dimer selected COVID-19 coagulopathy driven by Tissue Factor (TF), treated with rNAPc2

1. President's Council of Advisors on Science and Technology, Priorities for Personalized Medicine, 2008.
2. National Research Council, Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease, 2011

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Atrial Fibrillation – A Significant Market Opportunity

- AF is the most common sustained cardiac arrhythmia
  - Affects ~5.2 million (2015) Americans[1]
  - 2015 worldwide prevalence of AF was estimated at 33 million[2]
- AF is considered an epidemic cardiovascular disease
  - Based on the rate of increase in incidence in the U.S. and industrialized countries[3]
- Estimated global atrial fibrillation market[4]
  - $7.2B in 2015 growing to $12.5B in 2020
- ARCA estimate of Gencaro opportunity
  - $400M to $900M peak revenue in US; similar in EU5

1- American Journal of Cardiology 2013: 112: 1142-1147 "Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population; AHA – "Cardiovascular Disease: A Costly Burden for America" (Jan 2017), page 7
2- AHA Statistical Update – Heart and Stroke Stats 2017, p306
3- Journal of the American Medical Association. 2001; 285(18):237 0-2375
4- DelveInsight – "Atrial Fibrillation – Market Insights & Drug Sales Forecast - 2020", May 2016

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Atrial Fibrillation in Heart Failure – An Unmet Medical Need

- No FDA approved drug treatments for this indication
- Approved antiarrhythmic agents are associated with significant side effects
  - Most are contraindicated or have warnings for HF patients
- New onset AF markedly worsens HF morbidity & increases mortality
- HF is the leading cause of death worldwide
  - Approximately 18.6 million people died from cardiovascular disease in 2019
- β-blockers approved for HF but used off-label for AF
  - Demonstrated only limited efficacy for AF prevention
- No agents approved for AF or HF have genetically influenced clinical response

Atrial Fibrillation and Heart Failure

AF/HF Patient Populations

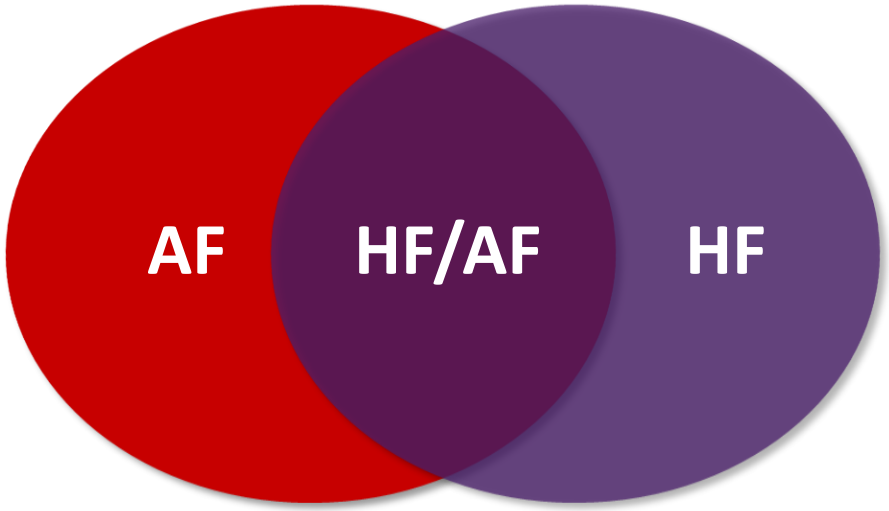
G7 Countries (US, EU5, and Japan) in 2022

LVEF	LVEF < 40%	40 ≤ LVEF < 50%	LVEF ≥ 50%
Total HF	5.6M	2.7M	7.6M
% with AF	30-50%	35-55%	40-60%
Total AF/HF	1.7 – 2.8M	1.0 – 1.5M	3.0 – 4.6M

Current BBs Approved for HF

No Approved or Effective Therapies for AF or HF

~50% of HF patients have optimal genotype



No FDA approved drug treatments for this indication

1- Decision Resources Group, Heart Failure Epidemiology 2018. 2- Piccini et al. JACC-HF 2019 online ahead of publication. 3- Panikowski P et al. Eur Heart J 2016.

