Cardiovascular Franchise Webcast

September 2, 2020

Forward Looking Language Statement

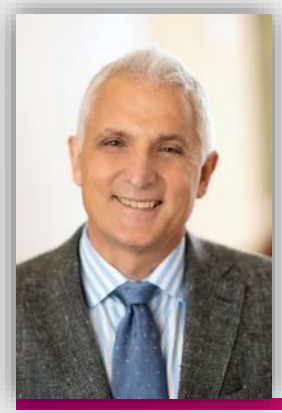
This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen) and Ionis' technologies and products in development, including Ionis' cardiovascular franchise. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2019 and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of this and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

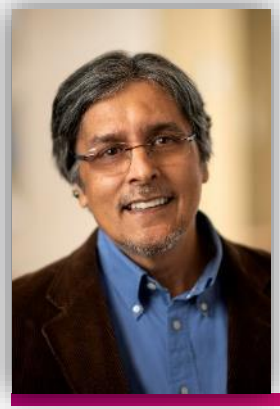
IONIS™

Today's Presenters

Brett Monia, Ph.D.
Chief Executive Officer
Ionis Pharmaceuticals



Sam Tsimikas, M.D.
SVP, Global Cardiovascular Development
Ionis Pharmaceuticals



Sanjay Bhanot, M.D. Ph.D.
SVP, Chief Medical Officer & Franchise Head: Metabolics and Liver Disease
Ionis Pharmaceuticals

Richard Geary, Ph.D.
EVP, Development
Ionis Pharmaceuticals

Today's Agenda

Welcome and Introductions	Wade Walke
Ionis – The Leader in RNA-targeted Drug Discovery and Development	Brett Monia
Ionis – Leading the Way in Targeting Cardiovascular Diseases	Sam Tsimikas
• **Medicines Targeting Triglyceride-driven Diseases**	Sam Tsimikas
• **AKCEA-APOCIII-L_{Rx}**	
• **Vupanorsen (AKCEA-ANGPTL3-L_{Rx})**	
• **Apolipoprotein(a): Pelacarsen (AKCEA-APO(a)-L_{Rx})**	Sam Tsimikas
• **Thrombosis: IONIS-FXI-L_{Rx}**	Sanjay Bhanot
• **Transthyretin Amyloid Cardiomyopathy: AKCEA-TTR-L_{Rx}**	Richard Geary
• **Treatment Resistant Hypertension: IONIS-AGT-L_{Rx}**	Richard Geary
Conclusion	Brett Monia
Q&A	All

Ionis – The Leader in RNA-targeted Drug Discovery and Development

Brett Monia

IONIS™

Where We Are Today

- Advancing and expanding the reach of our Antisense platform technology
- Prioritizing our Ionis-owned pipeline
- Optimizing our commercial capabilities
- Delivering transformative medicines to the patients we serve

Delivering Medicines for Most Major Severe Diseases

- NEUROLOGICAL
- NEUROMUSCULAR
- CARDIOVASCULAR
- METABOLIC
- PULMONARY
- CANCER
- HEMATOLOGICAL
- KIDNEY
- OPHTHALMOLOGY
- INFECTIOUS DISEASE

IONIS™

Delivering Medicines for Most Major Severe Diseases

NEUROLOGICAL

NEUROMUSCULAR

CARDIOVASCULAR

≥ 10 Marketing Applications through 2025

HEMATOLOGICAL

KIDNEY

OPHTHALMOLOGY

INFECTIOUS DISEASE

IONIS™

Delivering Medicines for Most Major Severe Diseases

NEUROLOGICAL

NEUROMUSCULAR

CARDIOVASCULAR

Ultra-rare to Common Diseases

HEMATOLOGICAL

KIDNEY

OPHTHALMOLOGY

INFECTIOUS DISEASE

IONIS™

Ligand Conjugated Antisense (LICA)

Enhancing delivery of our medicines

- LICA is a technology we developed to enhance the delivery of our medicines
- LICA continues to deliver value today and sets a foundation for even better performance of our medicines in the future

LICA Precisely Delivers Our Medicines to the Intended Target Organs and Cell Types

Liver **LICA** is enabling more **therapeutic benefit** and delivering **value** to patients today

- 20-30x increase in potency
- Allows monthly or less frequent dosing
- Excellent safety and tolerability across 15 LICA medicines in development today

