Glaucienne
Diagnosed with AHP (Brazil)

Zilebesiran (ALN-AGT), in Development for the Treatment of Hypertension

RNAi ROUNDTABLE 2021

June 30, 2021

Alnylam® PHARMACEUTICALS

Agenda

Welcome
- Christine Lindenboom – Senior Vice President, Investor Relations & Corporate Communications

Introduction
- Pushkal Garg, M.D. – Chief Medical Officer

Hypertension Background
- Elizabeth Ofili, M.D., MPH, FACC; Professor of Medicine (Cardiology), Morehouse School of Medicine

Zilebesiran Background and Development Program
- Stephen Huang, M.D. – Senior Director, Clinical Research

Commercial Outlook
- Eric Green – Senior Vice President, Development Programs

Q&A Session

Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface

Replay, slides and transcript available at www.alnylam.com/capella

Alnylam Forward Looking and Disclosure Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including expectations regarding the potential of RNAi therapeutics to reimagine the treatment of hypertension, results from our Phase 1 study of zilebesiran (formerly known as ALN-AGT) supporting further development and the expected timing of additional Phase 1 data readouts, the design and conduct of our KARDIA-1 Phase 2 study of zilebesiran and the expected timing of the initiation of add-on studies, targeting 24 hour blood pressure control with the goal of minimizing CV risk and reducing the risk of organ failure, the potential features of zilebesiran and the potential commercial outlook, our aspiration to become a leading biotech company, and the planned achievement of our "Alnylam P^5x25" strategy. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

Zilebesiran has not been reviewed or approved for any indication by any regulatory authority and conclusions regarding the safety or efficacy of this investigational drug have not been established.

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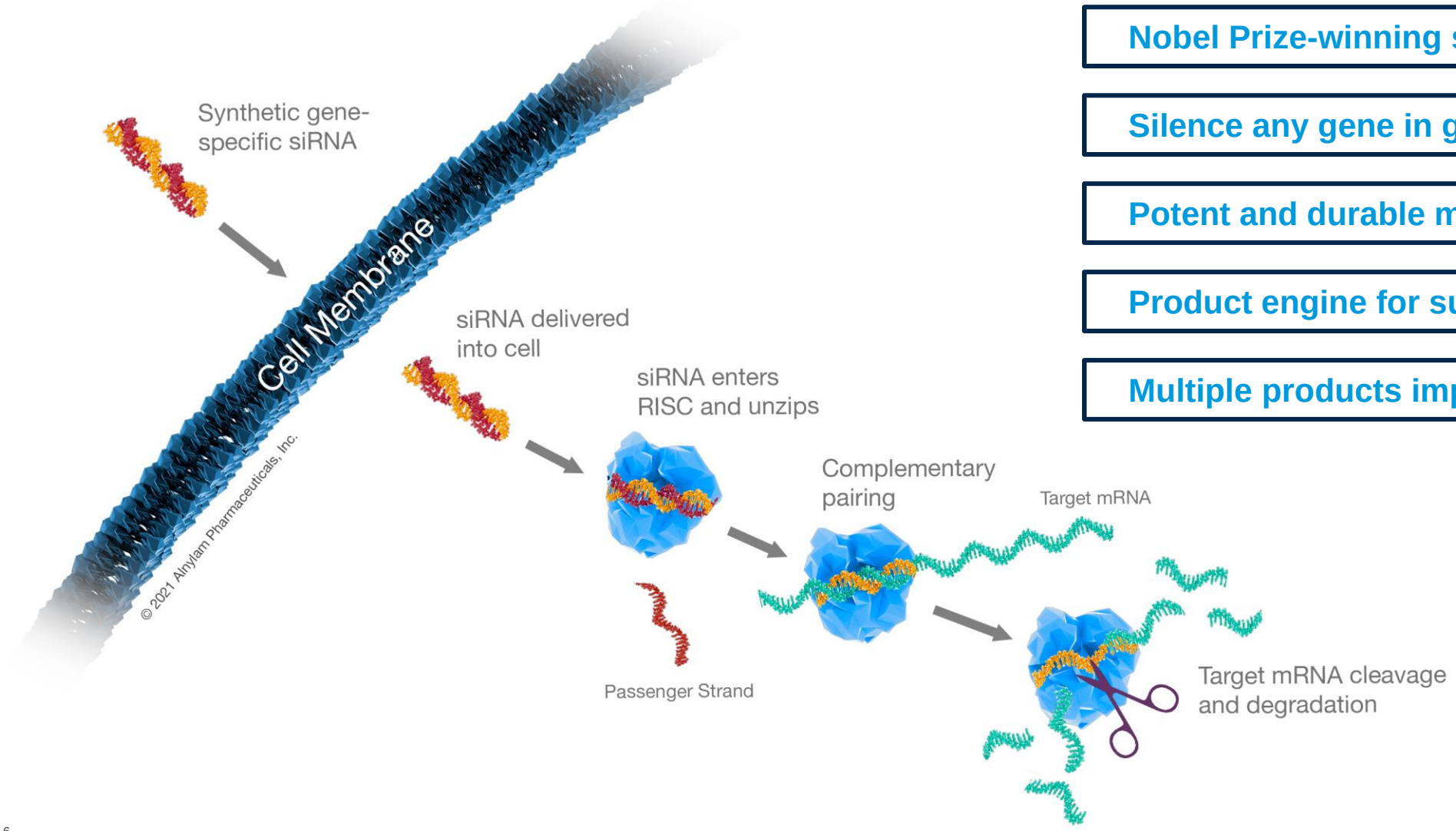
RNAi Therapeutics: New Class of Innovative Medicines

Clinically and Commercially Established Approach with Transformational Potential



- **Nobel Prize-winning science**
- **Silence any gene in genome with siRNAs**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products impacting patients globally**

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STARs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

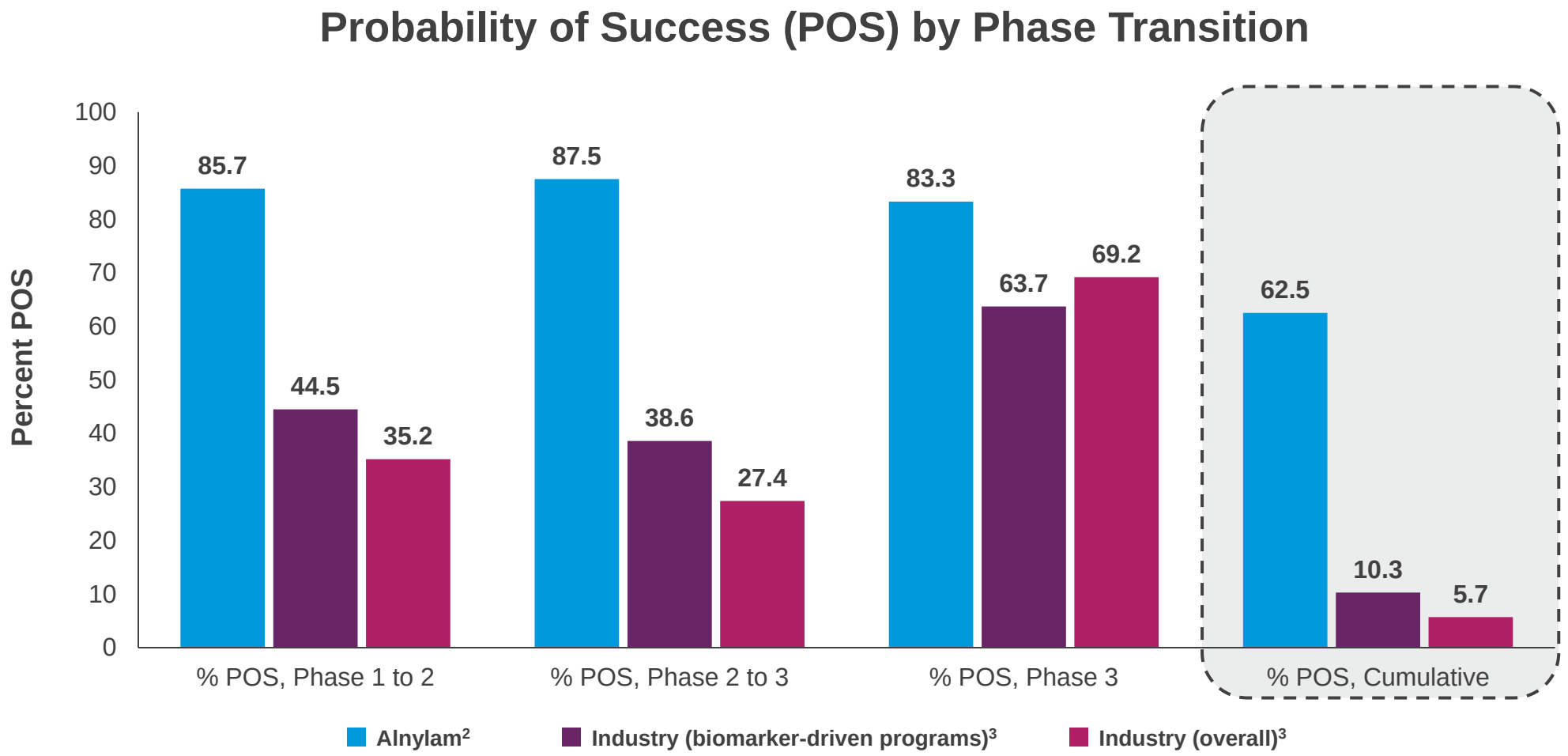
		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●	●		Global
Cemdisiran*	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]*	*Complement-Mediated Diseases*	●			Milestone/Royalty
Belcesiran[7]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT*)	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of June 2021

High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



[1] Analysis as of January 2021; Past rates of Alnylam and industry respectively may not be predictive of the future

[2] Alnylam programs biomarker-driven at all stages of development (100%); figures include ALNY-originated molecules now being developed by partners

[3] Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

Potential RNAi Therapeutics Profile Supports Expansion to Prevalent Diseases

- Durability
- Clamped pharmacology
- Safety profile evaluated in clinical trials
- Improved access

RARE

ONPATTRO: hATTR-PN[1]
GIVLAARI
OXLUMO
Vutrisiran: hATTR-PN[3]
Fitusiran
Belcesiran
ALN-APP
ALN-HTT

SPECIALTY

Patisiran: ATTR-CM[2]
Vutrisiran: ATTR-CM[3]
Cemdisiran

PREVALENT

Leqvio® (inclisiran)[4]
ALN-HBV02 (VIR-2218)
Zilebesiran (ALN-AGT)
ALN-HSD
ALN-XDH
ALN-KHK

[1] ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; [2] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population; [3] Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; NDA submitted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing; [4] Leqvio is approved in the EU for the treatment of adults with hypocholesterolemia or mixed dyslipidemia; in the U.S., Novartis received a Complete Response Letter on the NDA for inclisiran and plans to resubmit an NDA in Q2/Q3 2021. None of the investigative therapeutics referenced herein has been reviewed by EMA, FDA or any other regulatory agency and no conclusions can or should be drawn regarding their respective safety or efficacy.

RNAi Therapeutics Could Potentially Reimagine Treatment of Hypertension

Opportunity for Tonic Blood Pressure Control

Disease Overview

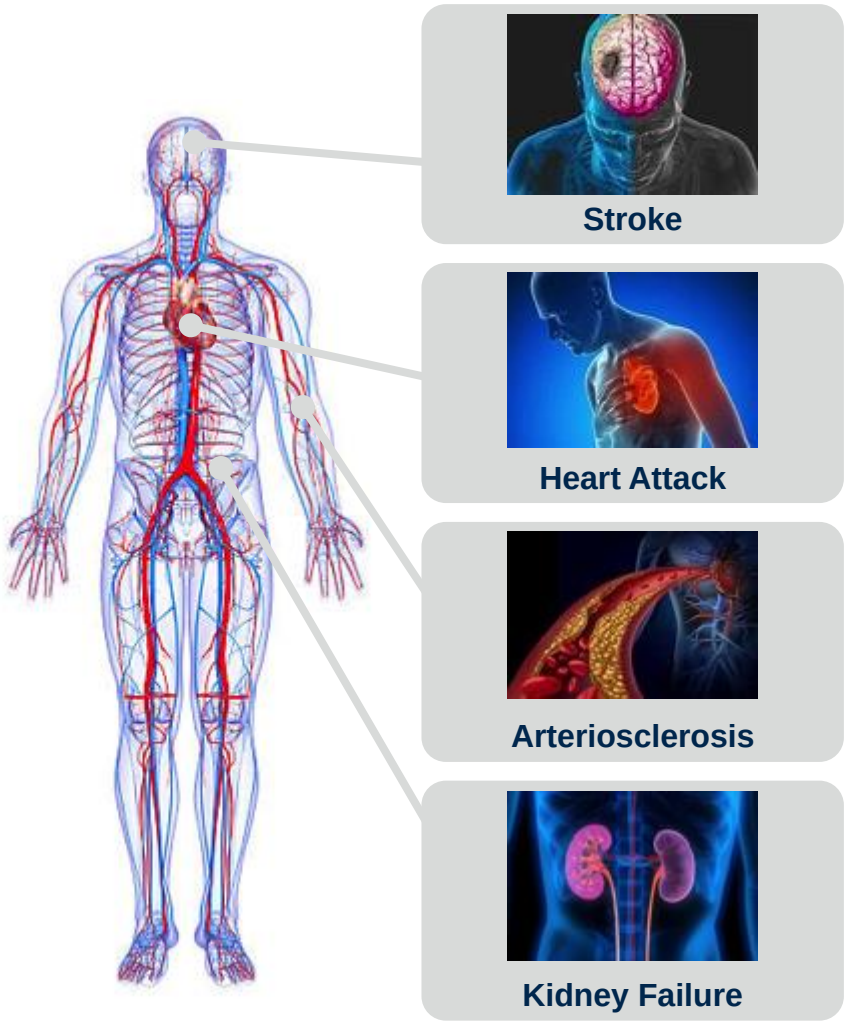
Primary Hypertension[1]	Hypertension at high CV risk[2]
~108 Million in U.S.	**~38 Million** in U.S.