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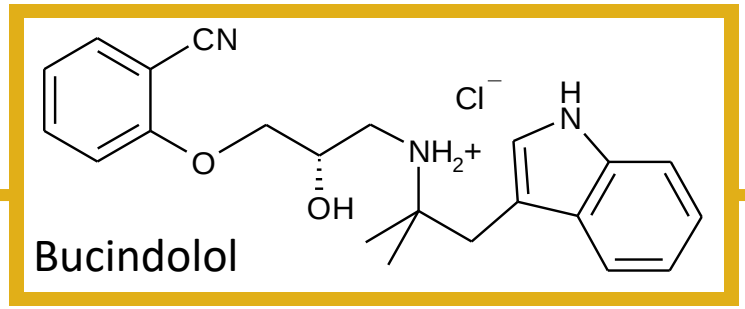
Gencaro (bucindolol hydrochloride)



Compound

- β-blocker/vasodilator – well characterized small molecule drug class
- β-blockers target cardiac myocytes to reduce adverse β_1-adrenergic receptor signaling that causes cardiac chamber remodeling
- Gencaro is only β-blocker with genetically differentiated response
- IP protection until at least 2031 in the U.S. and Europe

Differentiated MOA

- Competitive antagonism similar to other β-blockers
- Sympatholysis – norepinephrine lowering
- Inverse agonism – inactivation of constitutively active receptors
- Other β-blockers lack these last 2 properties

Genotype Specific Response

- Clinical response differentiated by patient genetic profile
- Specific β_1 adrenergic receptor (AR) polymorphism
- Optimal genotype is *ADRB1* Arg389Arg
  - Present in ~50% of US & EU population
- Companion diagnostic test
  - Rapid, low-cost standard test

Extensive Clinical Data

- Favorable safety profile with over 3,400 HF patients studied
- 74% reduction in AF onset compared to placebo for genetically-defined HF population with LVEF ≤ 35%
- 46% reduction in AF recurrence compared to Toprol-XL for genetically-defined HF population with LVEF ≤ 55% (58% reduction with LVEF 40-55%)

