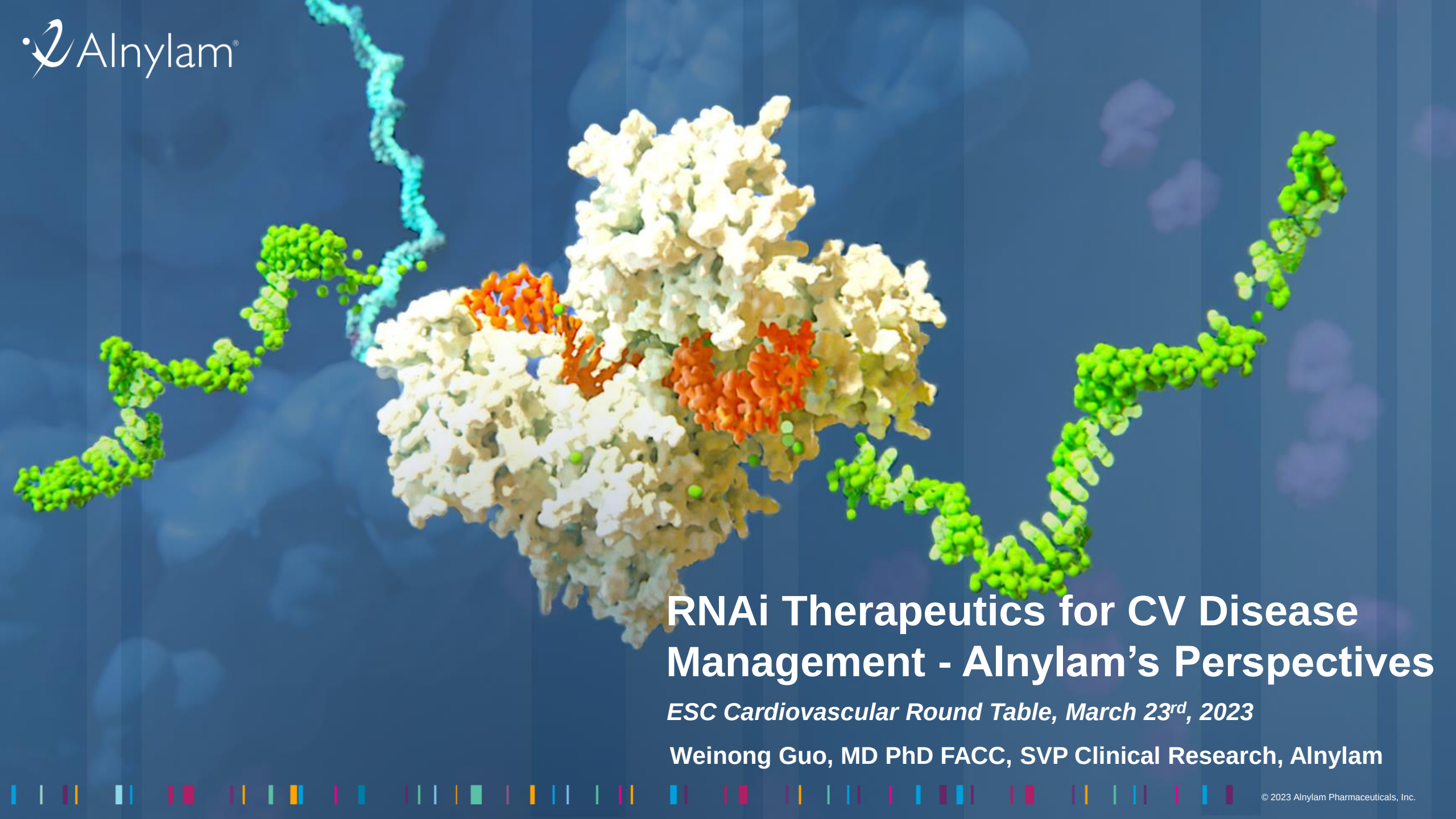
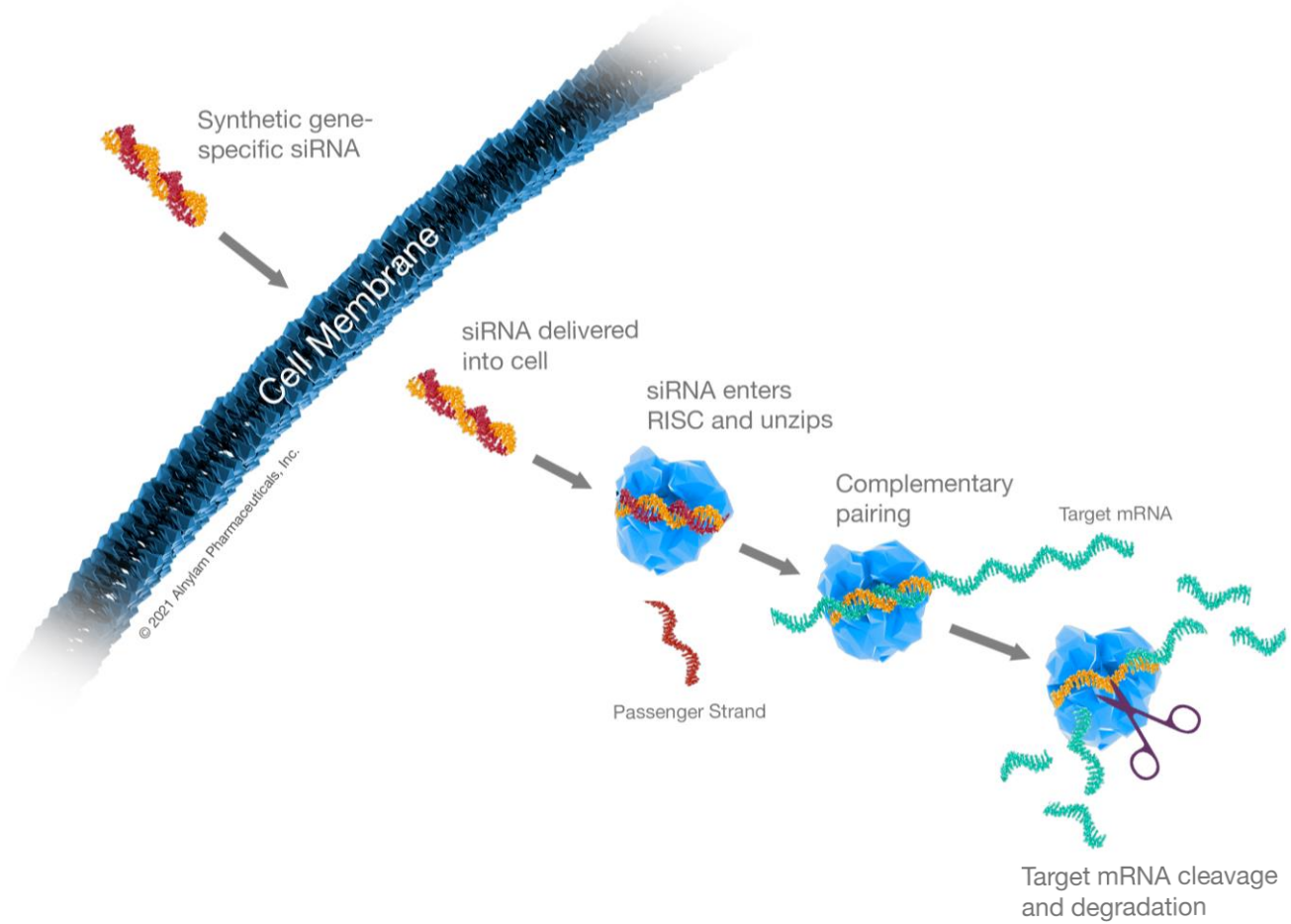