Enhancing the **delivery** of our medicines through **LICA** sets a foundation to further **increase** the **scope** of **our medicines**

- Expanding our LICA platform to include more organ systems and cell types
- Optimizing intracellular distribution
- Potential for oral delivery

IONIS™

All Medicines Targeting Cardiovascular Diseases Utilize Our LICA Technology

MEDICINE	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis				
Pelacarsen[1]	Cardiovascular disease				
Vupanorsen[2]	Cardiovascular disease				
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease				
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension				
IONIS-FXI-L_{Rx}	Clotting disorders				
IONIS-AZ4-2.5-L_{Rx}	Cardiovascular disease				
ION547 (Gen 2.5-L_{Rx})	Cardiometabolic disease				
ION904 (Gen 2.5-L_{Rx})	Cardiometabolic disease				

IONIS™

1. Previously AKCEA-APO(a)-L_{Rx}; 2. Previously AKCEA-ANGPTL3-L_{Rx}

Ionis: Leading the Way in Targeting Cardiovascular Diseases

Sam Tsimikas

IONIS™

Cardiovascular Disease Franchise Pipeline

MEDICINE	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis				
Pelacarsen[1]	Cardiovascular disease				
Vupanorsen[2]	Cardiovascular disease				
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease				
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension				
IONIS-FXI-L_{Rx}	Clotting disorders				
IONIS-AZ4-2.5-L_{Rx}	Cardiovascular disease				
ION547 (Gen 2.5-L_{Rx})	Cardiometabolic disease				
ION904 (Gen 2.5-L_{Rx})	Cardiometabolic disease				

IONIS™

1. Previously AKCEA-APO(a)-L_{Rx}; 2. Previously AKCEA-ANGPTL3-L_{Rx}

Cardiovascular Disease Franchise Pipeline

MEDICINE	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis				
Pelacarsen[1]	Cardiovascular disease				
Vupanorsen[2]	Cardiovascular disease				
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease				
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension				
IONIS-FXI-L_{Rx}	Clotting disorders				
IONIS-AZ4-2.5-L_{Rx}	Cardiovascular disease				
ION547 (Gen 2.5-L_{Rx})	Cardiometabolic disease				
ION904 (Gen 2.5-L_{Rx})	Cardiometabolic disease				

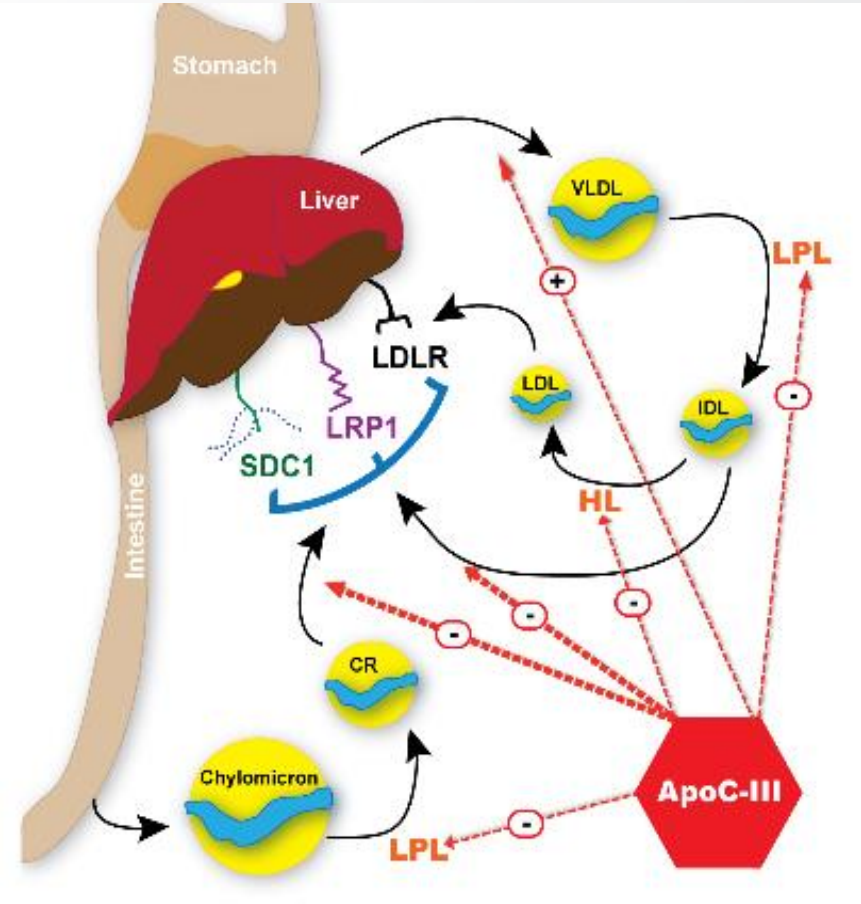
1. Previously AKCEA-APO(a)-L_{Rx}; 2. Previously AKCEA-ANGPTL3-L_{Rx}