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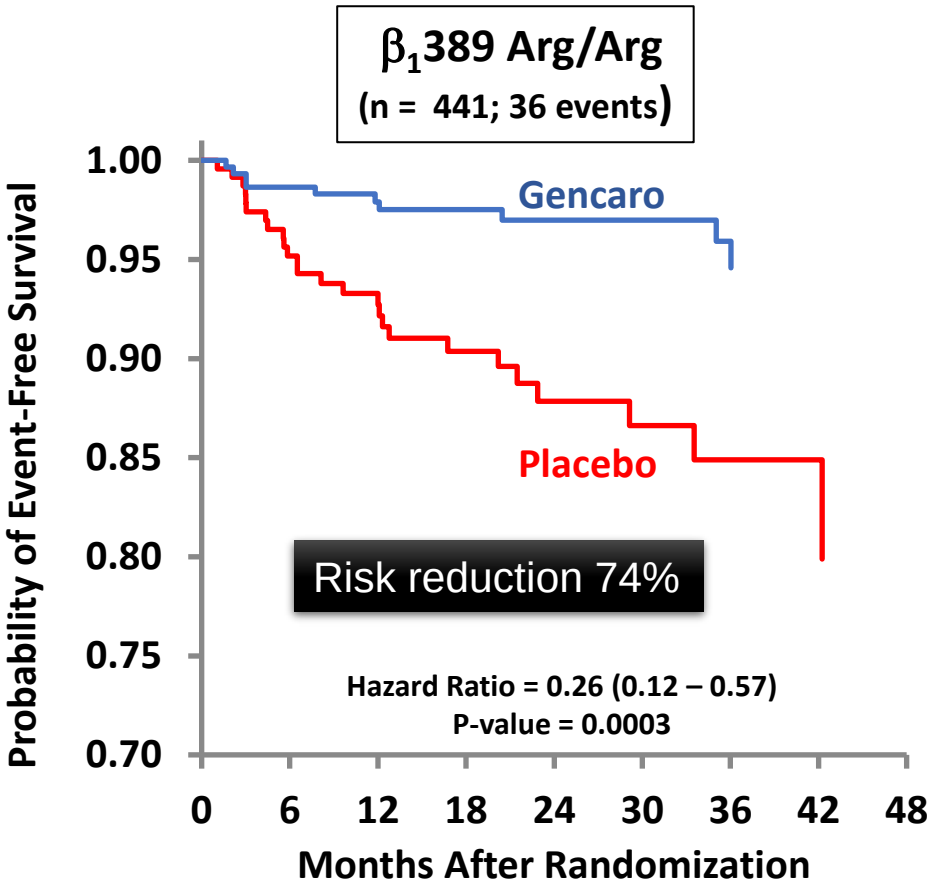
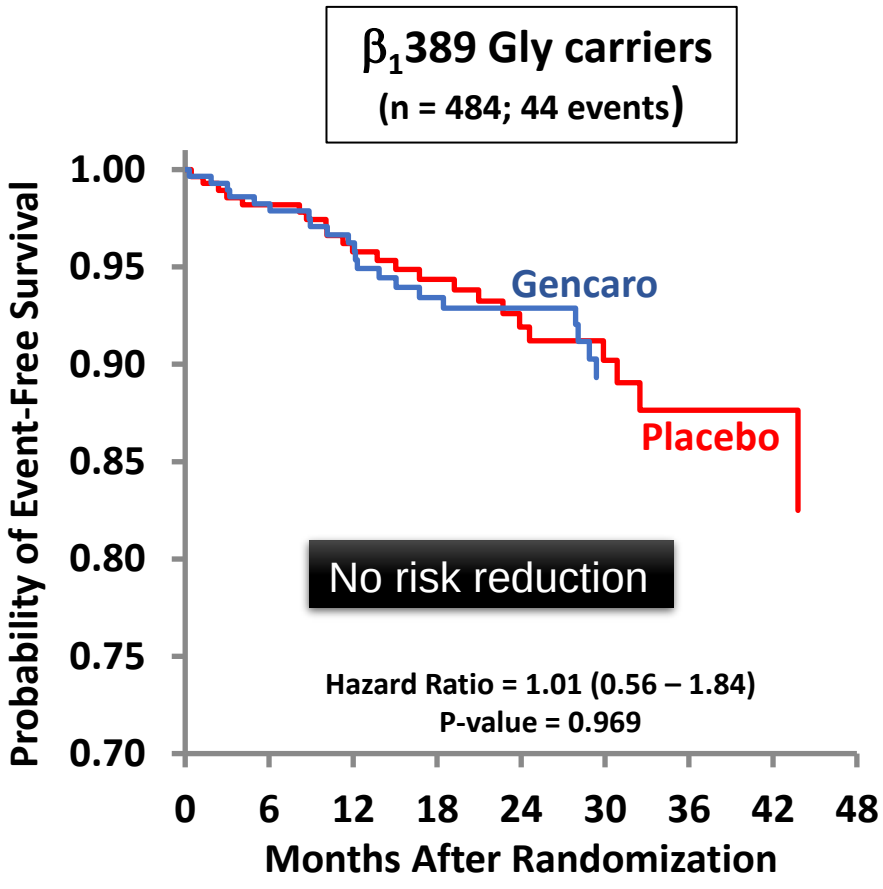
Differentiated AF Response by Genotype Seen in BEST DNA Substudy[1]





- β-blocker class 27% average risk reduction in AF onset in ~12,000 patient meta-analysis of Phase 3 HF trials.[2]
- Metoprolol and Carvedilol are not influenced by ADRB1 Arg389Gly[3,4]

Data from the BEST DNA pharmacogenetic substudy for patients with NYHA Class III/IV, LVEF ≤ 35% who were not in AF at randomization.