RNAi Therapeutics for CV Disease Management - Alnylam's Perspectives

ESC Cardiovascular Round Table, March 23rd, 2023

Weinong Guo, MD PhD FACC, SVP Clinical Research, Alnylam

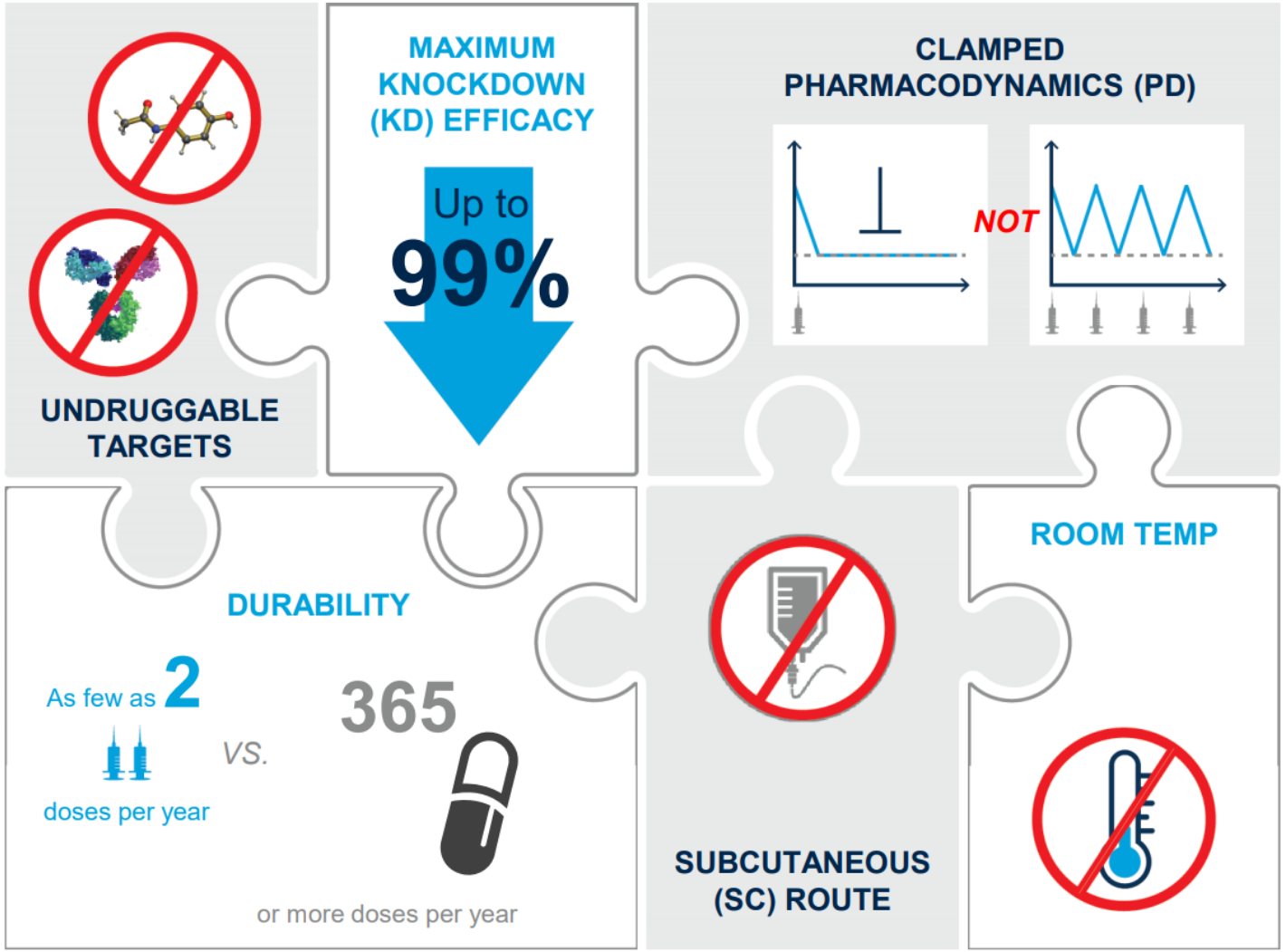
Alnylam Poised to Harness the Power of RNAi Technology



- 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®

Key Features of Alnylam RNAi Therapeutics



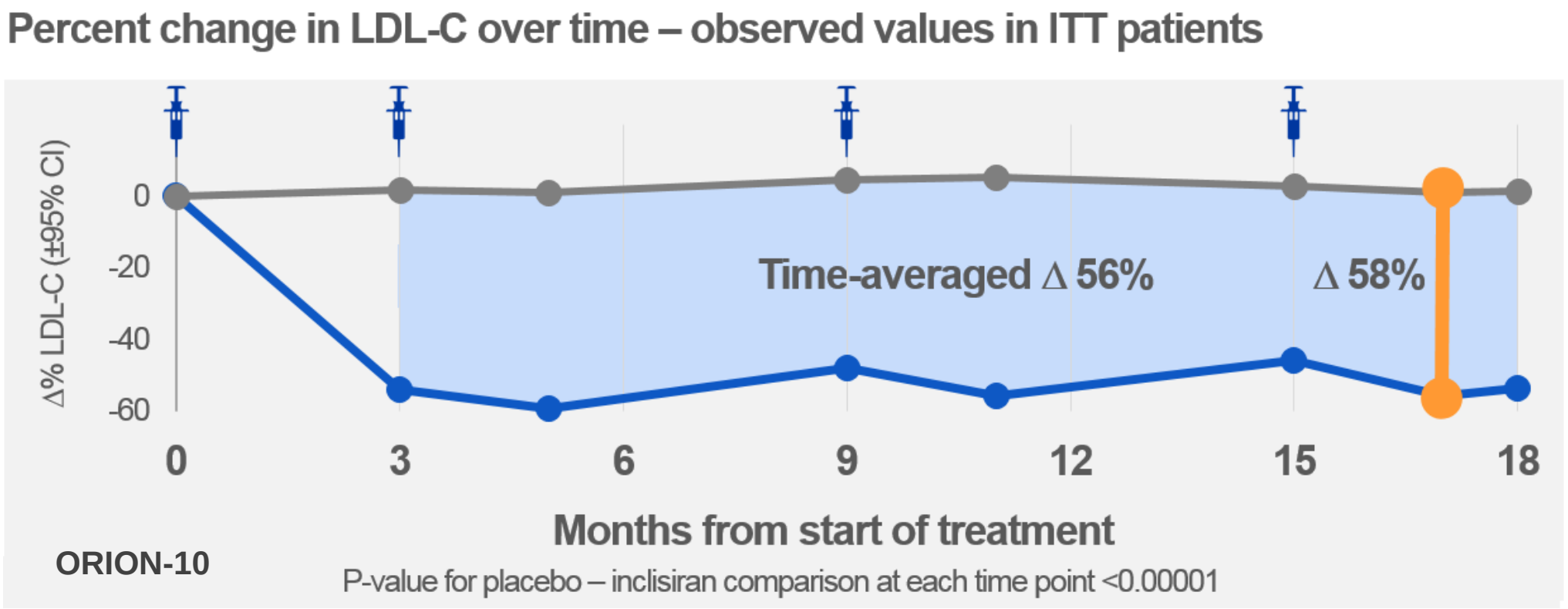
Alnylam RNAi Platform

- Infrequent, subcutaneous administration creates dosing flexibility for patients and eases treatment burden
  - Potential for quarterly and biannual dosing
  - Potential for improved adherence
- Wide therapeutic index with potential for transformative outcomes
- Extensive human safety experience across multiple indications, including large market indications such as hypercholesterolemia

Alnylam®

Inclisiran ORION-10+11 Results

Durable, Potent, and Consistent LDL-C Lowering Over 18 Months



- Inclisiran safety profile similar to placebo, with no adverse changes in laboratory markers
- Injection site events 2.6-4.7% - predominantly mild and none persistent
- ORION-10+11: Numerically fewer CV events reported for inclisiran than placebo (exploratory endpoint)

Wright et al., AHA 2019; Ray et al., ESC Congress 2019
All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

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]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis with PN*			●	Global
amvuttra (vutrisiran)	*hATTR Amyloidosis with PN*			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*			●	Global
LEQVIO (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[2]
Patisiran**	*ATTR Amyloidosis with CM*			●	Global
Vutrisiran	*ATTR Amyloidosis with CM*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Cemdisiran (+/- Pozelimab)[3]*	*Complement-Mediated Diseases*		●		Global; Milestone/Royalty
ALN-TTRsc04*	*ATTR Amyloidosis*	●			Global
Belcesiran[4]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[5]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran*	*Hypertension*	●			Global
ALN-HSD[6]*	*NASH*	●			Royalty
ALN-APP*	*Alzheimer's Disease; Cerebral Amyloid Angiopathy*	●			50-50
ALN-PNP*	*NASH*	●			50-50
ALN-KHK*	*Type 2 Diabetes*	●			Global

[1] Includes marketing application submissions; [2] 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; [3] Alnylam and Regeneron are evaluating potential combinations of the investigational therapeutics cemdisiran and pozelimab; [4] Dicerna is leading and funding development of belcesiran; [5] Vir is leading and funding development of ALN-HBV02; [6] Regeneron is leading and funding development of ALN-HSD; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established; ** U.S. sNDA has been filed. **As of January 2023**

Alnylam®

ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

Description

Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract[1]