Apolipoprotein C-III (apoC-III)

Targeting apoC-III for patient diseases driven by high triglycerides

IONIS™

ApoC-III is a Genetically Validated Target for Triglyceride-driven Diseases



Gordts PL, et al J Clin Invest. 2016;126:2855

- Apolipoprotein C-III (apoC-III)
  - Synthesized mainly in the liver
  - Key regulator of triglyceride-rich lipoprotein (TRL) hepatic uptake and plasma triglyceride (TG) levels through lipoprotein lipase (LPL)-dependent and LPL-independent mechanisms
- Epidemiological studies show that apoC-III levels predict CVD risk
- Loss of function mutations in apoC-III result in reduced TG and TRL, elevated HDL-C and ~40% reduction in risk of CVD compared to noncarriers
- Hypertriglyceridemia can result in familial chylomicronemia (FCS) and multifactorial chylomicronemia syndrome (MCS) and is associated with increased residual risk for CV events in patients receiving appropriate lipid lowering therapies
- Elevated triglyceride levels associated with major medical issues
  - Acute pancreatitis, which is associated with significant morbidity and mortality
  - Higher risk of cardiovascular disease

IONIS™

AKCEA-APOCIII-L$_{Rx}$

LICA medicine we designed to specifically target apoC-III for reduction of CVD risk

- Positive topline Phase 2 data reported in early 2020
- Full Phase 2 data presented at the 2020 European Society of Cardiology
- Phase 3 start in FCS expected in 2020
- Planning underway for additional disease indications

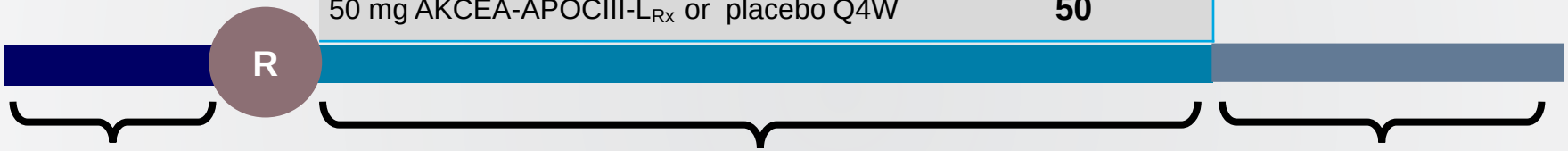
IONIS™

AKCEA-APOCIII-L_{Rx} Phase 2 Study Design

Treatment	Monthly equivalent dose (mg)
10 mg AKCEA-APOCIII-L_{Rx} or placebo Q4W	**10**
15 mg AKCEA-APOCIII-L_{Rx} or placebo Q2W	**30**
10 mg AKCEA-APOCIII-L_{Rx} or placebo QW	**40**
50 mg AKCEA-APOCIII-L_{Rx} or placebo Q4W	**50**

Total N= 114
4 cohorts, within cohort randomized
(4:1 active:placebo)

QW=every week
Q2W= every 2 weeks
Q4W=every 4 weeks
R-randomization



Screening and Diet Run-in
Up to 5 weeks

Treatment duration:
Min 6 months, max 12 months

Follow up
13 weeks

The primary endpoint was mean percentage change in fasting triglycerides from baseline at the primary analysis timepoint of 6 months (Week 25 for Q4W and Week 27 for QW dosing) in each AKCEA-APOCIII-L_{Rx} group compared with the pooled placebo group

Secondary endpoints included change from baseline at the primary analysis timepoint in:

- Percent change from baseline in apoC-III, VLDL-C, non-HDL-C, LDL-C, apoB, HDL-C, and apoA-I
- Proportion of patients who achieve serum TG ≤ 150 mg/dL (≤ 1.7 mmol/L)

IONIS™

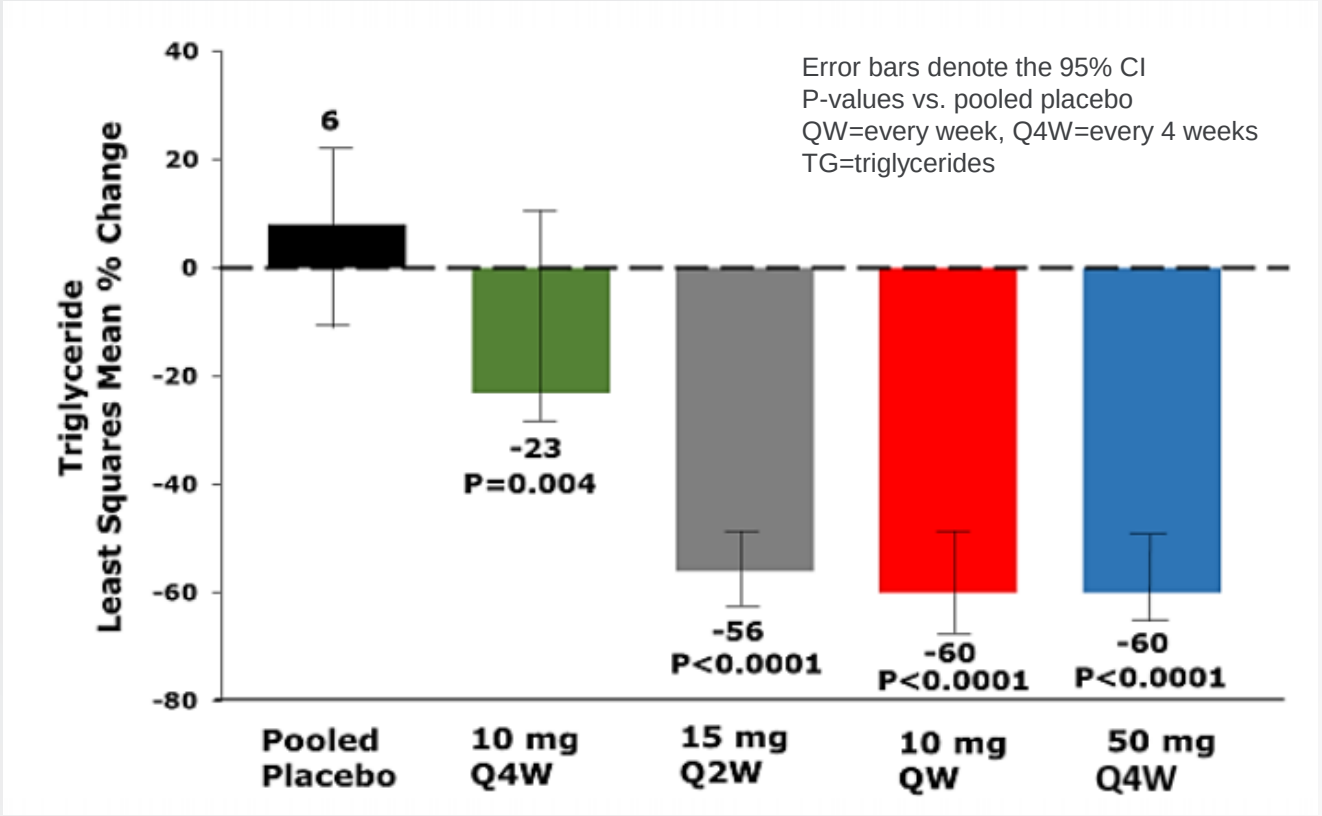
AKCEA-APOCIII-L_{Rx} Phase 2 Results

Met primary endpoint of significant triglyceride lowering

>90% of patients achieved serum triglycerides of <150 mg/dL

Primary Endpoint Analysis:

Pairwise comparison between each AKCEA-APOCIII-L_{RX} group and pooled placebo group using an ANCOVA model, with treatment group as a fixed factor and log-transformed baseline triglycerides as a covariate.