1- Aleong RG et al, JACC-HF 1:338-344, 2013. 2- Abi Nasr I et al, EHJ 28: 457–462, 2007. 3- Sehnert AJ, et al. JACC 52:644-651, 2008; 4- Data on file at ARCA.

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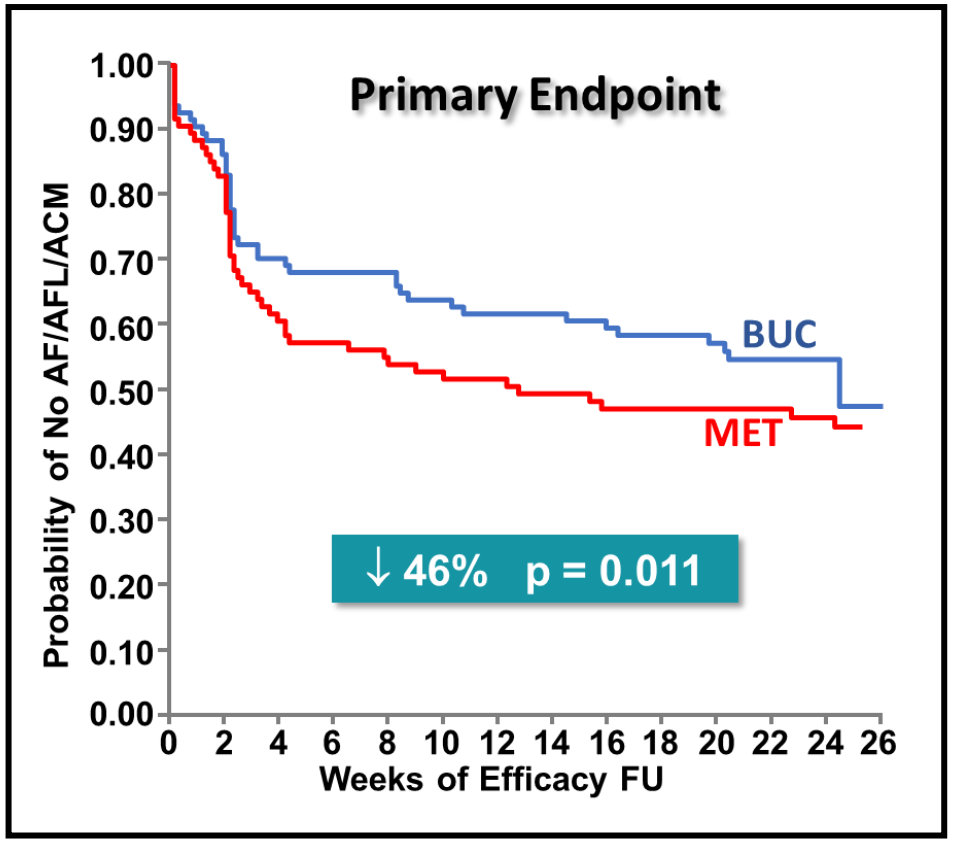
GENETIC-AF Phase 2B Trial: Design and Results

Trial Design

- 267 HF patients, US, EU, Canada
- LVEF range 12% to 55%
- Recent AF event last 180 days
- Limited to optimal genotype
- 94% on BBs prior to enrollment
- Superiority against TOPROL-XL
- Time to recurrent AF or death
- 6-month efficacy follow-up period
- Device substudy to assess AF burden

- **Gencaro comparable to SOC for 1EP in overall population but evidence of efficacy identified for Phase 3**
- **If long-standing and heavily pretreated AF/HF excluded, remaining patients (73%) had strong bucindolol response**



PTP Cohort = AF & HF onset < 12 years and AF onset not >2 years prior to HF onset.
Piccini et al. JACC Heart Fail. 2019 Jul;7(7):586-598.