>71% of patients have uncontrolled hypertension (>130/80 despite treatment)[3]

Hypertension risk further exacerbated by variability in BP **control**, lack of nighttime **dipping**, and poor medication **adherence**

Together, contribute to substantial risk of CV morbidity and mortality

Potential Complications of Uncontrolled Hypertension



[1] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016. Atlanta, GA: US Department of Health and Human Services; 2019.

[2] Estimated from multiple sources and internal estimates: Dorans. JAHA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD

[3] U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Control Hypertension. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General; 2020.

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Health Disparities and Treatment Gaps in Blood Pressure Control

Elizabeth Ofili, MD, MPH, FACC
Professor of Medicine (Cardiology)
Morehouse School of Medicine

Chief Medical Officer, Morehouse Choice ACO (Accountable Care Organization)

Chair of the Board, Association of Black Cardiologists

Founder and Chief Science Officer, AccuHealth Technologies Inc. and Health 360x

Disclosures

Elizabeth O. Ofili, MD, MPH, FACC

- **Grant/Research support:** National Institutes of Health
- **Advisory Board/Consultant:** Pfizer; Bristol Myers Squibb; Alnylam; AMGEN.
- **Patent:** A System and Method for Chronic Illness Care (Ofili et al. Patent # US 8,234,131 B2) issued in 2012
- **AccuHealth Technologies** Small Business Innovation Research (SBIR) NIH; Award Number**:** 1R44TR003832-01 April 1, 2021
- **Founder and Chief Science Officer:** AccuHealth Technologies Inc. and Health 360x

MOREHOUSE SCHOOL OF MEDICINE

Objectives

- Outline disparities in hypertension prevalence and control rates
- Discuss treatment gaps in hypertension
  - -Declining BP control rates across all demographic groups
  - -Multi-level barriers to treatment adherence
  - -Patient centered approach to BP treatment
- Introduce Health 360x culturally congruent coaching for CV risk management
- Highlight the Association of Black Cardiologists (ABC) Cardiovascular Implementation Study-Integrating Social Determinants for Care of Underserved Patients

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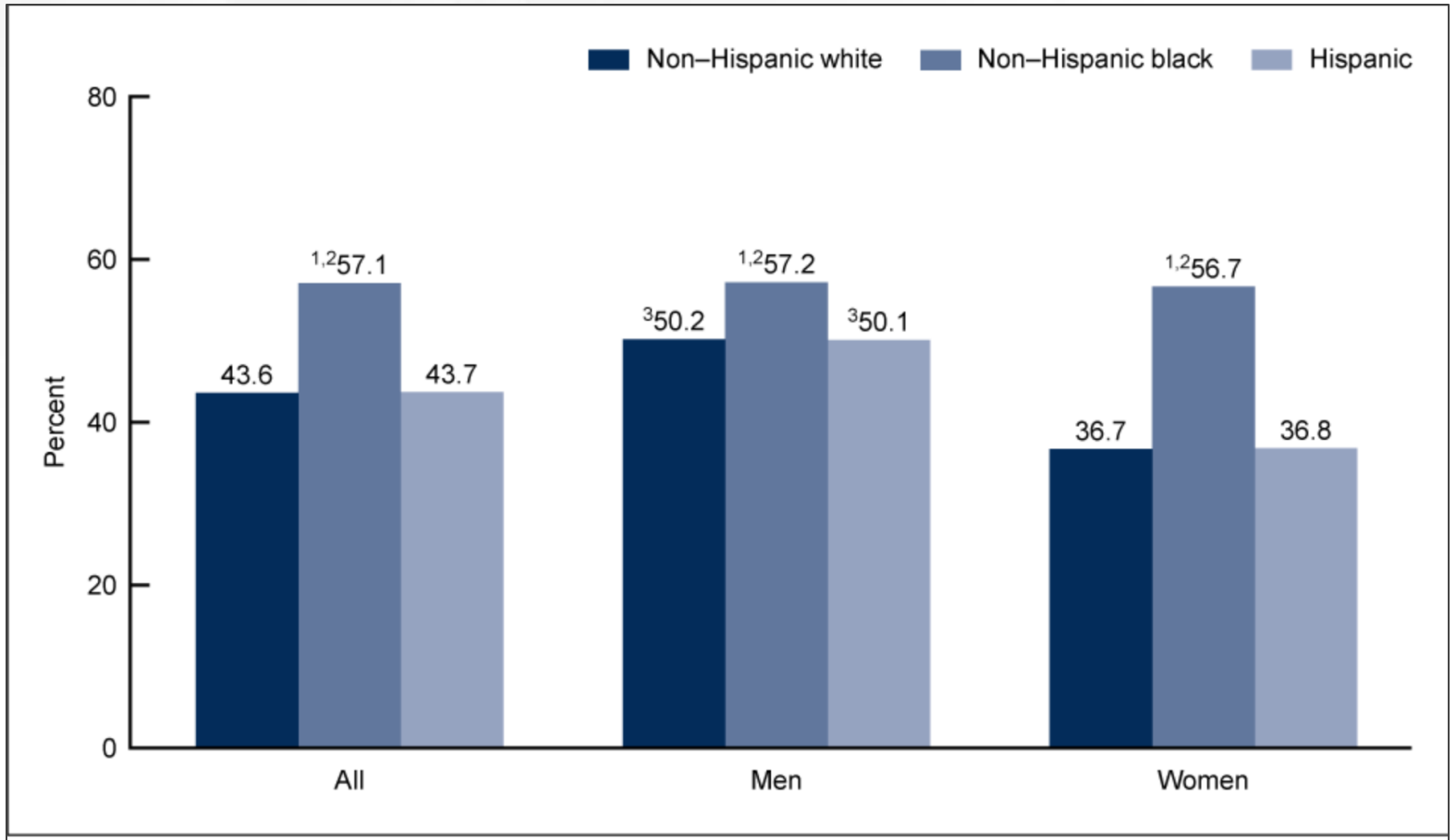
New Blood Pressure (BP) Categories

Normal	**less than 120** *and* **less than 80**
Elevated	**120-129** *and* **less than 80**
High BP Stage 1	**130-139** *or* **80-89**
High BP Stage 2	**140** *or* **higher** *or* ***90*** *or* ***higher***
Hypertensive Crisis (Call your doctor immediately)	**Higher than 180** *and/or* **higher than 120**

Whelton PK et al. J Am Coll Cardiol. 2017; doi: 10.1016/j.jacc.2017.11.006.

MOREHOUSE SCHOOL OF MEDICINE

Age Adjusted Prevalence of Hypertension : Adults 18 and over (2017-2018)



[1]Significantly different from non-Hispanic white.
[2]Significantly different from Hispanic.
[3]Significantly different from women in the same race and Hispanic-origin group.
NOTES: Hypertension is defined as systolic blood pressure greater than or equal to 130 mmHg or diastolic blood pressure greater than or equal to 80 mmHg, or currently taking medication to lower blood pressure. All estimates are age adjusted by the direct method to the U.S. Census 2000 population using age groups 18–39, 40–59, and 60 and over. Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db364-tables-508.pdf#2.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 2017–2018.

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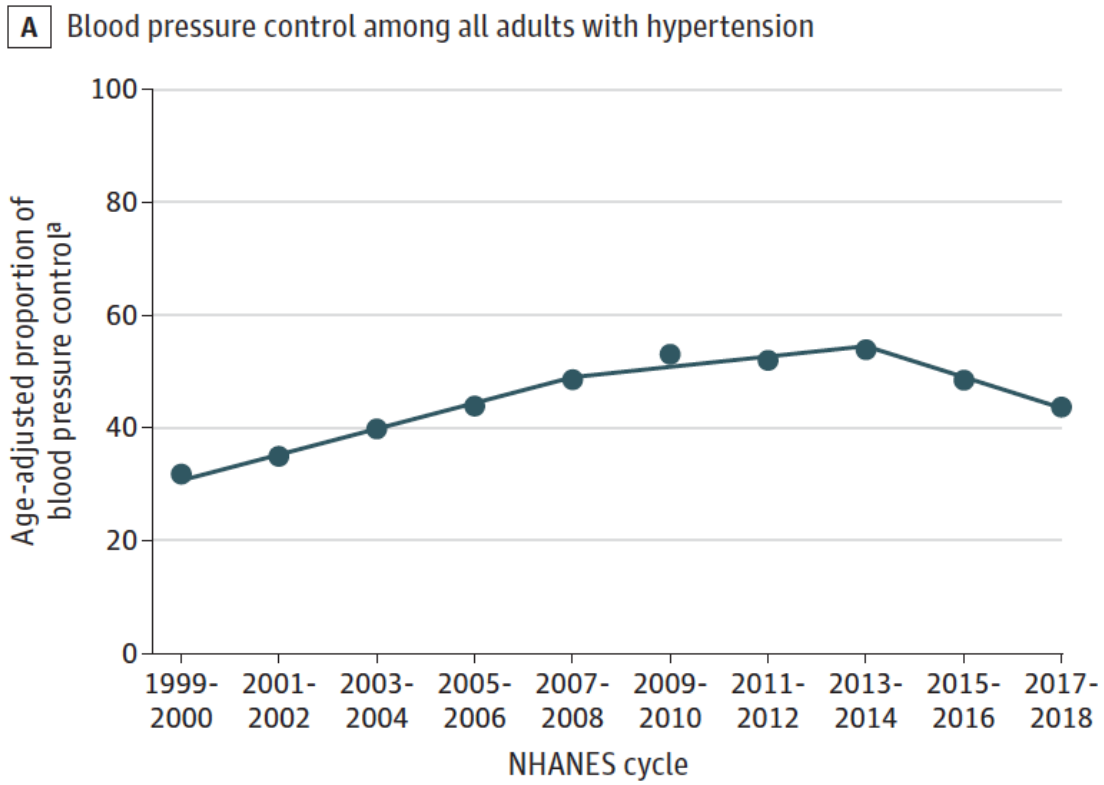
Treatment Gaps in Hypertension

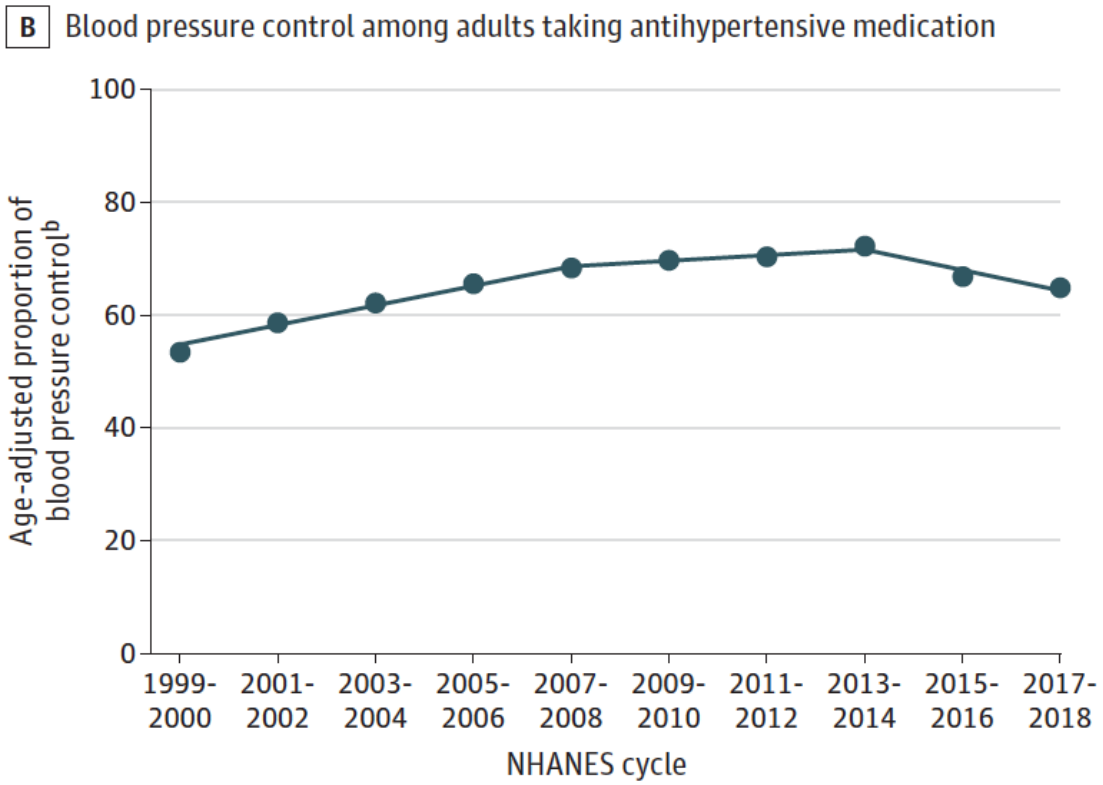
- The 2017 ACC/AHA hypertension guidelines lowered the blood pressure threshold for diagnosis of stage I hypertension to 130-139/80-89 mm Hg.
- This change resulted in a substantial increase in the prevalence of hypertension from ~32% to ~46% in the United States (US) adult population.
- Hypertension control rates among non-Hispanic white adults (55.7%) was significantly higher than non-Hispanic black adults (48.5%),non-Hispanic Asians (43.5%), and Hispanic (47.4%) adults
- Non-Hispanic black adults have higher nocturnal blood pressures and less circadian 'dipping' compared to their non-Hispanic white counterparts