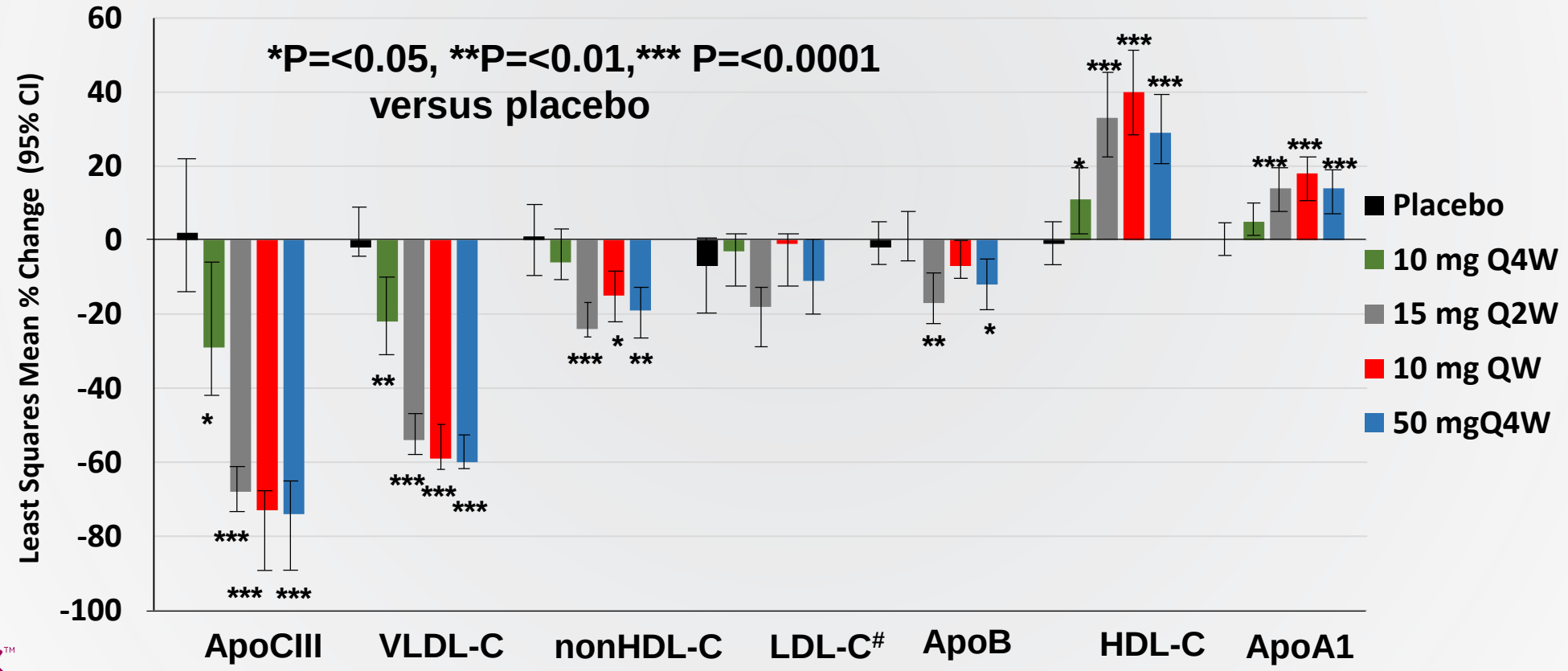


TG <150 mg/dL at Month 6 % of patients	4%	14% *p<0.2590*	65% *p<0.0001*	76% *p<0.0001*	91% *p<0.0001*

AKCEA-APOCIII-L_{Rx} Phase 2 Results

Met multiple secondary endpoints

- **Significant reductions in apoC-III, very low-density lipoprotein (VLDL-C), non-HDL-C & remnant cholesterol**
- **Statistically significant increases in high-density lipoprotein cholesterol (HDL-C)**



#estimated using Martin's equation, ultracentrifugation results pending

Martin SS et al, JAMA 2013;310:2061

AKCEA-APOCIII-L_{Rx} Demonstrated a Favorable Safety and Tolerability Profile in Phase 2 Study