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GENETIC-AF Analysis: EPs positive for full cohorts are basis for Phase 3

Endpoint	Entire GENETIC-AF Cohort				
Time to 1st AF/AFL/ACM (Primary Endpoint)	**1.01 (neutral)**	(0.71, 1.42) p = 0.961 N = 267			
Cumulative 24-week AF Burden (substudy)	**0.64 (↓36%)**	(0.46, 0.86) p =0.002 N = 67			
AF Burden at Week 24	**0.45 (↓55%)**	(0.39, 0.50) p < 0.001 N = 67			
ECGs in Normal Sinus Rhythm	**1.39 (↑39%)**	(1.22, 1.58) p < 0.001 N = 257			
AF Interventions (ECVs, Ablations, & Class 3 AA Drugs)	**0.68 (↓32%)**	(0.50, 0.91) p = 0.011 N = 257			
Bradycardia prevalence (Buc. vs. met., VR< 60 bpm)	**0.39 (↓61%)**	(0.31, 0.49) P < 0.001 N = 256	**Dose reductions** (pts. w/bradycardia vs. non-b.)	**4.22 (↑4X)**	(2.05, 9.54) P < 0.001 N = 256

Time to first AF/AFL/ACM treatment effect = hazard ratio (95% CI). AF burden = % time in AF per day. Cumulative AF burden treatment effect = AUC ratio (i.e., AUC_{BUC}/AUC_{MET}) over 24-week follow-up period with significance assessed via null permutation. AFB at Week 24 = Instantaneous estimates of average daily AF burden at week 24 with comparison between groups expressed as the ratio of the estimates and tested for significance using a Wald test. Normal Sinus Rhythm = total # ECGs in sinus rhythm with ventricular rate ≥ 60 and ≤ 100 bpm during efficacy follow-up period. AF Interventions = ECV, ablation, or guideline recommended antiarrhythmic use during efficacy follow-up period. Treatment effect for normal sinus rhythm, AF interventions and bradycardia = prevalence rate ratio (i.e., PRR_{BUC}/PRR_{MET}) modeled to test significance using Poisson regression.

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Precision-AF Pivotal Phase 3

Gencaro Strategic Vision and Phase 3 Strategy

Vision

First line therapy in genotype-positive AF patients with heart failure

Phase 3 Registrational Trial

Focus Development on HF with LVEF ≥ 40%

- Strongest Phase 2 data | **Moderately sized trials**
- Optimal regulatory path | **Need only demonstrate effect on AF**
- Highest unmet medical need | **Two-thirds of all heart failure**
- Greatest commercial differentiation | **No approved therapies**

Expansion Options

Registries, Publications, Education and Investigator Trials

- AF in non-HF patients
- HF patients prior to AF onset
- HF with permanent AF
- AF in HF with LVEF < 40%

PRECISION-AF (Pivotal Study)

AF Prevention in LVEF ≥ 40%

- 400-550 genotype-positive HF patients
- Recent paroxysmal or persistent AF
- 1EP: Time to first symptomatic AF event
- 2EPs: Interventions, AF burden, NSR, bradycardia, rate control and QoL
  125 sites in N. America, EU and Australia
- 27 months to topline data

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PRECISION-AF - *FDA Special Protocol Assessment*

FDA agreement that a Phase 3 protocol design, clinical endpoints, trial population and statistical analyses adequately address objectives that, if met, would support an NDA submission

Key elements of agreement

- ✓ Comparative efficacy against TOPROL-XL for prevention of AF recurrence
- ✓ 400 patient sample size, interim analysis with potential to expand to 550 patients
- ✓ One successful trial to support an NDA with regulatory threshold of $p < 0.01$
- ✓ Entry criteria based on precision therapeutic phenotype identified in GENETIC-AF (i.e., AF & HF < 12 years and AF not diagnosed more than 2 years before HF)
- ✓ HF population with LVEF ≥ 40% and ≤ 55%