Whelton PK et al. J Am Coll Cardiol. 2017; doi: 10.1016/j.jacc.2017.11.006.
Muntner P. et al. JAMA. doi:10.1001/jama.2020.14545

MOREHOUSE SCHOOL OF MEDICINE

Age-Adjusted Estimated Proportion of Adults With Hypertension and Controlled Blood Pressure





Muntner P. et al. JAMA. doi:10.1001/jama.2020.14545

MOREHOUSE SCHOOL OF MEDICINE

Adults With Hypertension in NHANES 2009–2014 and 2015–2018

NHANES	2009-2014	2015-2018	P value
Systolic BP	134.7	137.8	<0.0001
Diastolic BP	72.9	75.2	0.002
BMI ≥ 30 %	49.6	53.6	0.02
Usual Source of care %	94.1	91.3	0.0003
Diabetes %	22.0	24.3	0.02

Egan BM et al. Hypertension. 2021;78:00–00. DOI: 10.1161/HYPERTENSIONAHA.120.16418

MOREHOUSE SCHOOL OF MEDICINE

Selected Characteristics of Adults With Hypertension by Race-Ethnicity Group in NHANES

	Non Hispanic White (n=2584)	(1404)	Non Hispanic Black (1642)	(1149)	Hispanic (1132)	(944)
NHANES	**2009-2014**	**2015-2018**	**2009-2014**	**2015-2018**	**2009-2014**	**2015-2018**
SBP	133.6	136.6**	137.1	141.9***	138.0	140.4*
<130/<80, %	37.3	29.9+++	30.0	24.9++	28.8	24.4+
BMI≥30, %	48.4	54.4##	57.9	59.9	56.7	56.2
Usual source of care	96.0	92.8	93.0	90.4	85.6	84.4

*** p<0.0001; ** p<0.001; * p<0.05; ++++p<0.002; p<0.02; p=0.09; ### p<0.01

Egan BM et al. Hypertension. 2021;78:00–00. DOI: 10.1161/HYPERTENSIONAHA.120.16418

MOREHOUSE SCHOOL OF MEDICINE

CHRONIC DISEASES IN AMERICA

6 IN 10
Adults in the US
have a **chronic disease**

4 IN 10
Adults in the US
have **two or more**

THE LEADING CAUSES OF DEATH AND DISABILITY
and Leading Drivers of the Nation's **$3.3 Trillion** in Annual Health Care Costs

HEART DISEASE | CANCER | CHRONIC LUNG DISEASE | STROKE | ALZHEIMER'S DISEASE | DIABETES | CHRONIC KIDNEY DISEASE

THE KEY LIFESTYLE RISKS FOR CHRONIC DISEASE

TOBACCO USE

POOR NUTRITION

LACK OF PHYSICAL ACTIVITY

EXCESSIVE ALCOHOL USE

MOREHOUSE SCHOOL OF MEDICINE

The Challenge of Chronic Disease

Meet Brenda

- **Wife**
- **Mother (2 children)**

- **Employed full time**
- **Commute = 45 min.**
- **Occasional travel**

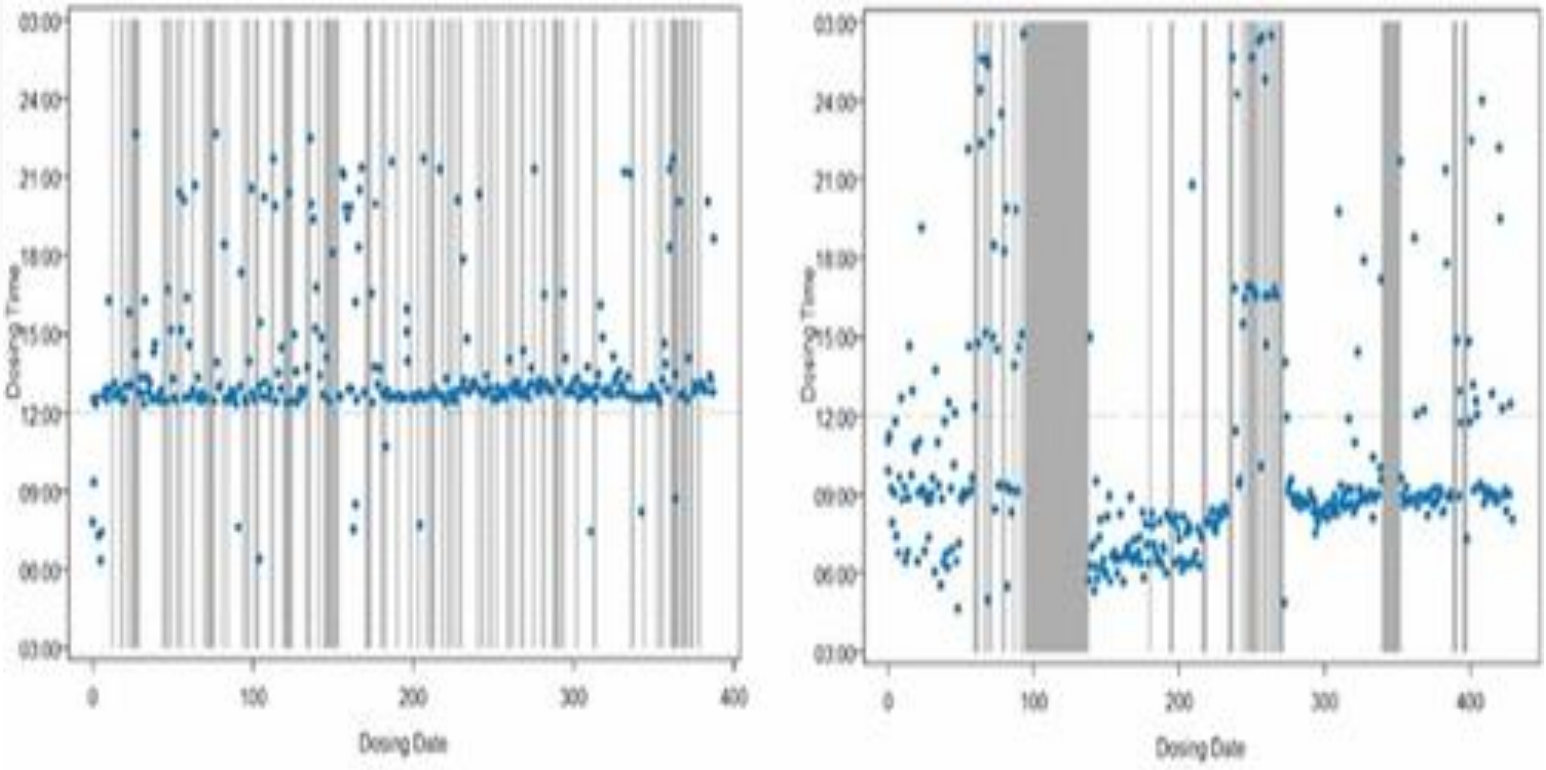
- **Type 2 diabetes**
- **Hypertension**
- **High Cholesterol**

- **Two prescribers**
- ***5* Rx medications daily**
- **Quarterly MD visits**

- Inconsistently controlled
- No plan for improvement
- Not activated, not empowered
- Inadequate knowledge
- Inadequate skills

= **Overwhelmed**

Dosing History of 2 Patients with 80% Adherence to their Medications Prescribed once a Day



Each vertical bar represents a missed dose.
Each blue point represents one opening of the Medication Event Monitoring System (MEMS) pillbox.
Note the variability of the timing with doses taken in the morning but also in the evening.
This illustrates the dynamic process of drug adherence.

Michel Burnier. Circulation Research. Adherence in Hypertension, Volume: 124, Issue: 7, Pages: 1124-1140, DOI: (10.1161/CIRCRESAHA.118.313220)

MOREHOUSE SCHOOL OF MEDICINE

Adherence: Five Categories of Factors Impacting Adherence to Prescription Medications*

Sociodemographic	Health Care Team/Health Care System	Therapy-Related	Condition-Related	Patient-Related
Young and very old adults	Patient-clinician relationship	Complex regimens	Multiple chronic conditions	Deny diagnosis
Minority race-ethnicity	Communication style	Treatment changes	Depression, psychoses	Perception of illness severity/future impact
Low income, poverty	Patient-centeredness	Treatment failure	Drug/alcohol abuse	Perception of treatment efficacy
Homeless, unstable home	Lack of team-based care	Time to benefit	Dementia	Fear dependence or adverse effects
Social support	Clinician burn out	Adverse effects	Major disability	Lack knowledge/misunderstanding
Copayments	Fail to detect clues	Treatment duration	Symptom severity	Forget
(Health) literacy	Lack knowledge/QI support	Refill frequency	Quality of life	Limited follow-up
Transportation, rural residents	Access to and cost of care	Refill consolidation		Low self-efficacy/discount future
War, disasters	Pay for volume			Alternative therapy

QI indicates quality improvement; and QOL, quality of life.

*Data derived from World Health Organization. Adherence to Long Term Therapies: Evidence for Action; 2003.

Burnier M and Egan BM. Circ Research 2019; 124: 1124-1140

MOREHOUSE SCHOOL OF MEDICINE

Interventions that May Improve Medication Adherence in Hypertension

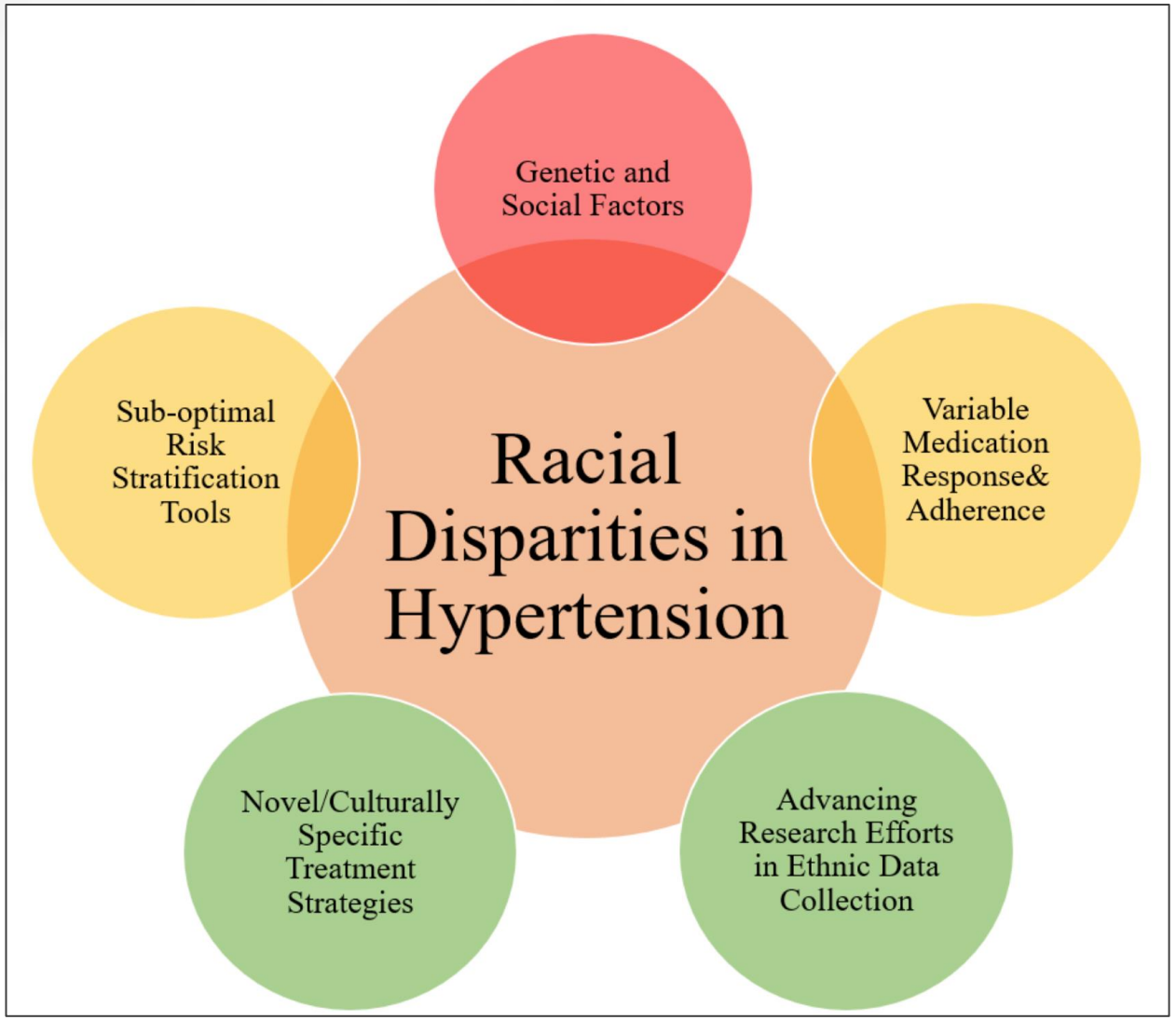
Physicians	Patient/Provider Communication Assess Barriers Team based care
Patients	Self monitoring of BP(includes telemonitoring) Self management Reminders Group Sessions
Medication Treatment	Simplify regimen Single pill/combination Long acting drugs Avoid high doses/side effects
Health Systems	Access to affordable drugs Reduce co-payments Reimbursement single pill combinations Telehealth