Hereditary ATTR (hATTR) Amyloidosis

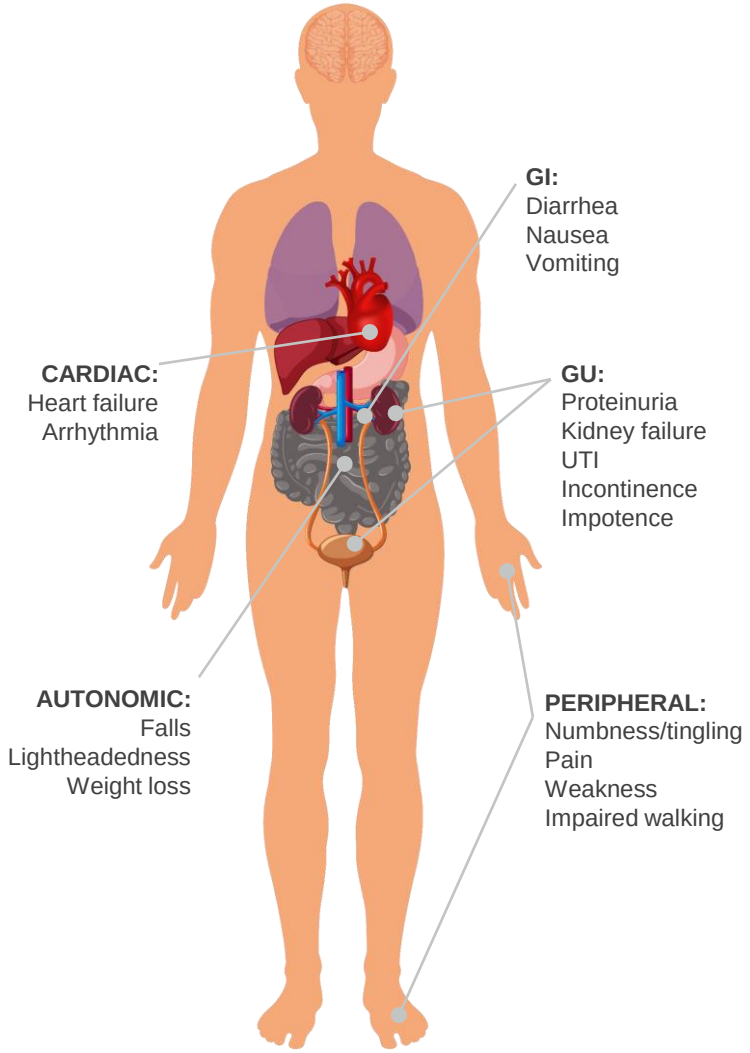
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide

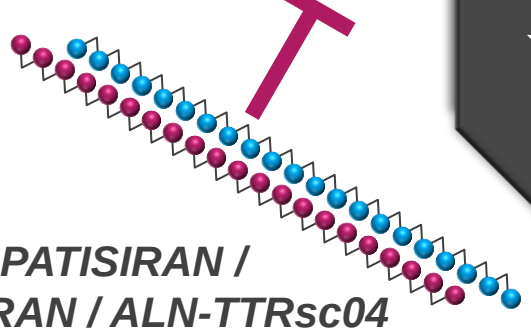


1 Coelho T, et al. N Engl J Med. 2013;369(9):819-829

* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012

RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression Can Potentially Address Underlying Cause of Disease



PATISIRAN / VUTRISIRAN / ALN-TTRsc04

siRNA sequences selected to silence both variant and wild-type TTR

Production of variant and wild-type TTR in liver*

Reduce circulating TTR

Prevent or clear tissue amyloid deposits

Halt or improve progressive manifestations of disease

* >95% of TTR in circulation produced in liver

Alnylam TTR Franchise

Approved Treatment Options and Investigational Clinical Programs

onpattro (patisiran) lipid complex injection 10 mg/5 mL

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis*

About ONPATTRO

- Based on APOLLO data, commercially available in >30 countries for hATTR amyloidosis with polyneuropathy
- Positive results from APOLLO-B‡
- IV administration, 1x every 3 weeks

amvuttra (vutrisiran) injection 25 mg/0.5 mL™

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis†

About AMVUTTRA

- Based on HELIOS-A data, approved in US, EU, UK, JP, and BR
- HELIOS-B ongoing in ATTR amyloidosis with CM††
- Subcutaneous administration, once quarterly, potential for biannual dosing

ALN-TTRsc04

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

About ALN-TTRsc04

- Phase 1 CTA submitted
- Potential for annual dosing and >90% serum TTR reduction
- No third-party royalties; exclusivity expected beyond 2040

* ONPATTRO is approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; see Full Prescribing Information; † AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults, in the EU for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy; in Japan for transthyretin (TTR) type familial amyloidosis with polyneuropathy and in Brazil for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults see Full Prescribing Information; ‡ 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; †† Vutrisiran 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

TTR Franchise Phase 3 Program

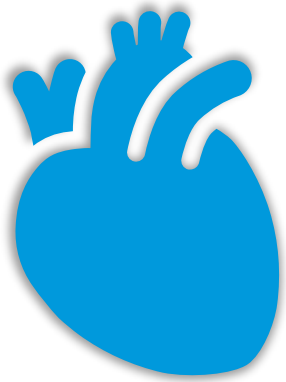
Randomized, Double-Blind, Placebo-Controlled Studies in ATTR Amyloidosis Patients with Cardiomyopathy

APOLLO-B

patisiran

N = 360
hereditary & wild-type
6-minute walk test
12 months

Results presented at
ISA and HFSA – September 2022



HELIOS-B

vutrisiran

N = 655
hereditary & wild-type
mortality & cardiovascular events
30 months

Enrollment **complete**

Topline results on 30-month endpoint expected **early 2024**

Patisiran APOLLO-B Phase 3 Study

Randomized, Double-Blind, Placebo-Controlled Study in ATTR Amyloidosis Patients with Cardiomyopathy

N = 360
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - With or without background TTR stabilizer
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Patisiran
IV q3w†
0.3 mg/kg

or

Placebo
IV q3w†

Primary Endpoint

- Change in 6-MWT at 12 months

Secondary Endpoints

- Cardiomyopathy symptoms and health status (KCCQ)
- Death and hospitalization outcomes*

Selected Exploratory Endpoints

- Cardiac biomarkers

Open-Label Extension

ClinicalTrials.gov Identifier: NCT03997383

APOLLO-B

Results presented at ISA and HFSA – Sep ‘22

sNDA submitted 8 Dec 2022

Concomitant use of local standard of care allowed during study, including TTR stabilizer

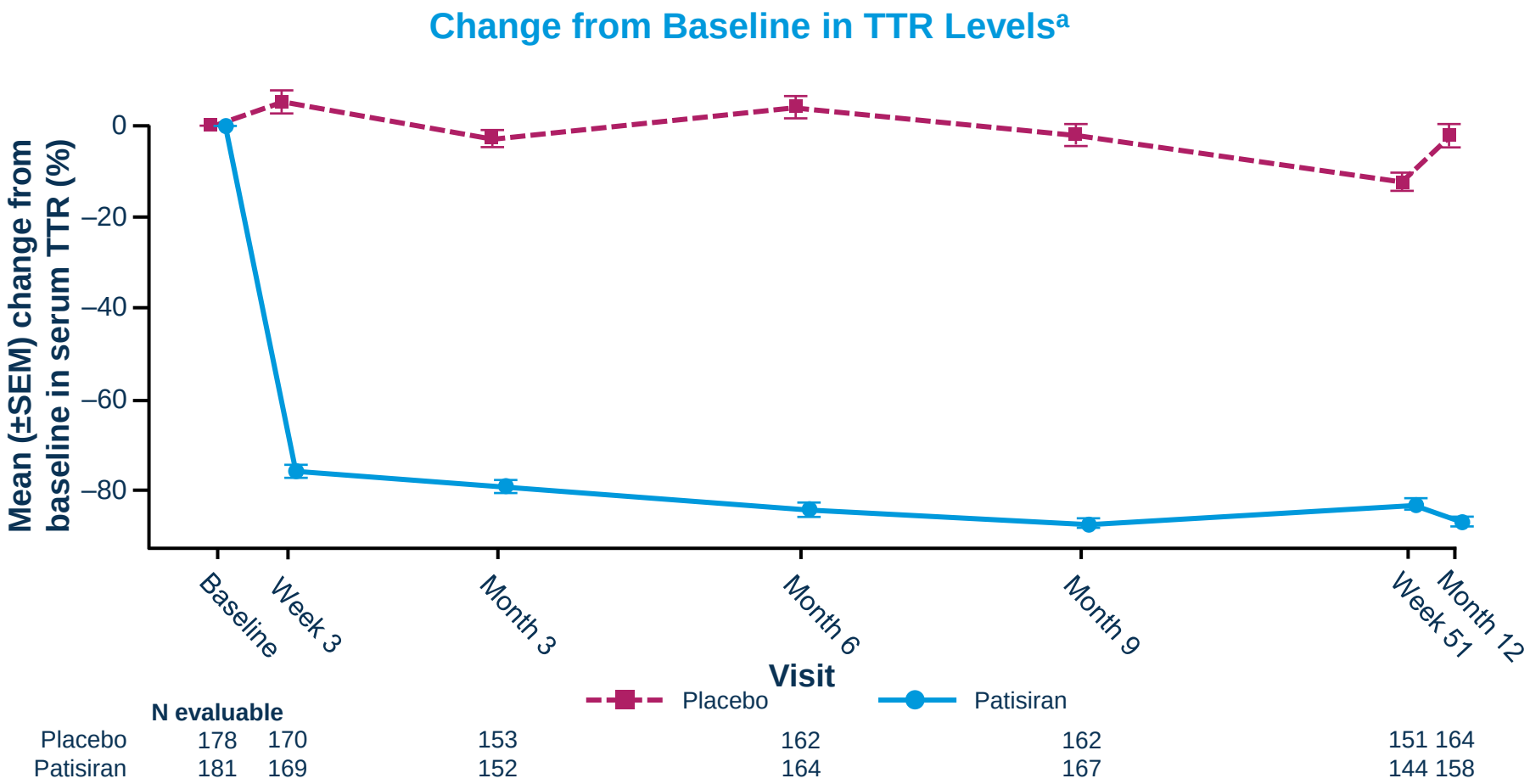
† To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers

NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWT: 6-Minute Walk Test

* Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in overall population

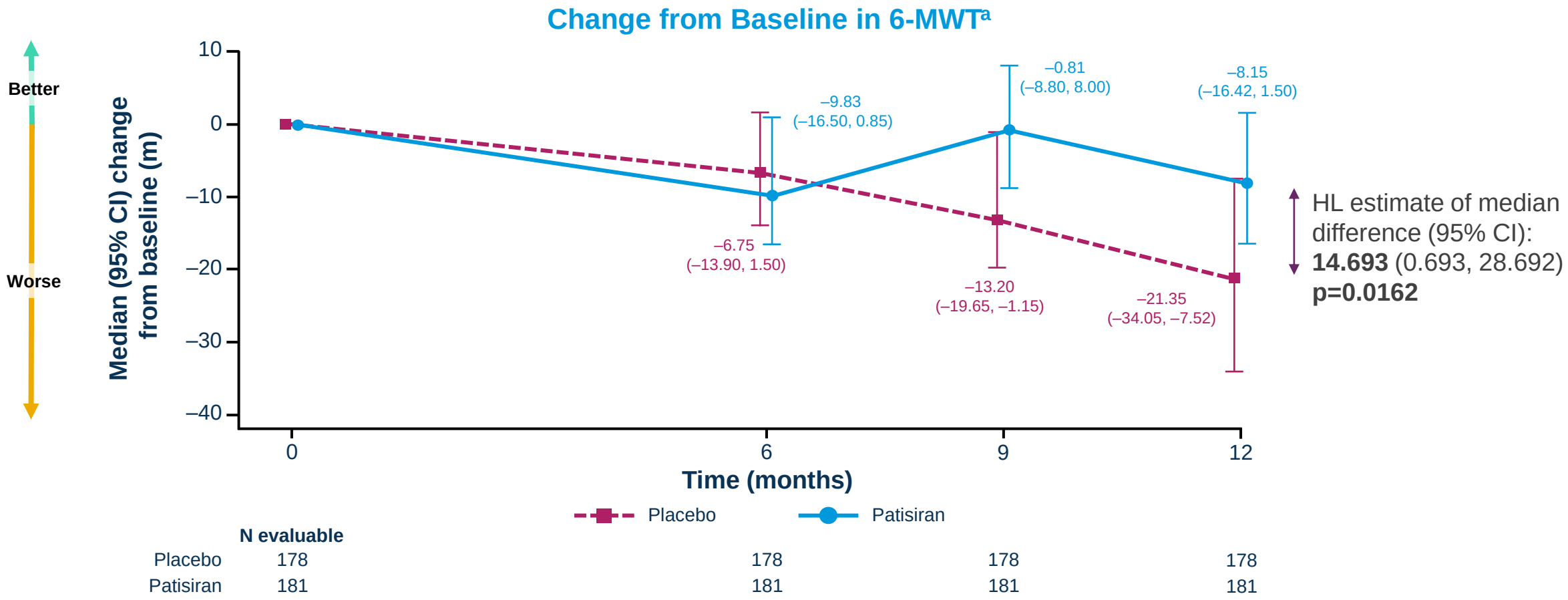
Rapid and Sustained Serum TTR Reduction with Patisiran

- Patisiran achieved a mean (SD) percent reduction in serum TTR of 86.8% (13.6) at Month 12



[a]At baseline mean (SD) serum TTR was 235.32 (68.05) mg/L in the patisiran group and 244.77 (73.17) mg/L in the placebo group. At Month 12 mean (SD) serum TTR was 30.93 (33.60) mg/L in the patisiran group and 229.40 (77.15) mg/L in the placebo group. **Abbreviations:** SD, standard deviation; SEM, standard error of mean; TTR, transthyretin.

Primary Endpoint: Patisiran Demonstrated Statistically Significant Improvement in Functional Capacity (6-MWT) Compared to Placebo at Month 12

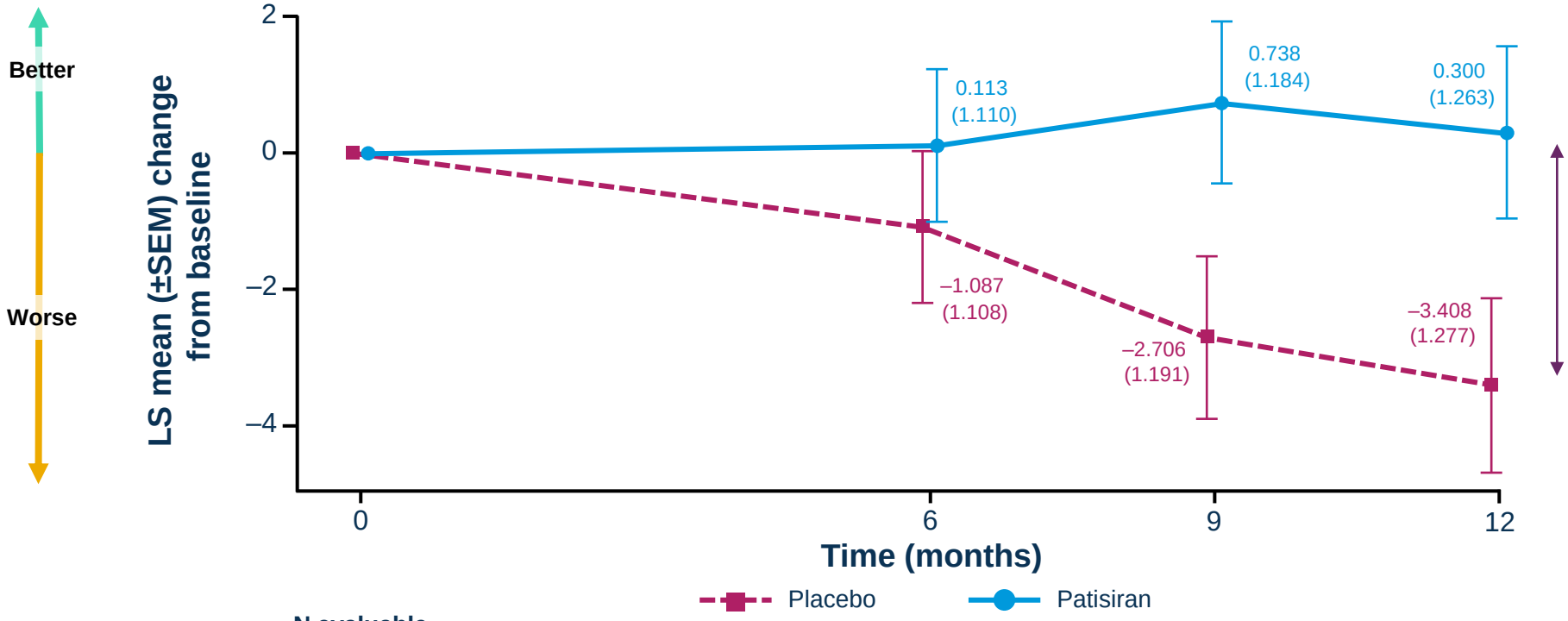


N evaluable				
Placebo	178	178	178	178
Patisiran	181	181	181	181

[a]Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values were based on the observed 6-MWT data and the imputed values; for each patient, the change from baseline was averaged across 100 complete datasets. Missing Month 12 values due to non-COVID-19 death or inability to walk due to progression of ATTR amyloidosis were imputed as the worst 10th percentile change observed across all patients in the double-blind period, capped by the worst possible change for the patient (i.e., 0 minus the patient's baseline 6-MWT). Missing Month 12 data due to other reasons were multiply imputed (assuming data were missing at random) to create 100 complete datasets. At baseline, the median (range) 6-MWT was 358.000 (155.70, 808.00) in the patisiran group and 367.740 (130.00, 740.00) in the placebo group. **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; HL, Hodges–Lehmann; m, meters.