	Placebo pooled N=24	AKCEA-APOCIII-L_{Rx}				
		10 mg Q4W N=22	15 mg Q2W N=23	10 mg QW N=26	50 mg Q4W N=22	Pooled N=90
Any TEAE*	20 (83.3%)	17 (77.3%)	20 (87.0%)	22 (95.7%)	21 (95.5%)	80 (88.9%)
Serious TEAE**	1 (4.2%)	3 (13.6%)	3 (13%)	1 (4.3%)	2 (9.1%)	9 (10.0%)
TEAE leading to discontinuation***	1 (4.2%)	0	1 (4.3%)	1 (4.3%)	0	2 (2.2%)
TEAE leading to death****	0	0	1 (4.3%)	0	0	1 (1.1%)

Treatment period: from the first dose through one dosing interval after the last dose

* The most frequent TEAEs : Injection site erythema (15.6%) in pooled AKCEA-APOCIII-L_{Rx} group

** None of the SAEs were related to study drug

*** Eosinophilia (mild, related) and myalgia (mild, not related); cardiac arrest (severe, unlikely related); hypertension (mild, related)

**** Cardiac arrest (severe, not related)

IONIS™

AKCEA-APOCIII-L_{Rx} Summary and Next Steps

- Phase 2 study **met** the **primary, key secondary endpoints** and demonstrated a **favorable safety** and **tolerability** profile
- **Initiate Phase 3 Study in FCS this year**
- Additional potential indications targeting elevated triglyceride levels
  - **Multifactorial Chylomicronemia Syndrome** (MCS) is a polygenic disorder exacerbated by the presence of secondary factors, such as diet rich in fats and simple sugars and obesity
  - **Very high triglycerides levels > 500** is a leading cause of pancreatitis and CVD, affecting tens of millions of people in the U.S.
  - **High triglyceride levels > 150-500** which increase the risk of CVD, including heart disease and stroke

IONIS™

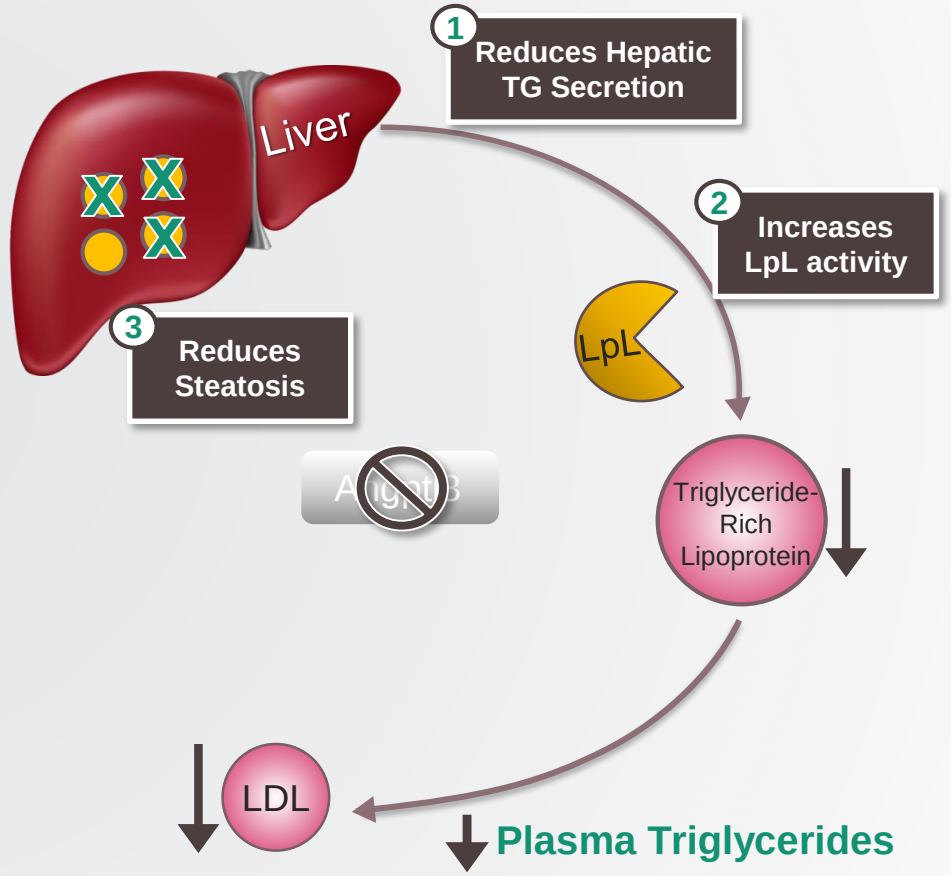
Angiopoietin-like 3 (ANGPTL3)