Adapted from: Burnier M and Egan BM. Circ. Research 2019; 124: 1124-1140

MOREHOUSE SCHOOL OF MEDICINE

Racial Disparities in Hypertension:

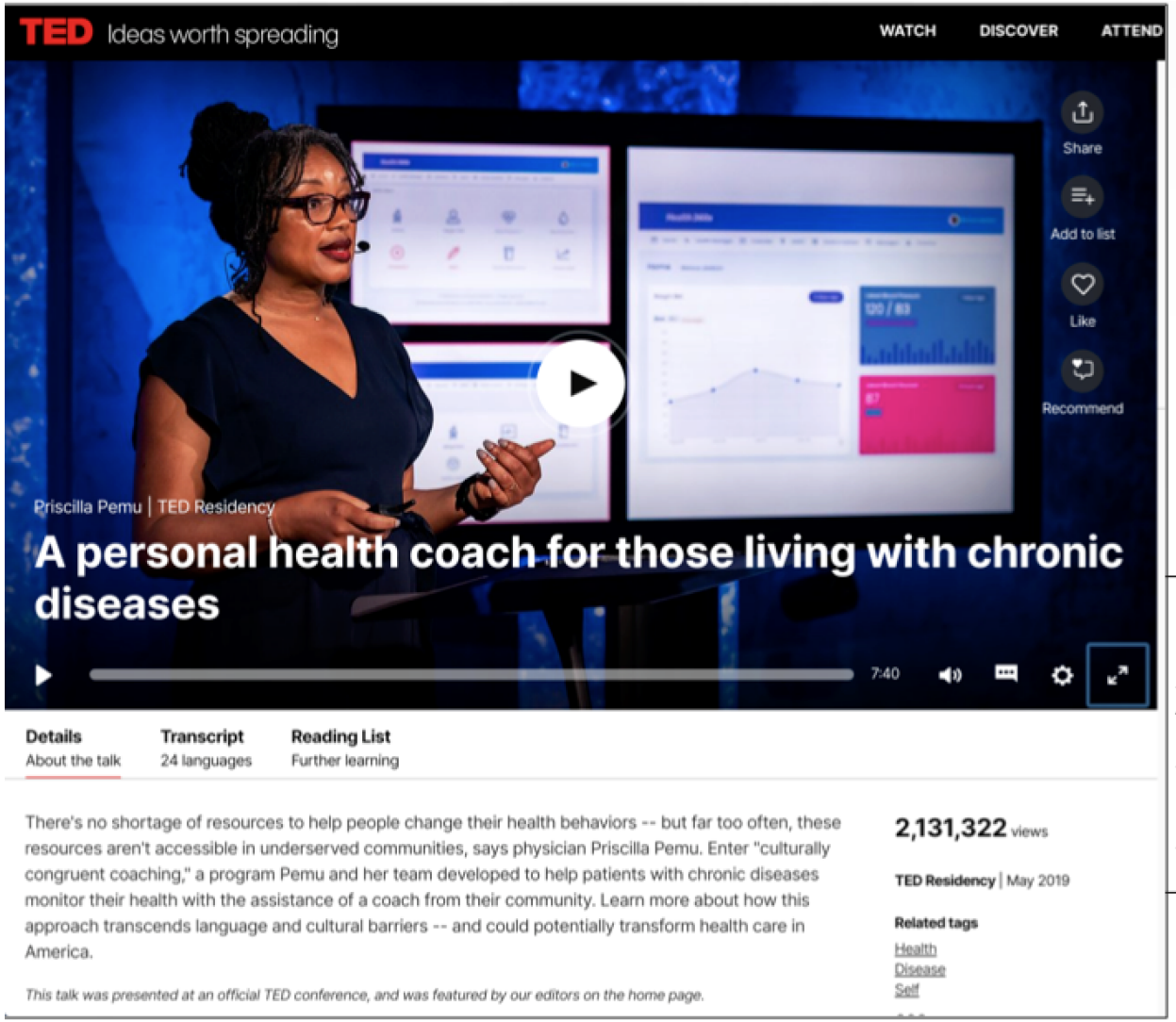
- Major factors (Red);
- Reasons for worse outcomes (Yellow)
- Future directions for improving disparities in ethnic minorities (Green)



Saeed A et al. https://www.acc.org/latest-in-cardiology/articles/2020/04/06/08/53/racial-disparities-in-hypertension-prevalence-and-management

MOREHOUSE SCHOOL OF MEDICINE

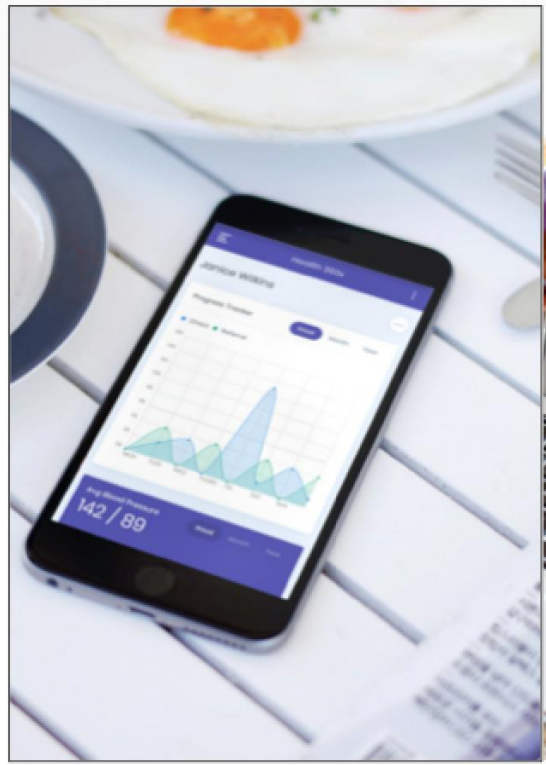
Health 360x™ Culturally Congruent Coaching on the TED Stage



- Health 360x™ is a patient engagement platform that integrates self monitoring and health coaching [1,2,3]
- A NCATS funded SBIR is implementing Health 360x™ in the practice workflow of community physicians serving predominant African American patients
- Novel EMR data integration and remote monitoring are key features

1. Ofili, E.O.; Pemu, P.E.; Quarshie, A.; Alema Mensah, E.; Rollins, L.; Ojutalayo, F.; McCaslin, A.; Saint Clair, B. Democratizing discovery health with me. Trans. Am. Clin. Climatol. Assoc. 2018, 129, 215–234. PMID: 30166716 .
2. Pemu P, Josiah Willock R, Alema Mensah E, Rollins R, Brown M, Saint Clair B, Olorundare E, McCaslin A, Akintobe T, Quarshie A, Ofili E. Achieving Health Equity with e-Healthystrides©: Patient Perspectives of a Consumer Health Information Technology Application. Ethnicity & Disease, Volume 29, Supplement 2, 2019:393-404
3. Pemu P. Health 360x Culturally Congruent Coaching to Manage your Health. TED TALK presented on TED Stage. 2020 and Editors Feature. Transcript in 24 languages and on multiple channels. TED Residency May 2019. Views: 2,131,322 and Counting..Accessed May 14, 2021

Health 360x™ Patient Engagement Platform



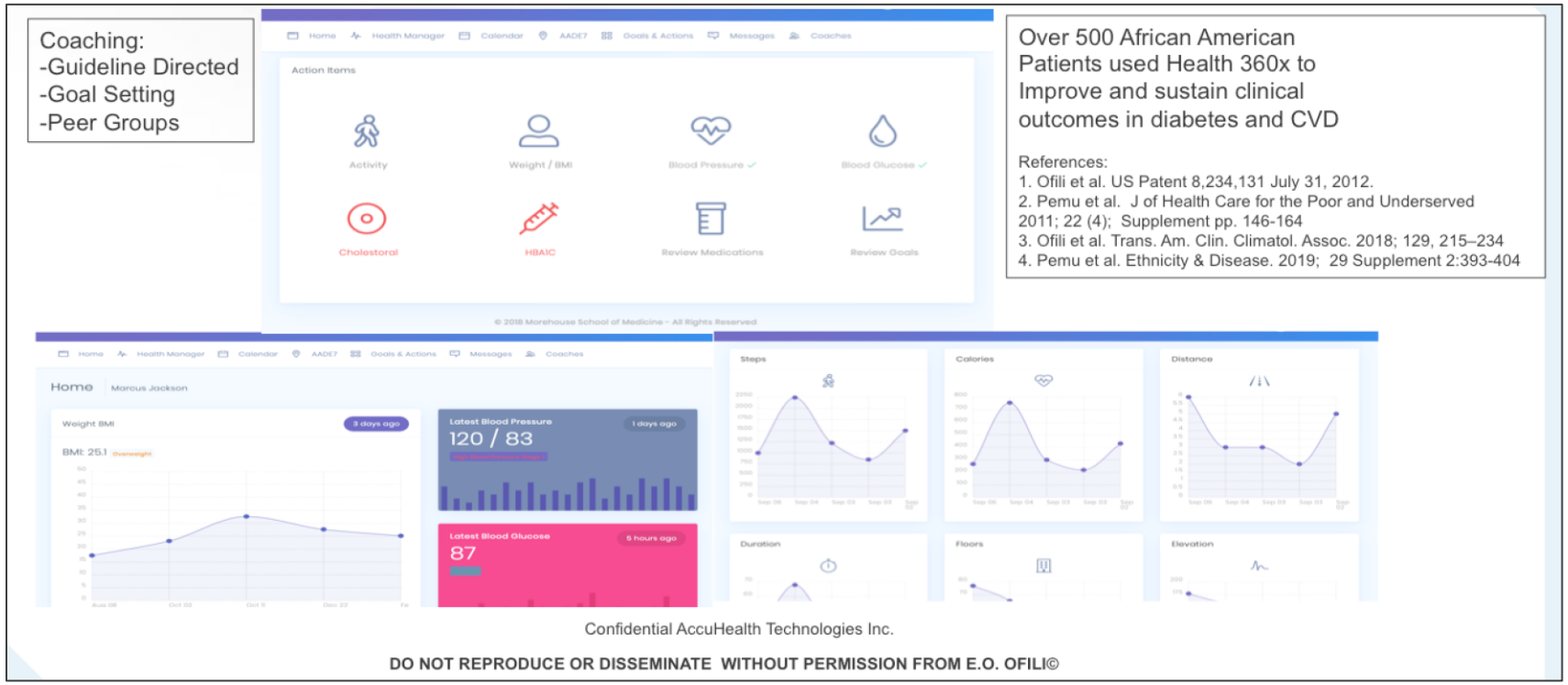
Mobile App

Web Platform

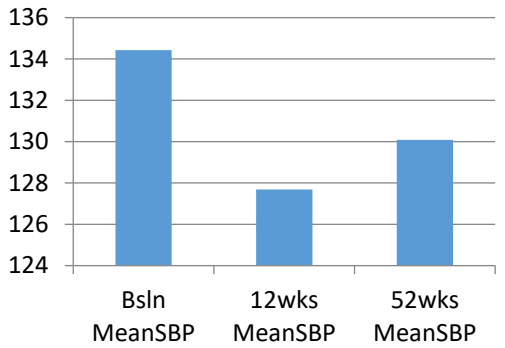
Coach Portal

Health360x.com

Health 360x™ Culturally Congruent Health Coaching: Patients Self Monitor Track and Securely Share Health Data with Trained Coaches



Change in Systolic BP Over Time



Health360x.com

Health 360x

NIH/NCATS Innovation Award to Implement Health Coaching in ABC CVIS Registry Vanguard Sites for Quality Improvement and Clinical Trials

PIs: P. Pemu and A. Quarshie

Dr. Barbara Hutchinson- MD
Dr. Marcus Williams-NJ
Dr. Phil Duncan-VA
Dr. Joe Hargrove-AR
Dr. Anthony Fletcher-AR
Dr. Andre Artis-IN
Dr. Felix Sogade- GA
Dr. Bola Sogade-GA
Dr. Adefisayo Oduwole-GA
Dr. Stephanie Kong (Peds)- GA
Dr. Osita Onyekwere-AL
Dr. Todd Seto-HI

International Journal of *Environmental Research and Public Health*

MDPI

Article

The Association of Black Cardiologists (ABC) Cardiovascular Implementation Study (CVIS): A Research Registry Integrating Social Determinants to Support Care for Underserved Patients

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Goals

- Integrate social determinants to optimize the care of cardiac patients
- Support clinical trial participation
- Culturally Congruent patient communication
- Innovation in data collection-FHIR Standards
- Testing and refining Algorithms for quality of care and patient centered outcomes

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#1 in Social Mission among US medical schools (Annals of Internal Medicine, June 2010)

MOREHOUSE SCHOOL OF MEDICINE

Agenda

Welcome
- Christine Lindenboom – Senior Vice President, Investor Relations & Corporate Communications

Introduction
- Pushkal Garg, M.D. – Chief Medical Officer

Hypertension Background
- Elizabeth Ofili, M.D., MPH, FACC; Professor of Medicine (Cardiology), Morehouse School of Medicine