Secondary Endpoint: Patisiran Demonstrated Statistically Significant Improvement in Health Status and Quality of Life (KCCQ-OS) Compared to Placebo at Month 12

Change From Baseline in KCCQ-OS using MMRM[a]



LS mean (SEM) difference:
3.709 (1.796)
p=0.0397

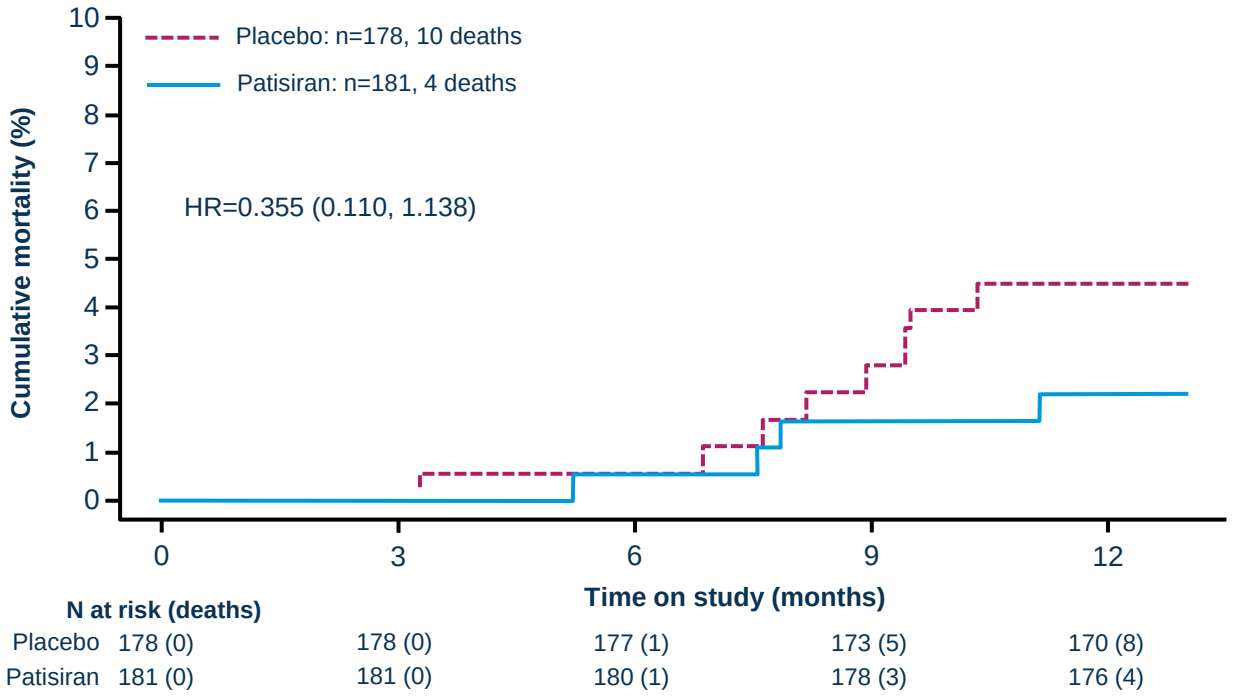
N evaluable				
Placebo	178	170	167	164
Patisiran	181	169	170	170

[a]MMRM model. Missing data not explicitly imputed and assumed to be missing at random. At baseline, the mean (±SD) KCCQ-OS was 69.836 (21.178) in the patisiran group and 70.330 (20.709) in the placebo group. **Abbreviations:** KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LS, least squared; MMRM, mixed model repeated measures; SD, standard deviation; SEM, standard error of mean.

All-Cause Mortality over 12-Month Double-Blind Period

- In the overall population, all-cause deaths[a,b] were observed in 10 (5.6%) placebo vs 4 (2.2%) patisiran patients
  - CV-related deaths: placebo 5 (2.8%); patisiran 2 (1.1%)
    - Heart transplant[a]: placebo 2 (1.1%); patisiran 0 (0.0%)
  - HR estimate (patisiran/placebo): 0.355 (95% CI: 0.110, 1.138)
- For patients on baseline tafamidis, all-cause deaths were observed in 3 (6.7%) placebo vs 1 (2.2%) patisiran patient
  - HR (95% CI): 0.296 (0.031, 2.863)
- For patients not on baseline tafamidis, all-cause deaths were observed in 7 (5.3%) placebo vs 3 (2.2%) patisiran patients
  - HR (95% CI): 0.396 (0.102, 1.538)

All-Cause Mortality over 12-Month Double-Blind Period[a,b]



[a]Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled the same as death in analyses. [b]Deaths, hospitalizations, and urgent HF visits due to COVID-19 were excluded from event rate calculations. Per SAP definition, for patients who discontinued the study, deaths up to Day 417 were counted in the double-blind period. The figure is truncated at Day 372 (end of Month 12 visit window). 2 placebo deaths that occurred after Month 12 and prior to Day 417 are included in the estimate of HR but not shown on the figure.

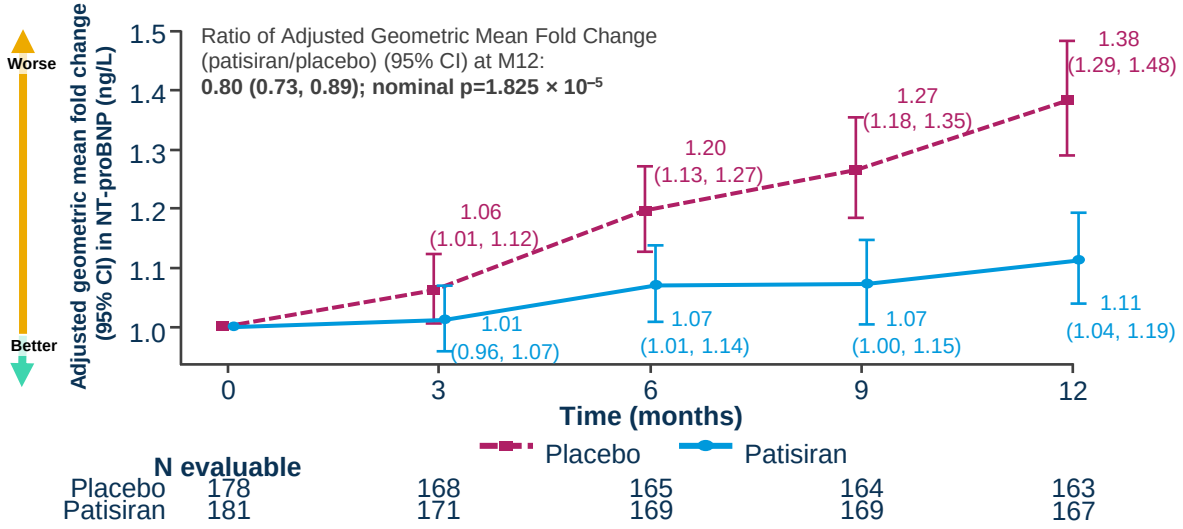
Abbreviations: CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SAP, statistical analysis plan.

Exploratory Cardiac Biomarkers Support Clinical Relevance of Observed Treatment Effect on Functional Capacity, Health Status and Quality of Life

Patisiran favorably impacted NT-proBNP and troponin I relative to placebo

- Important cardiac biomarkers monitored in clinical practice
- Incorporated in recognized ATTR amyloidosis disease staging systems[1] and expert consensus for defining disease progression[2]

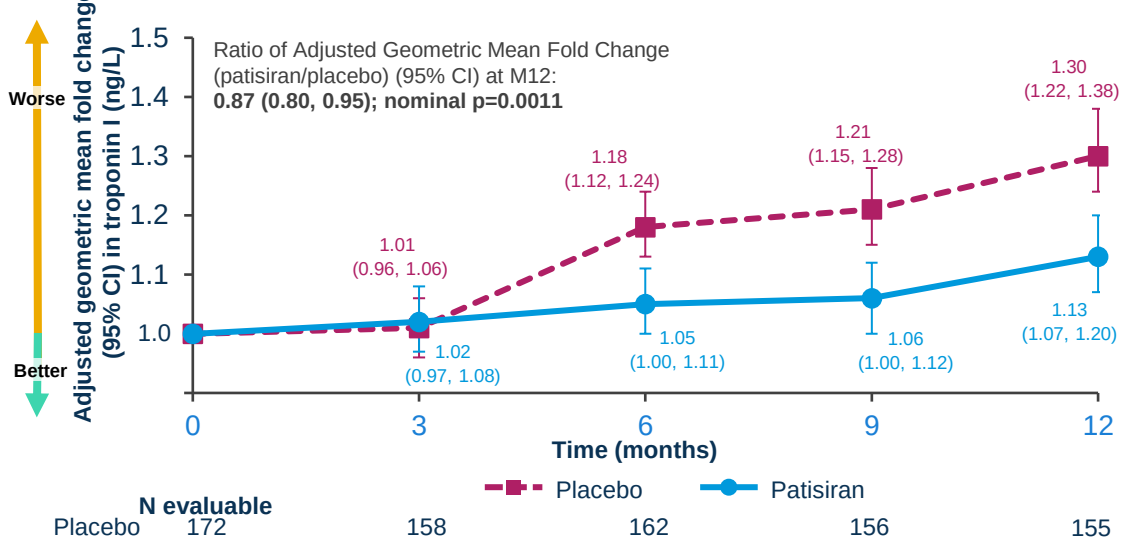
Change from Baseline in NT-proBNP at Month 12[a]



N evaluable

Placebo	178	168	165	164	163
Patisiran	181	171	169	169	167

Change from Baseline in Troponin I at Month 12[b]



N evaluable

Placebo	172	158	162	156	155
Patisiran	174	171	162	160	158

[a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. At baseline, median (IQR) NT-proBNP was 2008 (1135–2921) ng/L in the patisiran group and 1813 (952–3079) ng/L in the placebo group. At Month 12, median (IQR) NT-proBNP was 1944 (1158–3726) ng/L in the patisiran group and 2299 (1180–4364) ng/L in the placebo group. Number of evaluable patients at each timepoint are shown. [b]Troponin I is a measure of myocardial injury, with higher values indicating a greater level of myocardial injury. Number of evaluable patients at each timepoint are shown. [c]Progression defined in Garcia-Pavia et al (2021) as ≥30% increase and change ≥300 ng/L for NT-proBNP, as ≥30% increase for troponin I, and as an increase for ATTR disease stage. REFERENCES 1. Pregenzer-Wenzler et al. *JACC Heart Fail* 2020; 8:701-11., 2. Garcia-Pavia et al. *Eur J Heart Fail* 2021; 23:895-905.