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PRECISION-AF

Phase 3 Genetically-Targeted Trial Design

- 125 sites in USA, Canada, Europe and Australia
- 400 HF patients with ADRB1 Arg/Arg genotype
  - LVEF ≥ 40% and AF in past 120 days
  - AF/HF DxT < 12 years and AF not >2 years prior to HF
- Randomization 1:1 to Gencaro or Toprol-XL
- Primary Endpoint: Time to First Symptomatic AF Event or ACM during 26-week Period
  - >90% power at α = 0.01 to detect a 45% treatment benefit (Phase 2: 58% Rx benefit)
  - >90% power at α = 0.05 to detect a 40% Rx benefit, >80% power for Rx benefit of 35%
- Interim analysis with potential to expand to 550 patients
- Estimated Timeline
  - Enroll 200 pts: 12 months
  - Enroll 400 pts: 19 months

Interim analysis: 18 months
Final data: 27 months

Initiation on hold due to COVID-19 pandemic and limits on access to CV clinical treatment centers

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GENCARO
Medical Need and Commercial Opportunity

- **AF in mid-range and preserved heart failure**
  - More than two-thirds of all HF patients have EF ≥ 40% | Current BBs not indicated for this population
  - 35-50% of HF patients have AF co-morbidity | Worsens HF prognosis including mortality
  - 50% have optimal Gencaro genotype | High frequency biomarker
  - No efficacious and safe drug therapies for AF/HF in EF ≥ 40% | Major unmet cardiovascular need
- **Significant commercial opportunity**
  - $400M to $900M peak revenue in U.S. for first indication | Substantial market
  - Options for label expansion that more than double the initial indication | Broad clinical application
  - Significant markets in EU and Asia | Global partnering opportunity

Potentially first precision medicine-based cardiovascular therapeutic

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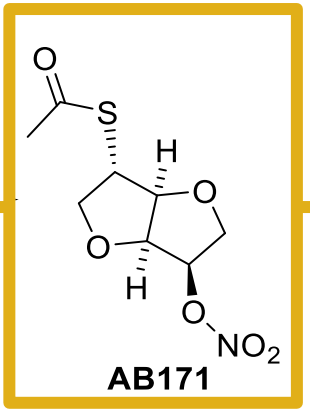
AB171 – Heart Failure & PAD



AB171

- Thiol-group containing derivative of isosorbide mononitrate
- Thiol moiety confers antioxidant activity compared to standard nitrates
  – Potentially greater anti-atherosclerosis, prevention of myocardial remodeling, and other favorable biologic effects
- Dual MOA → direct NO donor and generates endogenous NO from NOS3
  – Much greater NO and less peroxynitrite (harmful by-product of NO donation)
- Markedly pharmacogenetic compared to ISDN or BiDil
  – Enhanced NO generation in a NOS3 major allele homozygote in preclinical studies
- Pharmacogenetic use patents issued to ARCA in Europe, pending in U.S.
- Goal is to conduct a Phase 1B POC study in HF and peripheral artery disease (PAD)

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Experienced Leadership

Management Team

Michael R. Bristow, MD, PhD: *President & CEO*

Thomas Keuer: *Chief Operating Officer*

Chris Ozeroff: *General Counsel*

C. Jeff Dekker: *Chief Financial Officer*

Debra Marshall, MD, FACC: *Chief Medical Officer*

Sharon Perry, RAC: *VP, Regulatory Affairs & Quality*

Christopher Graybill, PhD: *VP, Clinical Development*

Board of Directors

Michael R. Bristow, MD, PhD

Robert E. Conway (Chairman)

Linda Grais, MD, JD

Anders Hove, MD

Dan Mitchell

Raymond L. Woosley, MD, PhD

Capital Structure

- Shares outstanding *(11/1/21)* 14.4 million
- Potentially dilutive securities 0.8 million
- Fully diluted 15.2 million

- No debt
- Cash and cash equivalents *(at 9/30/21)* $58.3 million

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Thank you

Nasdaq: ABIO