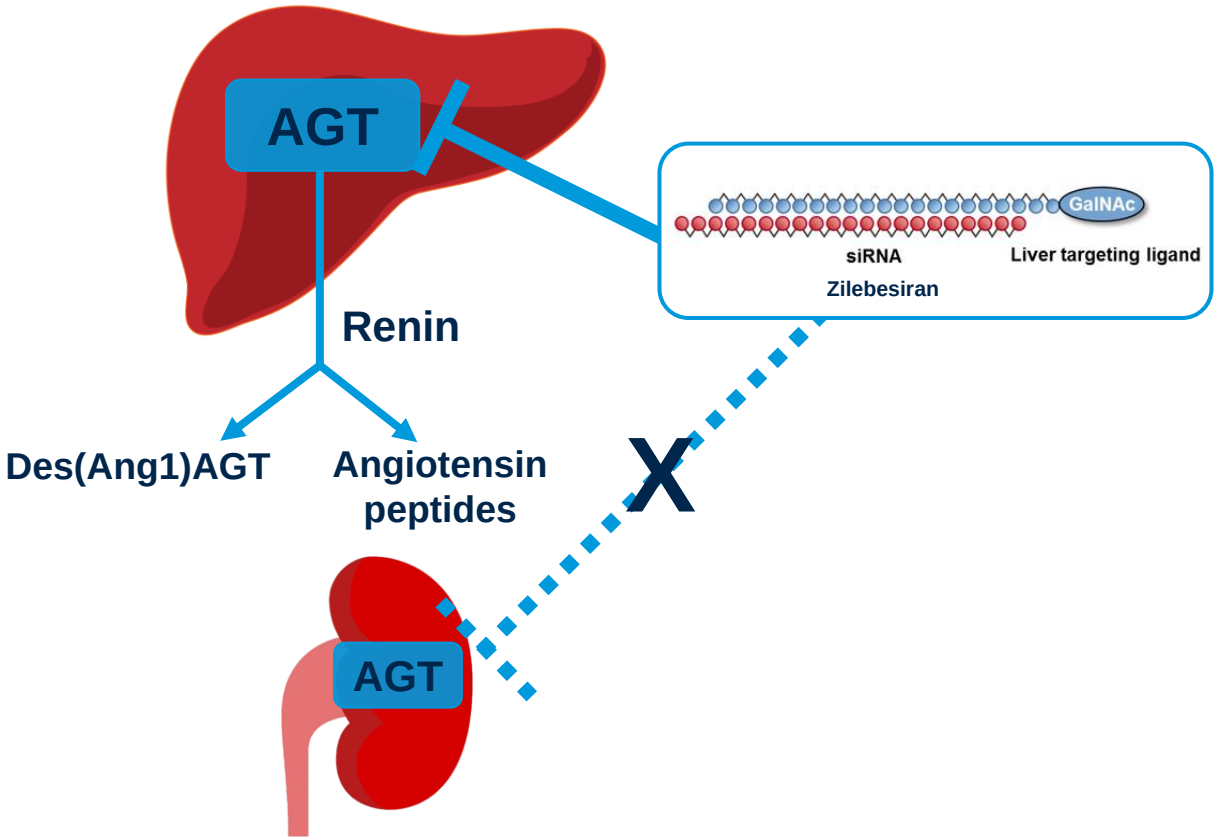
Zilebesiran Background and Development Program
- Stephen Huang, M.D. – Senior Director, Clinical Research

Commercial Outlook
- Eric Green – Senior Vice President, Development Programs

Q&A Session

Zilebesiran Therapeutic Hypothesis

Liver-specific AGT Knockdown



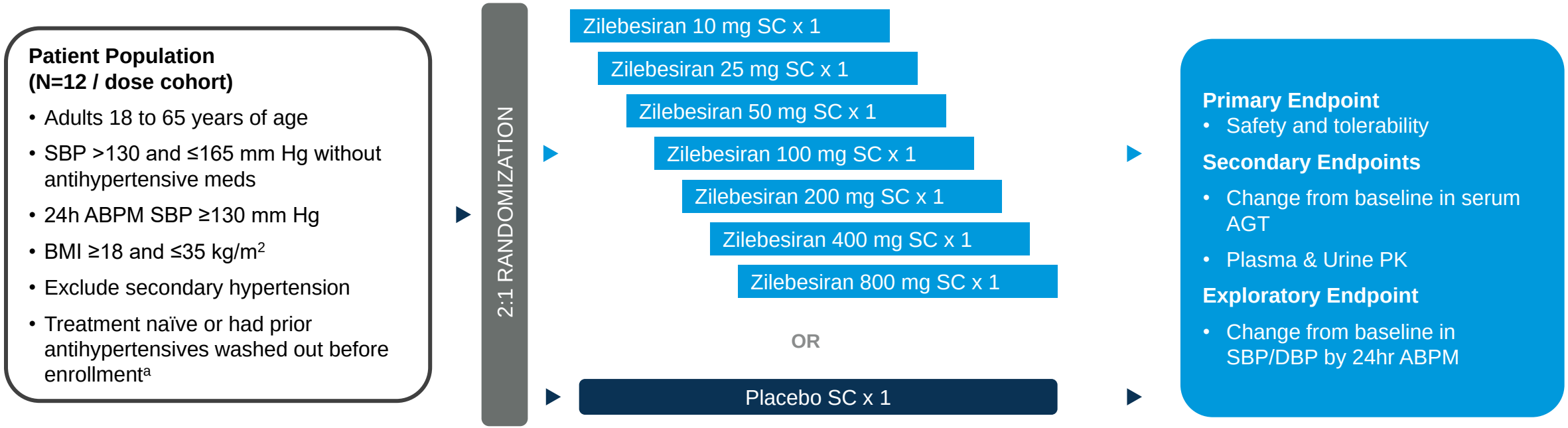
Potential Mechanistic Advantages

- **Liver-specific silencing of AGT**
- **Prolonged duration of action**
  - Consistent and durable BP response
  - Infrequent dose administration
  - Potential for improved adherence

AGT, angiotensinogen; BP, blood pressure; GalNAc, N-acetylgalactosamine; siRNA, small interfering ribonucleic acid

Zilebesiran First-in-Human Single Ascending Dose Study

- A total of 84 patients with hypertension completed treatment as of 25-February-2021
- Patients received either placebo (n=4 per cohort) or zilebesiran (n=8 per cohort)
- Study conducted in outpatient setting with usual activity and dietary sodium intake



[a] Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to screening

ClinicalTrials.gov Identifier: NCT03934307

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; DBP, diastolic blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous

Baseline Demographics and Characteristics

Diverse Study Population with Mild to Moderate Hypertension

Characteristic		Placebo (N=28)	Zilebesiran Dose Cohort						All Zilebesiran (N=56)
			10 mg (N=8)	25 mg (N=8)	50 mg (N=8)	100 mg (N=8)	200 mg (N=8)	400 mg (N=8)	800 mg (N=8)	
Age, years; median (range)		52 (36, 64)	53 (37, 60)	56 (47, 63)	41 (35, 64)	56 (35, 65)	56 (43, 64)	58 (44, 64)	61 (45, 62)	55 (35, 65)
Gender	**Male**	16	7	2	7	3	5	7	4	35
	Female	12	1	6	1	5	3	1	4	21
Race	**White**	21	6	4	3	4	6	6	6	35
	Black	6	1	4	4	2	2	1	2	16
	Asian	0	1	0	0	2	0	0	0	3
	Other	1	0	0	1	0	0	1	0	2
Blood Pressure	**24h ABPM SBP median (range)**	142 (126, 153)	139 (130, 147)	140 (132, 157)	135 (113, 144)	137 (131, 152)	139 (129, 154)	138 (132, 160)	142 (131, 167)	137 (113, 167)
	24h ABPM DBP median (range)	88 (72, 103)	84 (76, 93)	91 (75, 103)	83 (74, 91)	86 (80, 90)	83 (75, 95)	90 (76, 99)	88 (75, 102)	85 (74, 103)

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure

Primary Endpoint: Interim Phase 1 Safety & Tolerability

Zilebesiran Was Generally Well Tolerated, Supporting Continued Development

At Least One Event, n	Placebo (N=28)	Zilebesiran Dose Cohort							All Zilebesiran (N=56)
		10 mg (N=8)	25 mg (N=8)	50 mg (N=8)	100 mg (N=8)	200 mg (N=8)	400 mg (N=8)	800 mg (N=8)	
Adverse Event	24	5	7	6	7	7	4	6	42
Serious Adverse Event	1	0	0	0	0	1	0	0	1
Severe Adverse Event	2	0	0	0	0	1	0	0	1

- Most AEs mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal
- No treatment-related Serious AEs (SAEs)
  - Severe and serious AE of prostate cancer reported in 1 patient who received 200 mg zilebesiran, based upon biopsy performed in screening period and reported as positive after dosing
- No patient has required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium
- 5 patients with injection site reactions, all mild and transient

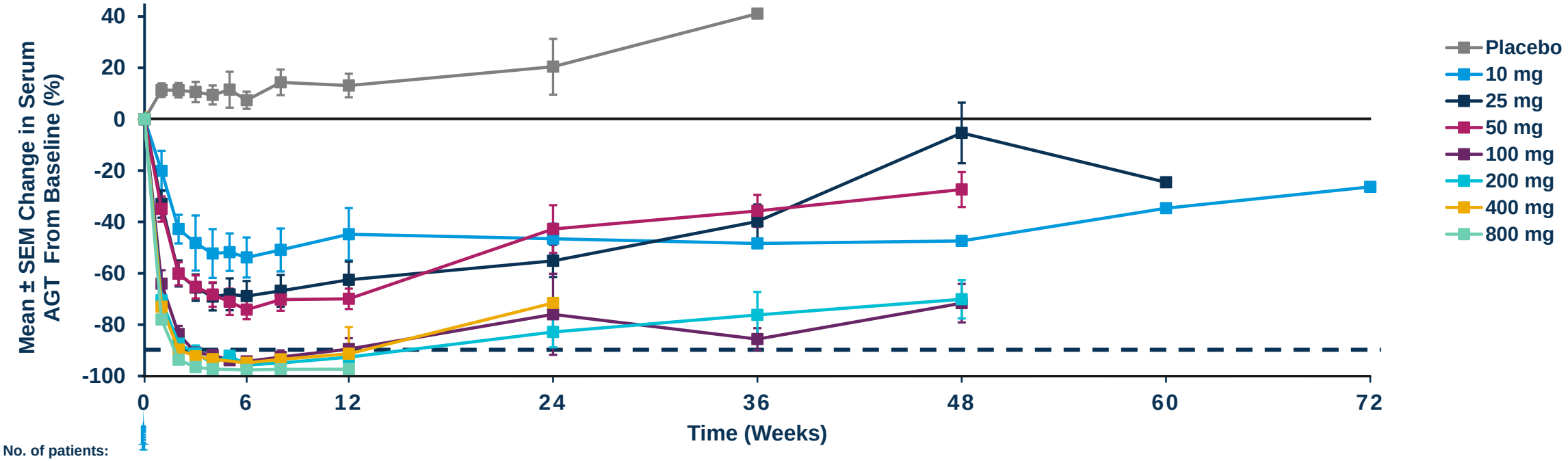
AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event

Data transfer date: 25 Feb 2021 (all patients completed 12 week treatment period before data transfer)

Secondary Endpoint: Dose-Dependent AGT Lowering

Phase 1 Interim Results Showed Reduction of Serum AGT >90% Sustained for 12 weeks After Single Doses of Zilebesiran ≥ 100 mg

- Serum AGT reduced 96 – 98% at Week 12 in all patients given single dose of 800 mg



No. of patients:													
Placebo	28	28	28	28	27	17	25	27	28	11	1	0	0
10 mg	8	8	8	8	8	8	8	8	8	5	2	1	1
25 mg	8	8	8	8	8	8	8	8	8	8	6	6	1
50 mg	8	8	8	8	8	8	8	7	7	7	4	2	0
100 mg	8	7	8	8	8	8	8	8	7	7	6	5	0
200 mg	8	8	8	7	6	2	3	7	8	8	4	5	0
400 mg	8	8	8	8	8	0	8	8	8	8	0	0	0
800 mg	8	8	8	7	8	0	8	8	8	0	0	0	0