Vutrisiran HELIOS·B Phase 3 Study

Randomized, Double-Blind Outcomes Study in ATTR Amyloidosis Patients with Cardiomyopathy

N = 655
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤ III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV events (when last patient reaches Month 30)

Select Secondary Endpoints

- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score
- Echocardiographic parameters
- All-cause mortality and recurrent all-cause hospitalizations and HF events
- All-cause mortality
- Recurrent CV events
- NT-proBNP

ClinicalTrials.gov Identifier: NCT04153149

HELIOS·B

Enrollment complete

Topline results on 30-month endpoint expected **early 2024**

RNAi Therapeutics Could Potentially Reimagine Treatment of Hypertension

Opportunity for Tonic Blood Pressure (BP) Control

Disease Overview

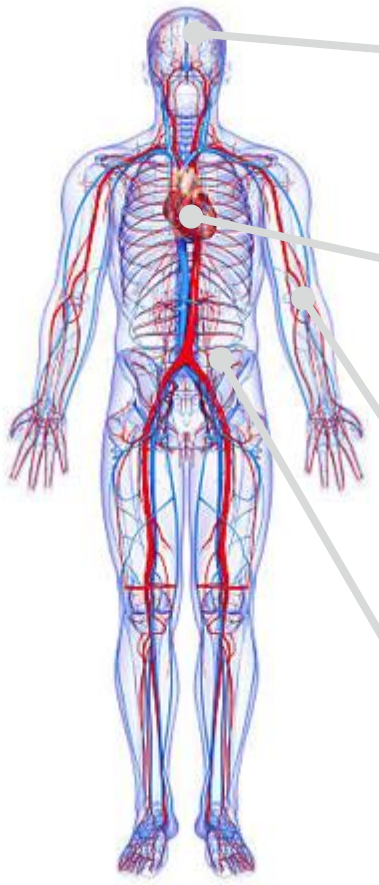
Primary Hypertension[1]	Hypertension at high CV risk[2]
~108 Million in U.S.	**~38 Million** in U.S.

>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**

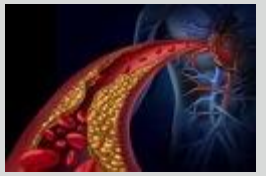
Together, contribute to substantial risk of CV morbidity and mortality

Potential Complications of Uncontrolled Hypertension



Stroke

Heart Attack



Arteriosclerosis

Kidney Failure

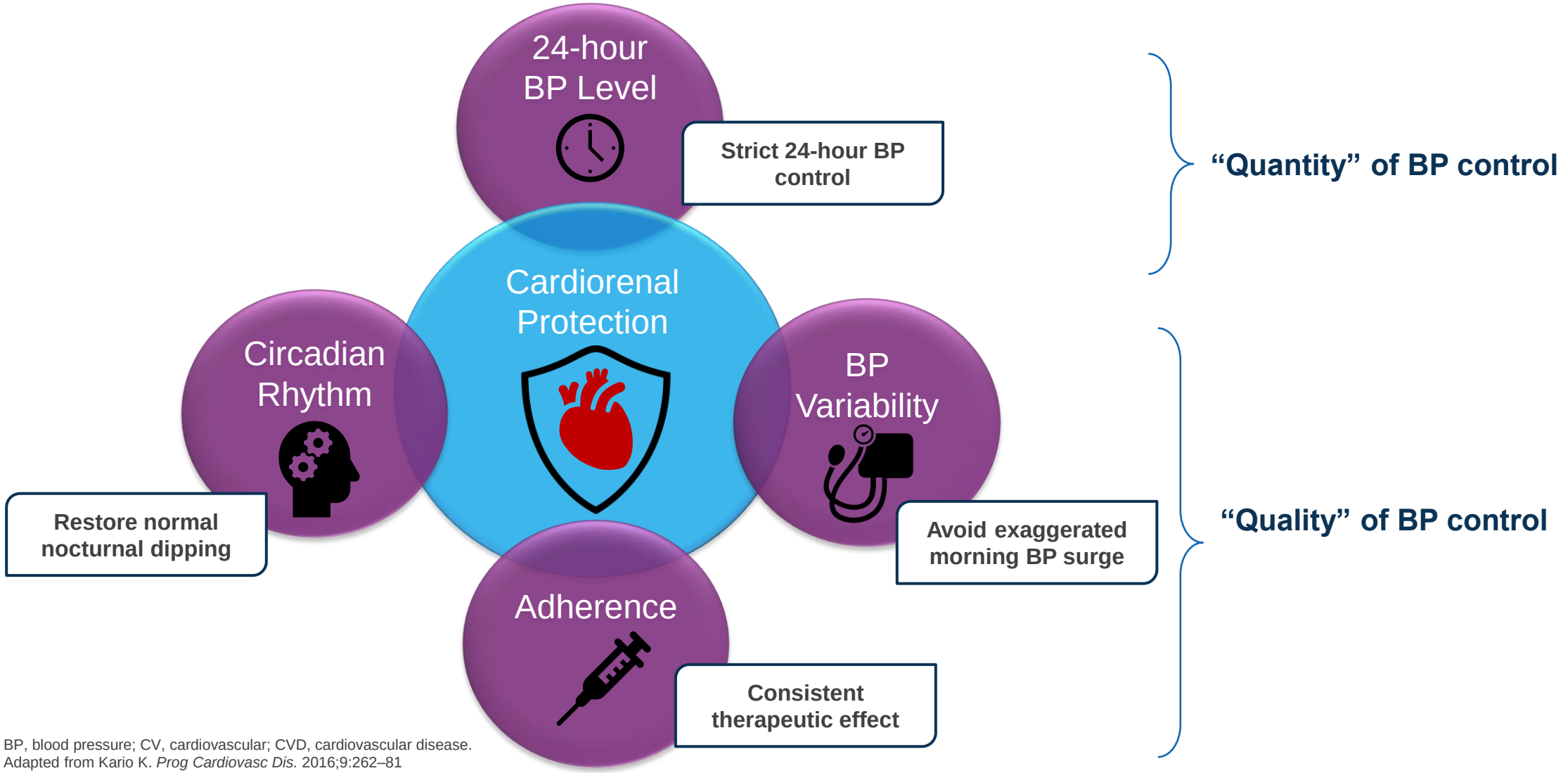
[1] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 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.

Targeting "Tonic" BP Control to Reduce Cardiorenal Risks

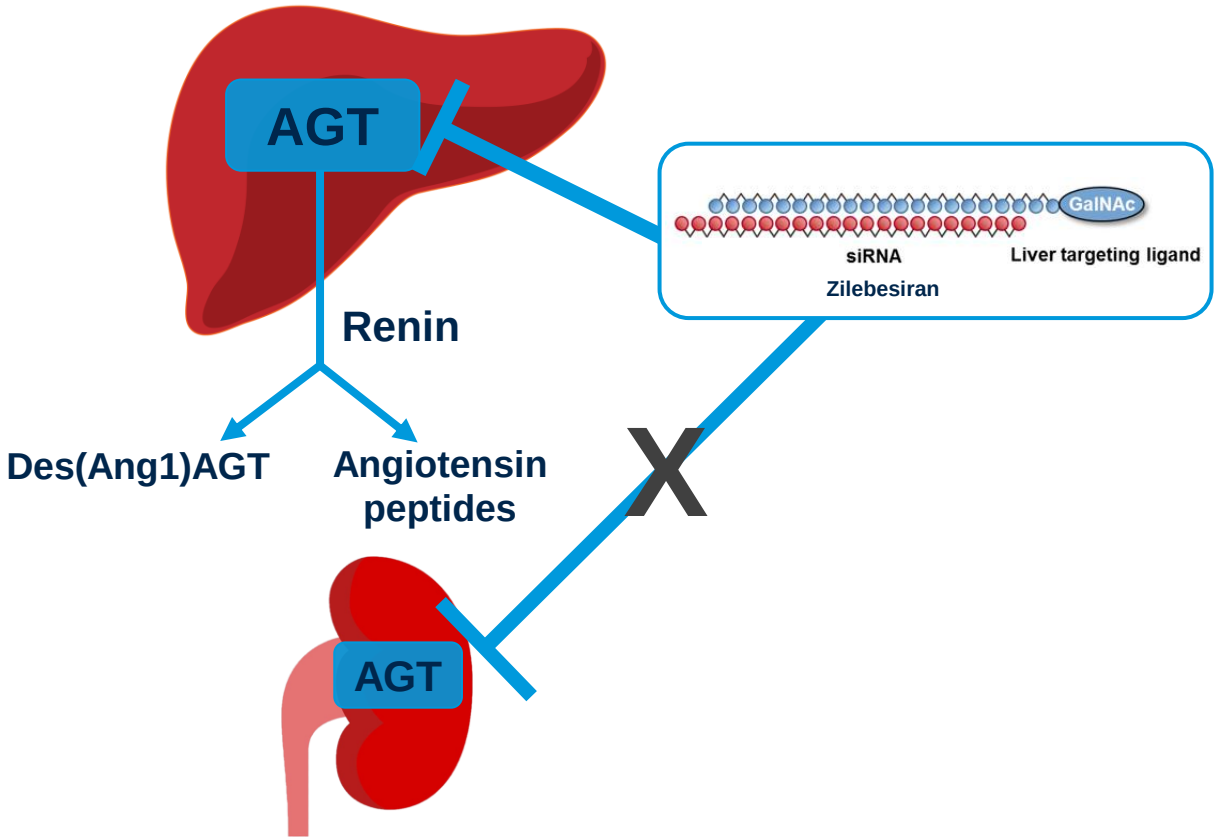
Achieving Quartet Could Reduce Risk of Organ Damage and Risk of CVD Events



BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease.
Adapted from Kario K. *Prog Cardiovasc Dis.* 2016;9:262–81

Zilebesiran Therapeutic Hypothesis

Liver-specific AGT Knockdown



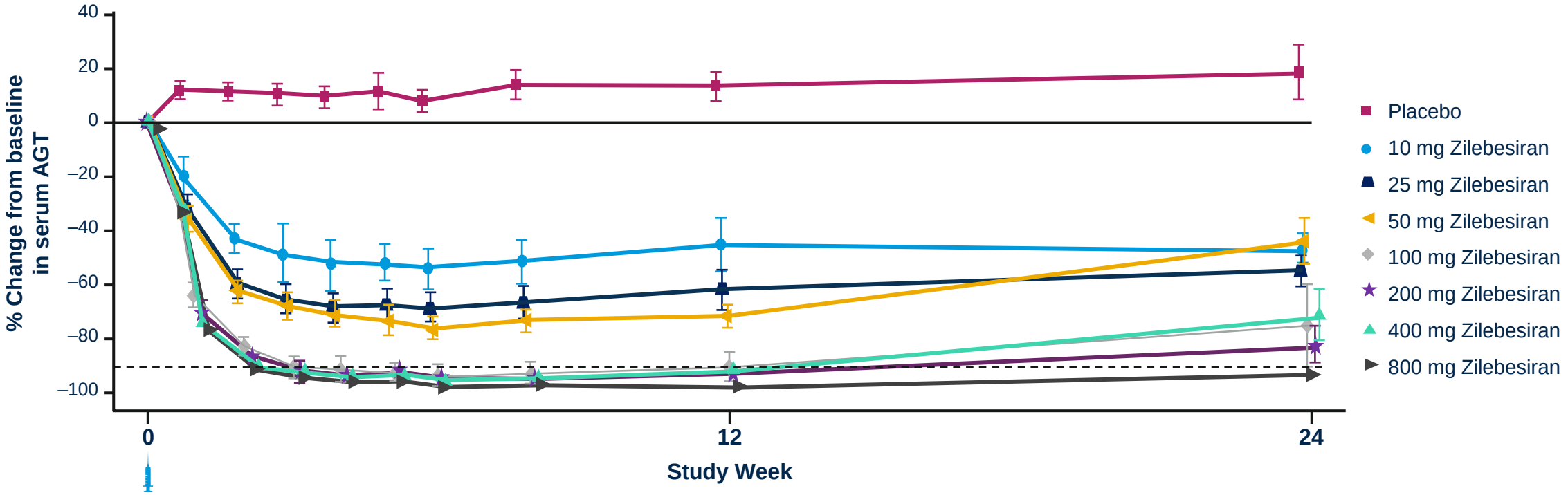
Potential Mechanistic Advantages

- **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

Durable Dose-Dependent Lowering of Serum AGT

- A reduction of ≥90% in serum AGT from baseline was observed with single doses of zilebesiran ≥100 mg from Week 3 and sustained to Week 12
- All patients who received a single dose of zilebesiran 800 mg maintained >90% reduction in serum AGT through Week 24



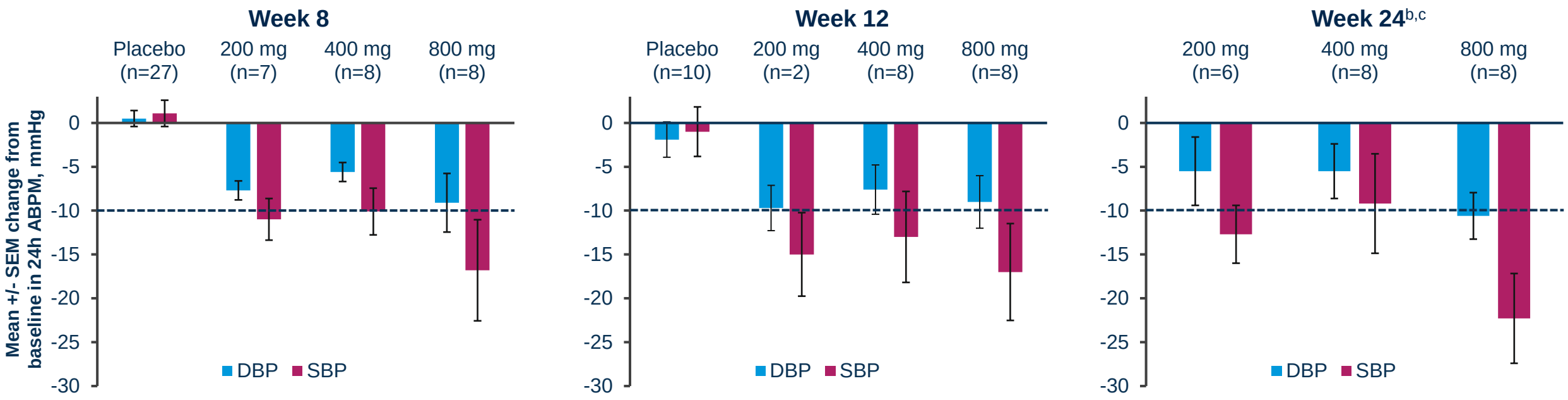
Placebo	28	28	12
10 mg	8	8	5
25 mg	8	8	8
50 mg	8	7	7
100 mg	8	7	7
200 mg	8	8	8
400 mg	8	8	8
800 mg	8	8	8

Huang AH, Taubel J, Casey S, et al., AHA Scientific Sessions 2021
AGT, angiotensinogen

Durable Antihypertensive Effect of Single Dose Zilebesiran

- A mean 24-hr SBP reduction of >10 mmHg was achieved at Week 8 across dose groups ≥200 mg
  - Clinically meaningful reductions in BP were maintained through Week 24
- After a single dose of 800 mg zilebesiran, a mean 24-hr SBP reduction of >20 mmHg was observed at Week 24
  - Of the 8 patients in this group, 6 achieved a mean 24-hr SBP reduction of >20 mmHg at Week 24 without add-on antihypertensives

Mean Change From Baseline in ABPM[a]



Huang AH, Taubel J, Casey S, et al., AHA Scientific Sessions 2021

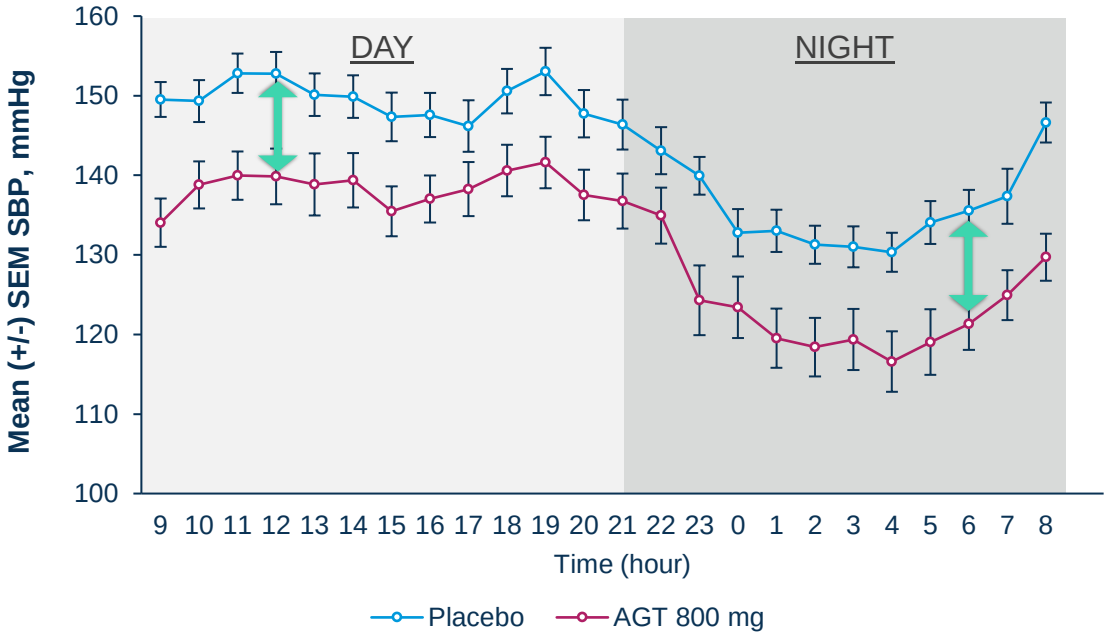
[a] Median SBP/DBP at baseline: Placebo - 142/88 mmHg; 200 mg - 139/83 mmHg; 400 mg - 138/90 mmHg; 800 mg - 142/88 mmHg.