AGT, angiotensinogen; SEM, standard error of the mean

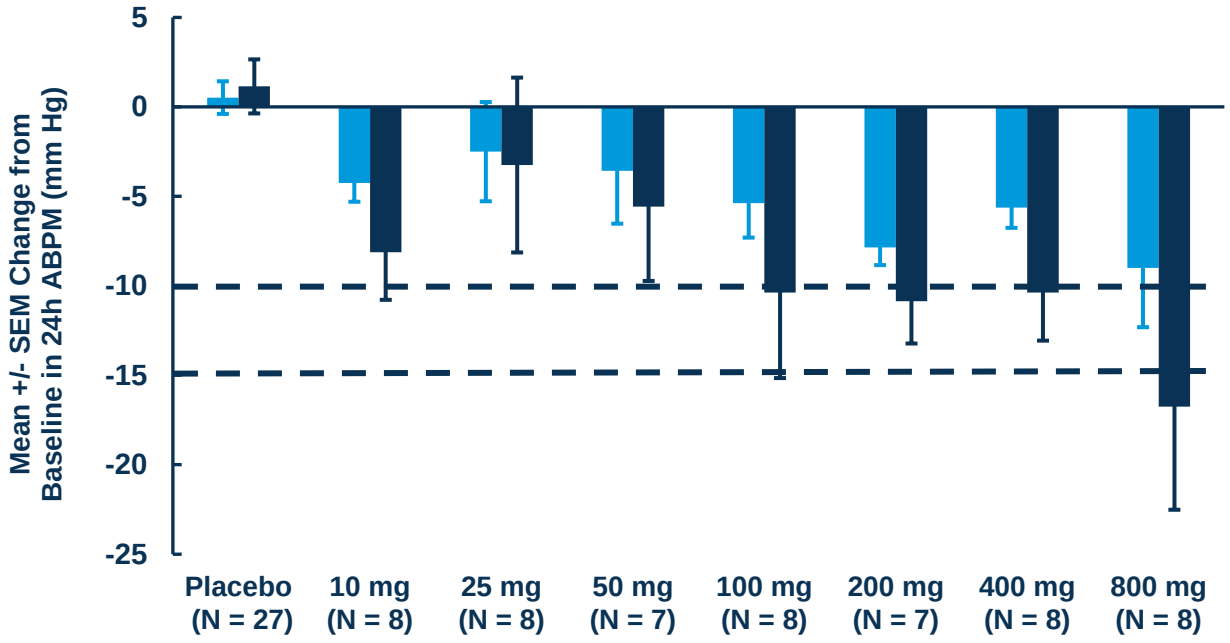
Exploratory Endpoint: Dose-Dependent Reductions in BP

24h SBP Reduction >10 mm Hg at 8 Weeks After Single Doses of Zilebesiran ≥100 mg

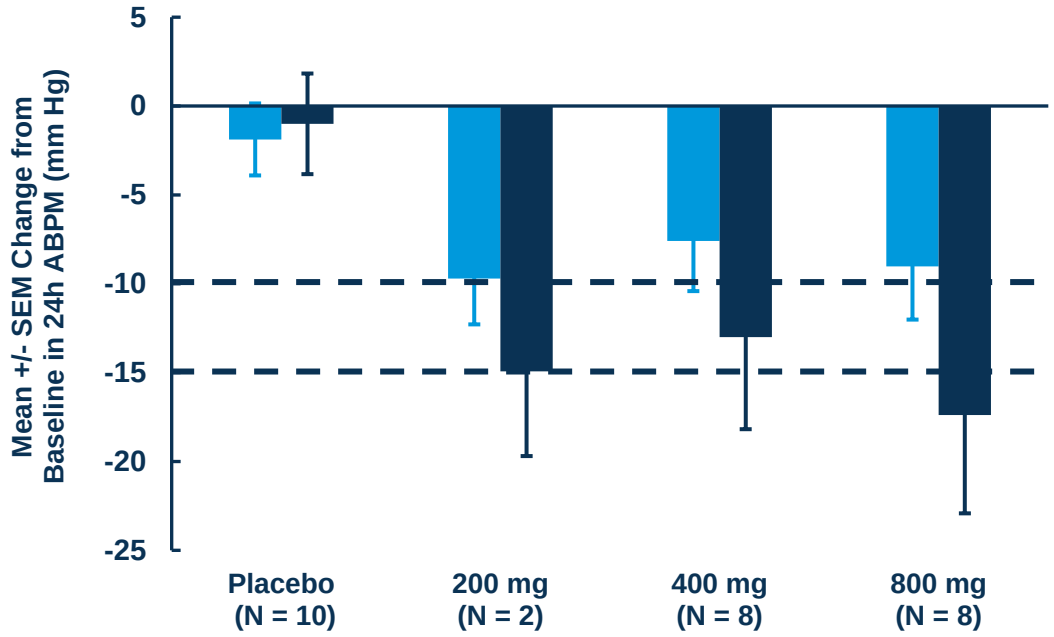
24h SBP Reduction >15 mm Hg at 8 Weeks After Single Doses of Zilebesiran 800 mg

- Mean 24h blood pressure reduction of 17 mm Hg / 9 mm Hg at Week 12 in patients given single dose of 800 mg

ABPM Change from Baseline at Week 8



ABPM Change from Baseline at Week 12*



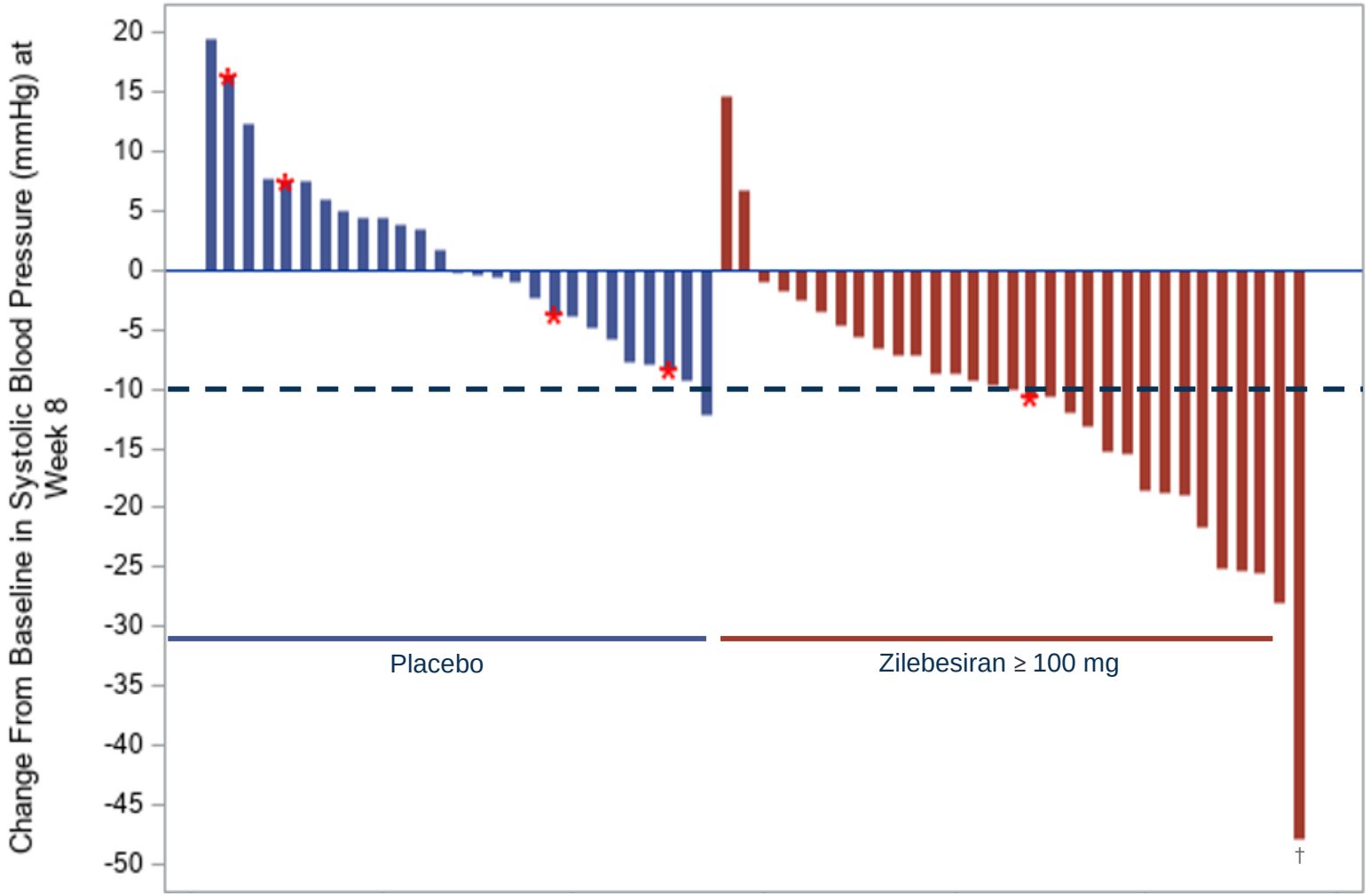
Diastolic Blood Pressure Systolic Blood Pressure

*Protocol amended to collect Week 12 ABPM data during dosing of the 200 mg cohort

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean

Exploratory Endpoint: Changes in 24-hour Ambulatory Systolic BP

Individual Patient Reductions in 24h Average SBP 8 Weeks After Single Doses of Zilebesiran



* Patient receiving oral antihypertensive medication; † Baseline BP of 167 mm HG in this patient

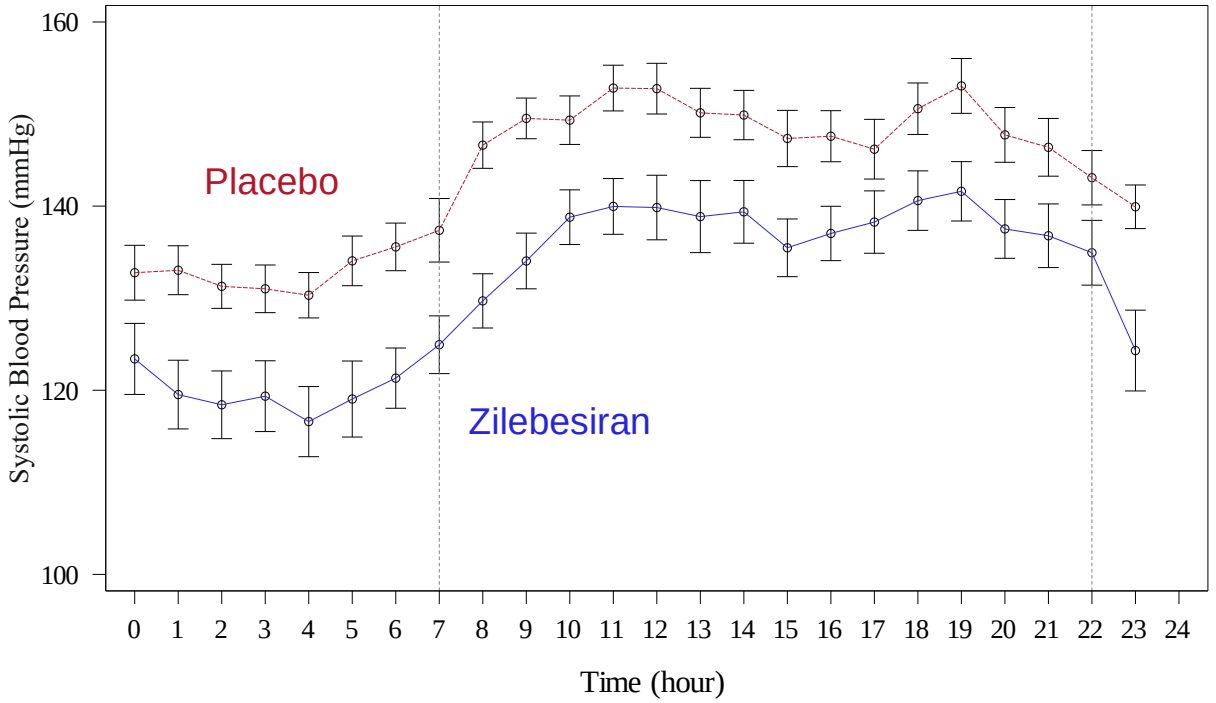
ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

Exploratory Endpoint: 24-Hour Blood Pressure Profile

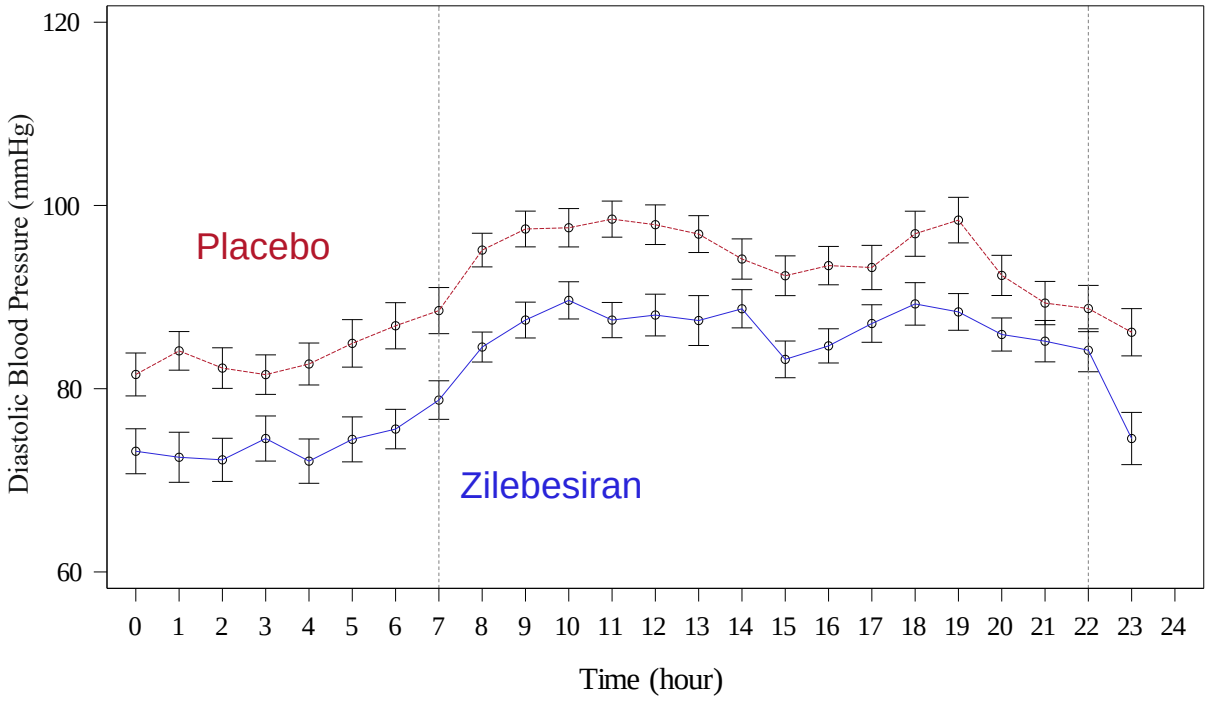
Tonic Control With Persistent BP Reduction at All Timepoints During the 24-Hour Period

Blood Pressure Profiles 6 Weeks After Single Dose of Zilebesiran (800mg) or Placebo

Systolic BP



Diastolic BP

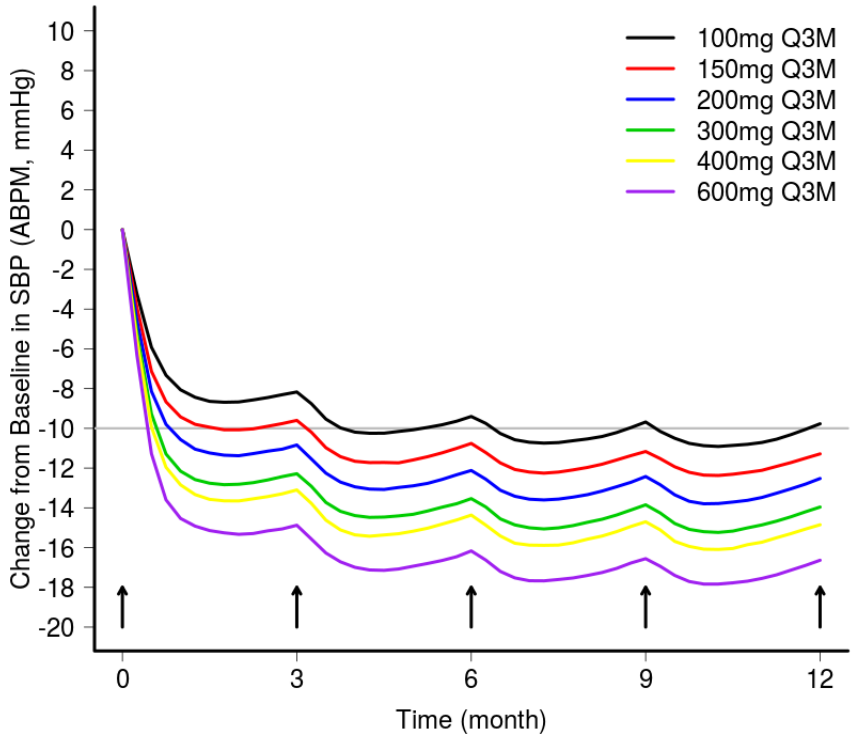


All Week 6 ABPM data as of 28-May-2021 pooled from patients treated with placebo (N = 28) vs. zilebesiran 800 mg (N = 32) in Phase 1

Predicted Change in 24-h ABPM with Different Dosing Regimens

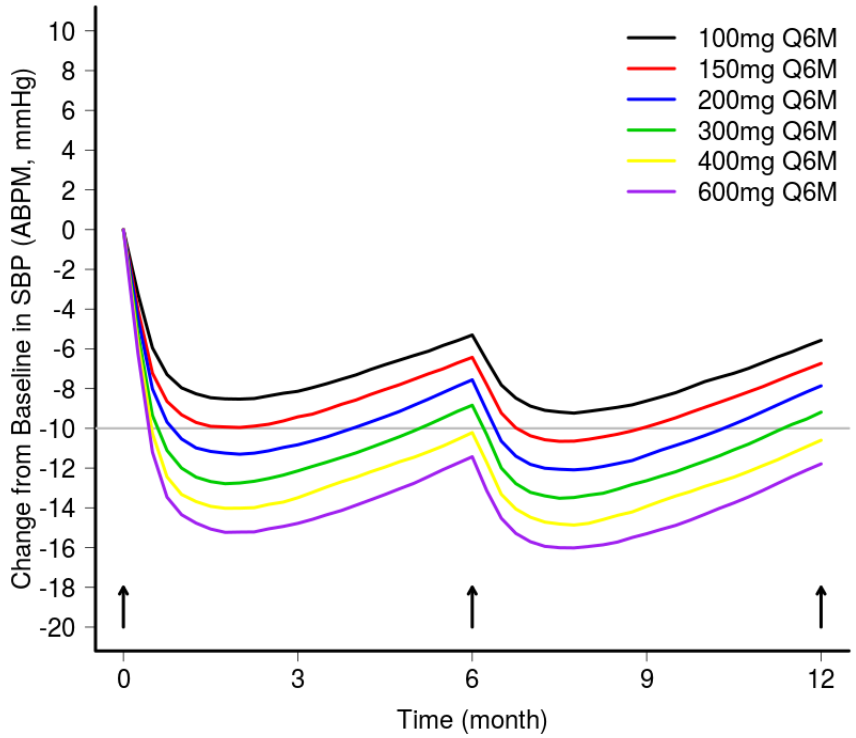
Modeling Based on SAD Data Suggests Potential for Quarterly or Biannual Dosing of Zilebesiran

Modeled Systolic BP



Quarterly Dosing (q3M)

Modeled Systolic BP



Biannual Dosing (q6M)

SAD: Single ascending dose

Ongoing Phase 1 Study Update

Additional Data Readouts Expected in Late 2021

- Dosing complete in single ascending dose cohort, with ongoing safety follow-up of individual patients during serum AGT recovery
- Dosing complete in salt depletion cohort designed to assess zilebesiran tolerability during extracellular fluid volume depletion
- Dosing complete in irbesartan-coadministration cohort designed to assess combinability with conventional RAAS blockade
- Multidose cohort in obese patients currently enrolling with goal of completion by year end

Phase 2 Clinical Development Plan

KARDIA$_1$

Monotherapy Phase 2 Study (N ~375)

- IND opened May 2021
- Evaluate efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension
- Exploring both quarterly and biannual dosing regimens
- Study initiated June 2021

KARDIA$_2$

Add-On Phase 2 Study (N ~800)

- Evaluate efficacy and safety of zilebesiran as add-on therapy in patients with hypertension despite treatment with a potent RAAS inhibitor, a calcium channel blocker, or a diuretic
- Targeting study initiation in late 2021

Zilebesiran KARDIA-1 Phase 2 Study

Randomized, Double-blind, Placebo-Controlled Study in Patients with Mild-to-Moderate Hypertension

N ~ 375
Patient Population

Key Inclusion Criteria:
- 18 - 75 years of age
- Daytime SBP ≥135 & ≤160 mm Hg
- Treatment naive or prior antihypertensives washed out before enrollment

Key Exclusion Criteria:
- Secondary HTN
- eGFR <30 ml/min/1.73m^2

ClinicalTrials.gov Identifier: NCT04936035

4-Week Washout

1:1:1:1:1 RANDOMIZATION

- **Zilebesiran** 150 mg SC q6M
- **Zilebesiran** 300 mg SC q6M
- **Zilebesiran** 300 mg SC q3M
- **Zilebesiran** 600 mg SC q6M
- **Placebo*** SC q3M

Primary Endpoint
- Change in SBP from baseline to Month 3 assessed by ABPM

Secondary Endpoints Include (through Month 6)
- Change in SBP and DBP by ABPM
- Time-adjusted change in SBP and DBP by office BP

Exploratory Endpoints Include (through Month 12)
- Change in 24h average, daytime average, and night-time average SBP and DBP
- Time-adjusted change in SBP and DBP assessed by office BP, home BP monitoring, and ABPM

Study Initiated
June 2021

* Placebo randomized across four zilebesiran treatment arms after 6 months on study

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; q3M: every 3 months (quarterly); q6M: every 6 months (semiannual); ABPM: ambulatory blood pressure measurement

Development Summary

- Single subcutaneous doses of zilebesiran were generally well tolerated in patients with mild to moderate hypertension in ongoing Phase 1 study, supporting continued development
- Zilebesiran led to dose-dependent and durable reduction of serum AGT
- Serum AGT reductions >90% sustained to 3 months after single doses of zilebesiran ≥100 mg
- Zilebesiran led to >10 mm Hg reduction in 24h SBP at 8 weeks after single doses of 100 mg or higher and >15 mm Hg reduction in 24h SBP after single doses of 800 mg
- Phase 1 data indicate potential for infrequent quarterly or biannual dosing; both regimens to be evaluated in Phase 2
- KARDIA-1 Phase 2 Monotherapy Trial initiated June 2021
- KARDIA-2 Phase 2 Add-on Trial targeting study initiation in late 2021

Agenda

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- Pushkal Garg, M.D. – Chief Medical Officer

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- Elizabeth Ofili, M.D., MPH, FACC; Professor of Medicine (Cardiology), Morehouse School of Medicine

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Commercial Outlook
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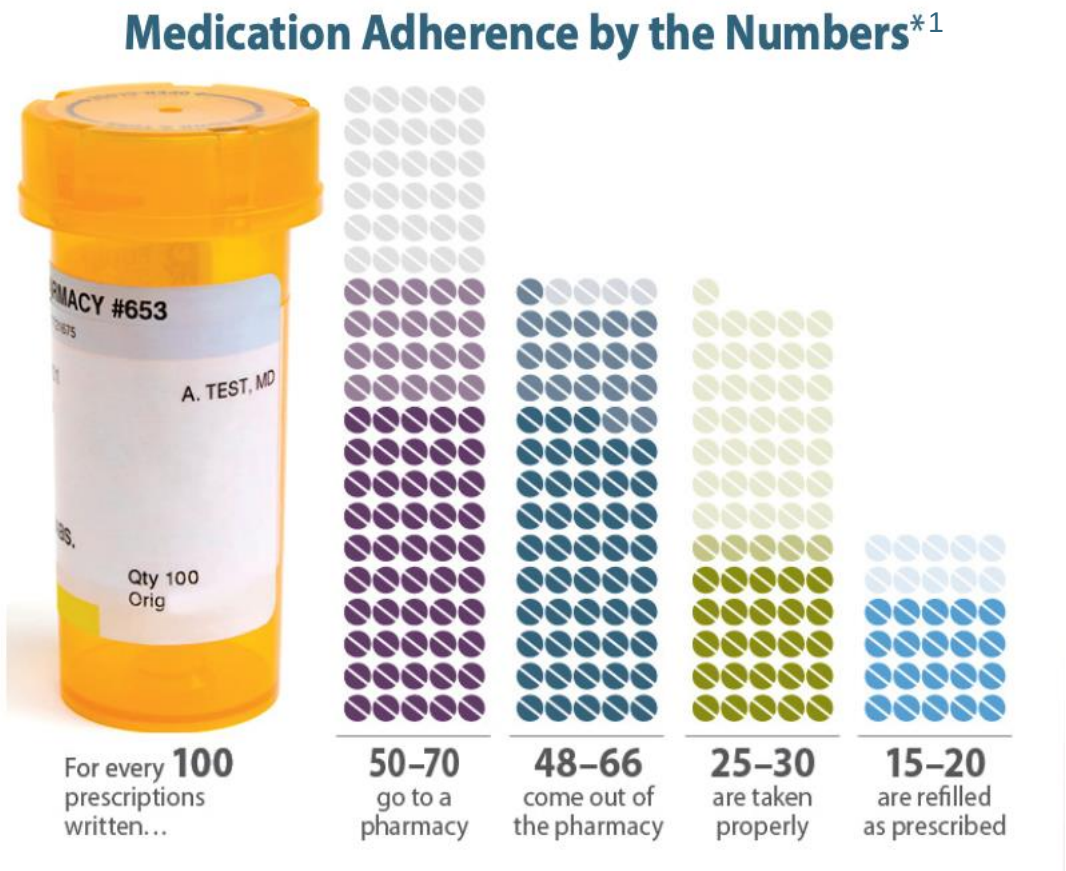
Q&A Session

Poor Medication Adherence adds to Cardiovascular Risk

Improving Medication Adherence, including Among Patients with Hypertension, is Significant Challenge



* These data apply to all medication types, not only hypertension medication

"*Drugs don't work in patients who don't take them.*"