[b] After Week 12, patients on placebo were not required to be followed. [c] 2 patients in the 200 mg dose group, 1 patient in 400 mg, and 2 patients in 800 mg received add-on antihypertensive therapy.

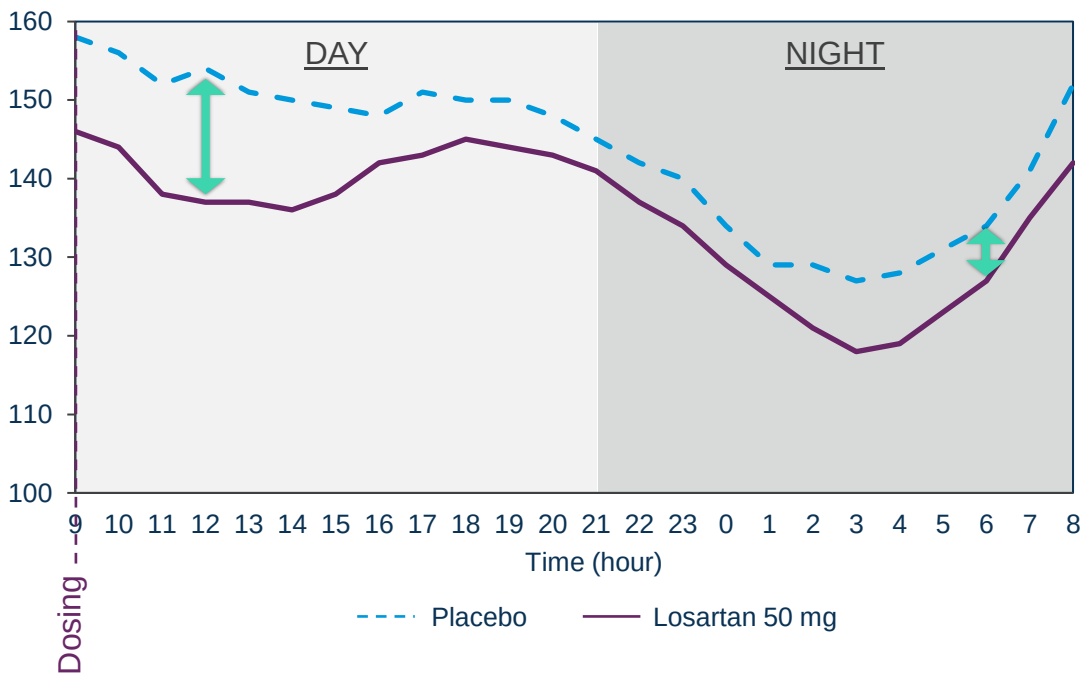
ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; SAD, single ascending dose; SBP, systolic blood pressure; SEM, standard error of the mean.

Early Evidence of Tonic BP Control over 24 Hours with Zilebesiran

Zilebesiran: 24-Hour SBP at Week 6



Losartan: 24-Hour SBP at Week 4[a]



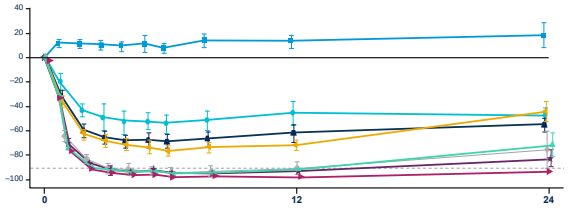
[a] Adapted from Fogari et al. (1999) Current Therapeutic Research 60(4):195-206

AGT, angiotensinogen; BP, blood pressure; SBP, systolic blood pressure

Zilebesiran: Potential Novel Treatment for Patients with Hypertension

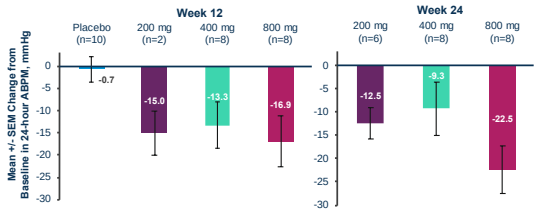
Compelling Phase 1 Data Support Transformative Product Profile

Serum AGT Lowering



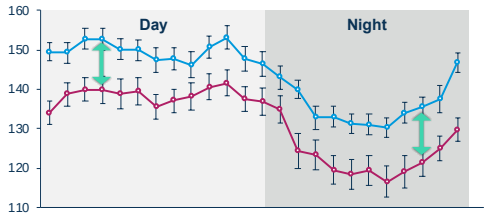
>90% mean serum AGT reduction for 6 months*

Blood Pressure Reduction



>10 mmHg SBP reduction at 6 months*

Consistent BP Reduction



Tonic BP control demonstrated over 24hr*

Change in RAAS Biomarkers

Durable reduction in Ang II & aldosterone*

KARDIA-1

Monotherapy Phase 2 Study (N = 394)

- Exploring multiple doses and dosing regimens
- Enrollment completed **December 2022**
- Topline results expected **mid-2023**

KARDIA-2

Combination Phase 2 Study (N ~ 630)

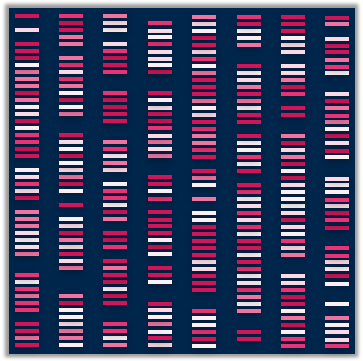
- Background treatment standardized with ARB, calcium channel blocker or diuretic
- Enrollment completion expected **early 2023**
- Topline results expected **at or around year-end 2023**

* After single dose of zilebesiran 800 mg

Alnylam®

Alnylam's Technology Innovation & Leadership in RNAi Therapeutics Support Future Breakthrough in Battle Against Global CV Disease Pandemic

Human Genetics

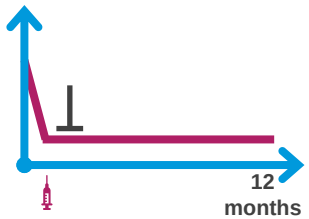


+ Our Future Health

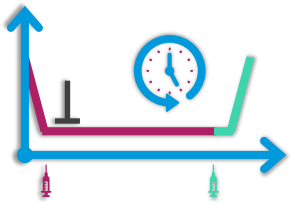
biobank uk

- Sourcing novel, genetically validated targets
- Secured access to large PheWAS databases
- Proven ability to uncover novel gene targets

Platform Designs



IKARIA™

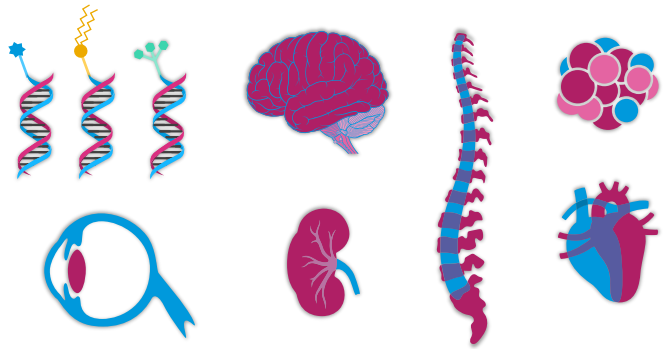


Reversir™

GEMINI™

- IKARIA™ enables robust target knockdown with annual dosing potential
- Reversir™ provides tailored control of RNAi pharmacology
- GEMINI™ combines siRNAs for simultaneous silencing of two transcripts

Extrahepatic Delivery



- Novel conjugates with variety of ligands for delivery beyond liver
- C16 conjugate provides robust target knockdown with wide biodistribution and long duration of action in CNS
- Peptide and antibody-based approaches being explored for targeted siRNA delivery to new tissues

Alnylam®


THANK YOU