- C. Everett Koop, MD, US Surgeon General, 1985

Potential Features of Zilebesiran

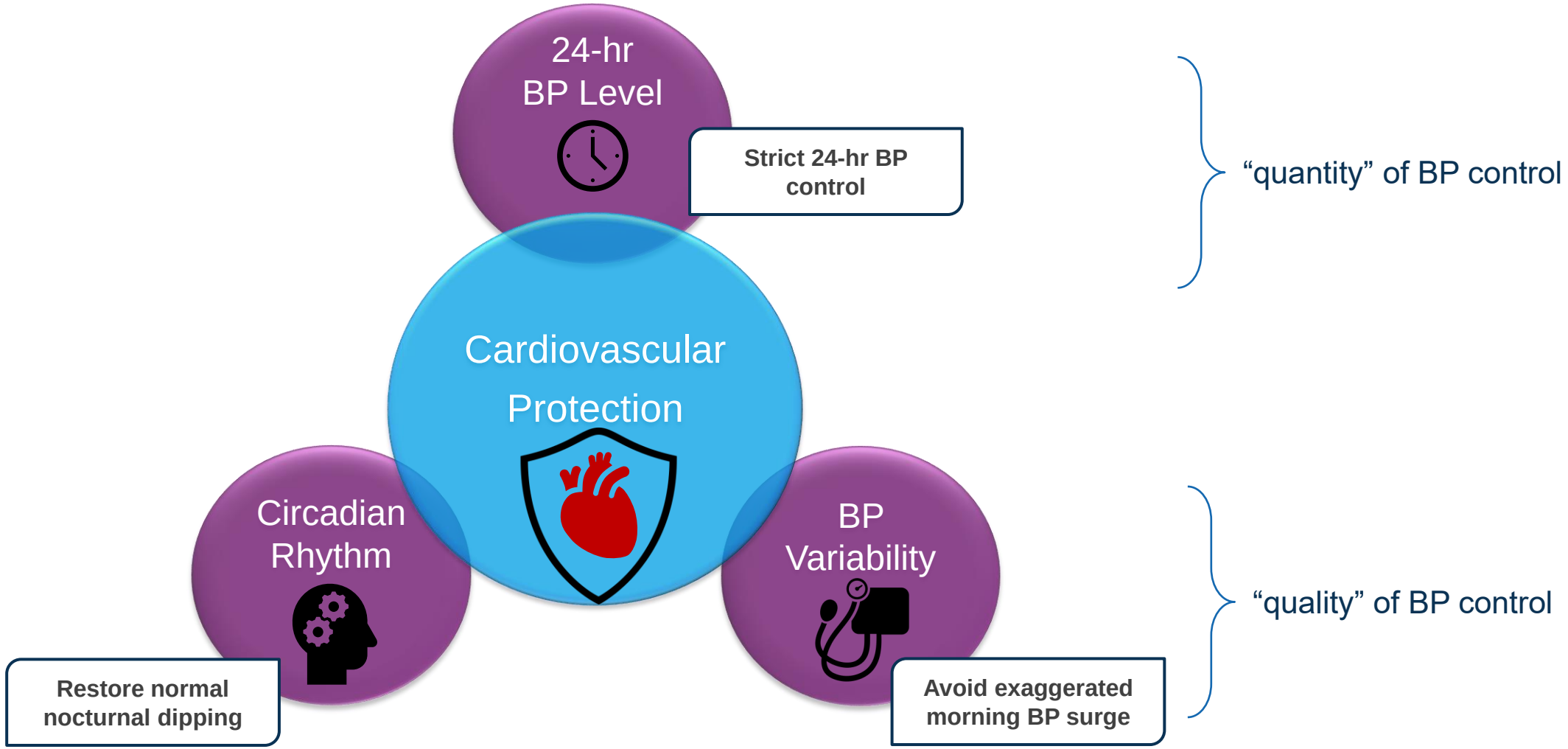
- Quarterly or biannual subcutaneous administration
- Reduced burden of daily oral hypertension medication between visits
- Consistent, durable blood pressure reduction during dosing interval

Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009;119:3028-3035.

[1] https://millionhearts.hhs.gov/data-reports/factsheets/adherence.html, accessed 24Jun2021

Targeting “24-hour Blood Pressure Control” with Goal of Minimizing CV Risk

Achieving Triad Could Reduce Risk of Organ Damage and Risk of CVD Events



Kario K. *Evidence and Perspectives on the 24-hour Management of Hypertension: Hemodynamic Biomarker-Initiated 'Anticipation Medicine' for Zero Cardiovascular Event*. Prog Cardiovasc Dis. 2016 Nov-Dec;59(3):262-281.

CV: cardiovascular; CVD: cardiovascular disease; BP: blood pressure

Zilebesiran Commercial Opportunity^: High Risk for Cardiovascular Events

Patients with Uncontrolled Blood Pressure at High Risk for Adverse CV Events

PREVALENCE

- ~38M patients in U.S. with high CV risk and HTN; **~20M have uncontrolled BP** on current regimen[1]
- High CV risk defined ≥20% 10-year **ASCVD risk or previous history** of myocardial infarction, angina, stroke, transient ischemic attack, heart failure, peripheral arterial disease, or type 2 diabetes

CURRENT TREATMENT LANDSCAPE

- **Guidelines specify treatment of HTN based on clinical severity and/or comorbidities**
- Patients initiated on mono or combo therapy; increased doses or additional agents added if BP not controlled
- **Uncontrolled HTN often due to non-adherence** of prescribed therapy given daily pill burden[2]

DISEASE BURDEN

- Uncontrolled hypertension is **major risk factor for CV disease** morbidity and mortality[3]
- ~1.5M people in U.S. have myocardial infarction or stroke annually, with ~50% of these major adverse cardiovascular events attributed to HTN[4,5]

COST BURDEN

- Annual direct and indirect cost of hypertensive disease and stroke in U.S.[6]: $55B and $45B*
- **Suboptimal BP control cost $370B globally in 2001** (~10% of world's overall healthcare expenditure at that time[7])

Treatment of Uncontrolled Blood Pressure in Patients with High CV Risk

>$4B potential global market opportunity at peak†

[1] Estimated based on historical rates of CV events: myocardial infarction, angina, stroke, transient ischemic attack, heart failure, peripheral arterial disease, type 2 diabetes. Sources: Virani et al, Circulation. 2020;141:e139–e596. Mainous et al, Am J Prev Med 2018;55(3):384–388. Sonawane et al, J Clin Hypertens. 2019;21:766–773. Gu et al, Circulation. 2012;126:2105-2114. Gu et al, Clin Med Insights Cardiol. 2019;13:1–9. Dorans. JAHA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019 National Diabetes Statistics report 2020. 2018 USRDS Annual Data Report. US Census Bureau. TriNetX USA Network, accessed May 2020. Estimate of ~50% of patients diagnosed with HTN and high CV risk are uncontrolled

[2] Burnier. Circulation Research. Adherence in Hypertension, Volume: 124, Issue: 7, Pages: 1124-1140; [3] Zhou. Sci Rep. 2018; [4] Lawes. Lancet. 2001. [5] Korsnes. JMCP. 2015; [6] Benjamin. Circulation. 2019; [7] Gaziano. J Hypertens. 2009

^ Subject to successful clinical development and regulatory approvals * Not all stroke costs are associated with hypertension; additional cost related to heart disease and hypertension are observed; † Market opportunities not additive.

ASCVD: Atherosclerotic Cardiovascular Disease, CV: cardiovascular; BP: blood pressure; HTN: hypertension

Zilebesiran Commercial Opportunity^: Primary Hypertension

Potential Foundational Antihypertensive Requiring Infrequent Dosing

PREVALENCE

- ~108M patients in U.S. have HTN
- Despite availability of multiple classes of antihypertensive medications, **~75% of hypertensive patients do not achieve controlled blood pressure**[1]

CURRENT TREATMENT LANDSCAPE

- Guidelines specify treatment of HTN based on clinical severity and/or comorbidities
- Patients initiated on mono or combo therapy; increased doses or additional agents added if BP not controlled
- **Uncontrolled HTN often due to non-adherence** of prescribed therapy given daily pill burden[2]

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Treatment of Uncontrolled Blood Pressure in Patients with Primary Hypertension

>$4B potential global market opportunity at peak†

[1] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016. Atlanta, GA: US Department of Health and Human Services; 2019.

[2] Burnier. Circulation Research. Adherence in Hypertension, Volume: 124, Issue: 7, Pages: 1124-1140; [3] Zhou. Sci Rep. 2018; [4] Lawes. Lancet. 2001. [5] Korsnes. JMCP. 2015; [6] Benjamin. Circulation. 2019; [7] Gaziano. J Hypertens. 2009

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Summary and Next Steps in Development of Zilebesiran

Significant unmet need for treatment of hypertension in patients with uncontrolled blood pressure could potentially be addressed by zilebesiran

- Sustained blood pressure control with infrequent dosing could benefit patients with difficult to treat hypertension or patients with uncontrolled blood pressure at risk for CV events
- Potential to become new antihypertensive treatment for patients with primary hypertension

Initial data from ongoing Phase 1 study in patients with mild-to-moderate hypertension supports continued development

- Interim results include encouraging safety and tolerability profile
- >10 mmHg persistent reduction in mean 24-h systolic blood pressure at Week 12 at single doses ≥100mg
- Durability supportive of once quarterly and possibly biannual dosing
- Additional Phase 1 clinical data expected in late 2021

Initiation of KARDIA Phase 2 Program

- KARDIA-1 study of zilebesiran as monotherapy is open and screening patients
- KARDIA-2 study of zilebesiran in combination with standard antihypertensive agents is expected to initiate in late 2021

Agenda

Welcome
- Christine Lindenboom – Senior Vice President, Investor Relations & Corporate Communications

Introduction
- Pushkal Garg, M.D. – Chief Medical Officer

Hypertension Background
- Elizabeth Ofili, M.D., MPH, FACC; Professor of Medicine (Cardiology), Morehouse School of Medicine

Zilebesiran Background and Development Program
- Stephen Huang, M.D. – Senior Director, Clinical Research

Commercial Outlook
- Eric Green – Senior Vice President, Development Programs

Q&A Session

Upcoming RNAi Roundtables

- **Patisiran and Vutrisiran, in Development for the Treatment of ATTR Amyloidosis**
  Friday, July 16, 11:00 am ET

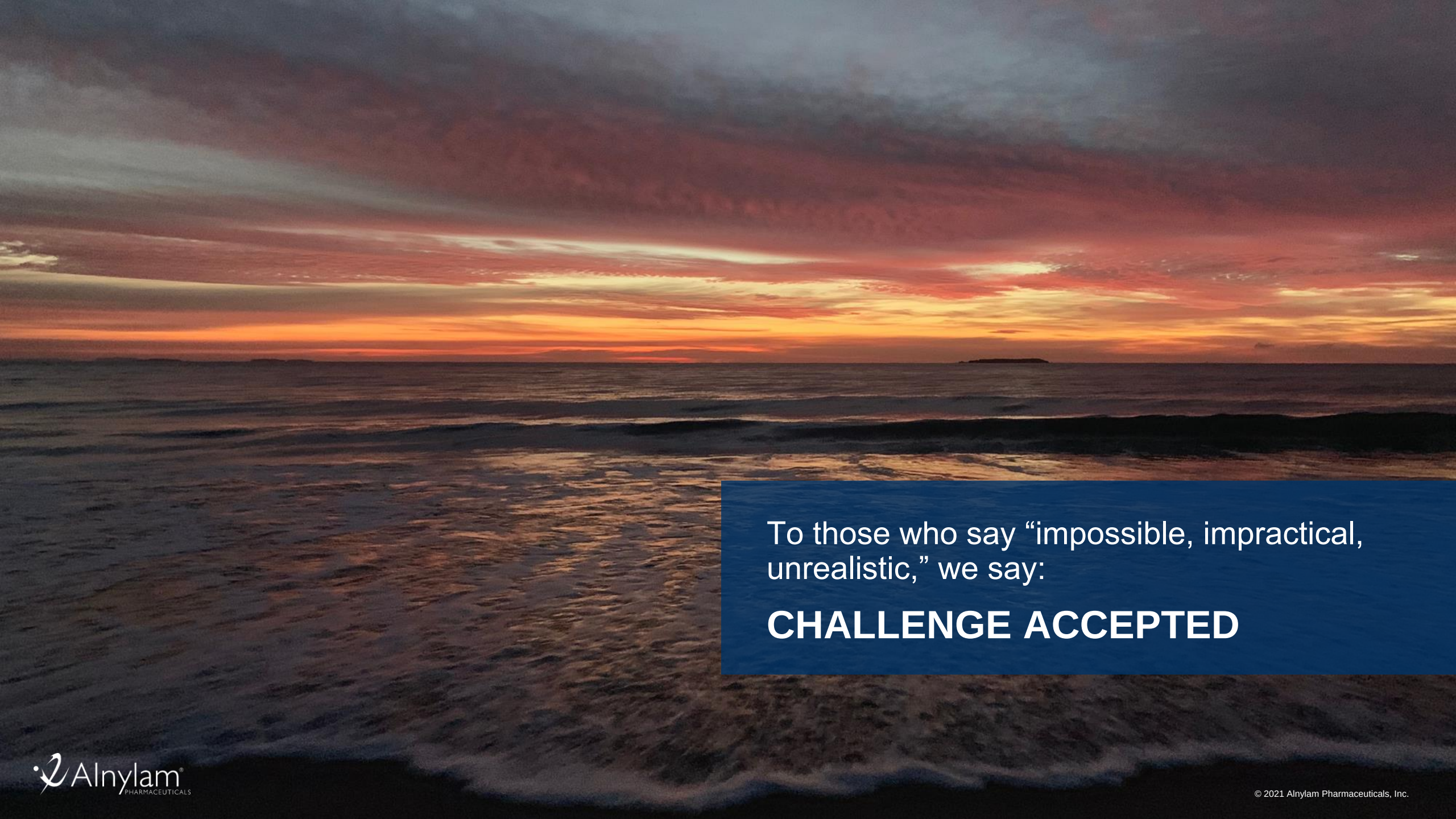
- **Givosiran, for the Treatment of Acute Hepatic Porphyria**
  Wednesday, August 4, 1:30 pm ET

- **Lumasiran, for the Treatment of Primary Hyperoxaluria Type 1**
  Thursday, August 19, 9:30 am ET (tentative)

- **Liver-Directed RNAi Pipeline Programs**
  Monday, September 20, 11:00 am ET

- **CNS & Extrahepatic RNAi Pipeline Programs**
  Friday, October 1, 1:30 pm ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella



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