Targeting ANGPTL3 for patient diseases driven by high triglycerides and cholesterol

IONIS™

Angiopoietin-like 3 is a Key Regulator of Triglycerides and Cholesterol

- ANGPTL3 is a genetically validated target, secreted by the liver as an inhibitor of lipoprotein lipase & endothelial lipase
- Loss of function mutations in ANGPTL3 are associated with familial combined hypolipidemia, type 2, FHBL2
  - Reduced triglyceride and triglyceride rich lipoproteins levels
  - Reduced plasma LDL-C via a non-LDLR pathway
  - Reduced plasma HDL-C
  - ~40% lower risk of coronary artery disease
- People with loss of function mutations and/or decreased ANGPLT3 levels have reduced risk for CVD



ANGPTL3 is Associated with an Increased Risk of CVD

- **ANGPTL3** is a well-established **regulator** of **triglycerides** and **LDL-C**
- **Low** levels of **ANGPTL3** are associated with a **lower risk** of cardiovascular disease
- **There are no approved therapies** to specifically lower ANGPTL3 levels
- **Vupanorsen**, formerly known as AKCEA-ANGPTL3-L_{Rx}, is a LICA medicine we designed to **reduce ANGPTL3** production
- **Pre-clinical** studies demonstrated **targeted reductions** of **ANGPTL3** resulted in **decreased TG** and **LDL-C**

IONIS™

Substantial Dose-dependent ANGPTL3 Reductions Observed in Vupanorsen Phase 1/2 Study

- Dose-dependent **reductions** in **ANGPTL3** protein of up to **85%** after six weeks of treatment in healthy volunteers
- Treatment also resulted in **substantial** and dose-dependent **reductions** in triglycerides, LDL cholesterol, VLDL cholesterol, non-HDL cholesterol, apolipoprotein B and apolipoprotein C-III protein
- **Favorable safety** and **tolerability** profile, with no serious adverse events
- These **results support vupanorsen** as an attractive **therapeutic approach**

IONIS™

Vupanorsen (AKCEA-ANGPTL3-L_{Rx})*

LICA medicine we designed to specifically target ANGPTL3 for reduction of CVD risk

- Positive topline Phase 2 Data reported in early 2020
- Full Phase 2 data presented at the 2020 European Society of Cardiology and published in the *European Heart Journal*
- Pfizer to conduct expanded Phase 2b in statin-treated patients with elevated non-HDL-C and triglycerides this year

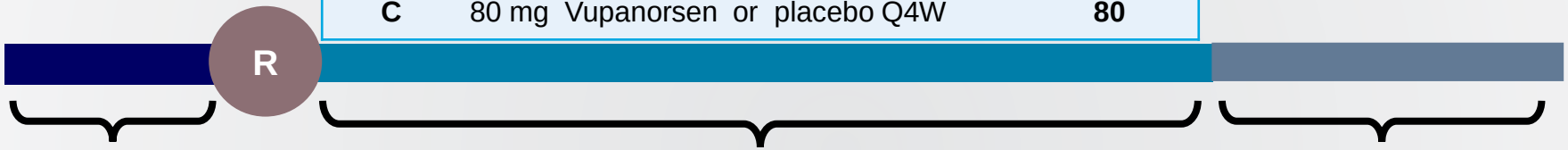
*Licensed to Pfizer

Vupanorsen Phase 2 Study Design

Total N= 105
3 cohorts, within cohort randomized
(3:1 active:placebo)

Cohort	Treatment	Monthly equivalent dose (mg)
A	20 mg Vupanorsen or placebo QW	80
B	40 mg Vupanorsen or placebo Q4W	40
C	80 mg Vupanorsen or placebo Q4W	80

QW=every week,
Q4W=every 4 weeks,
R-randomization



Screening and Diet Run-in
Up to 5 weeks

Treatment duration:
6 months

Follow up
13 weeks

The primary endpoint was mean percentage change in fasting triglycerides from baseline at the primary analysis timepoint of 6 months (Week 25 for Q4W and Week 27 for QW dosing) in each vupanorsen group compared with the pooled placebo group

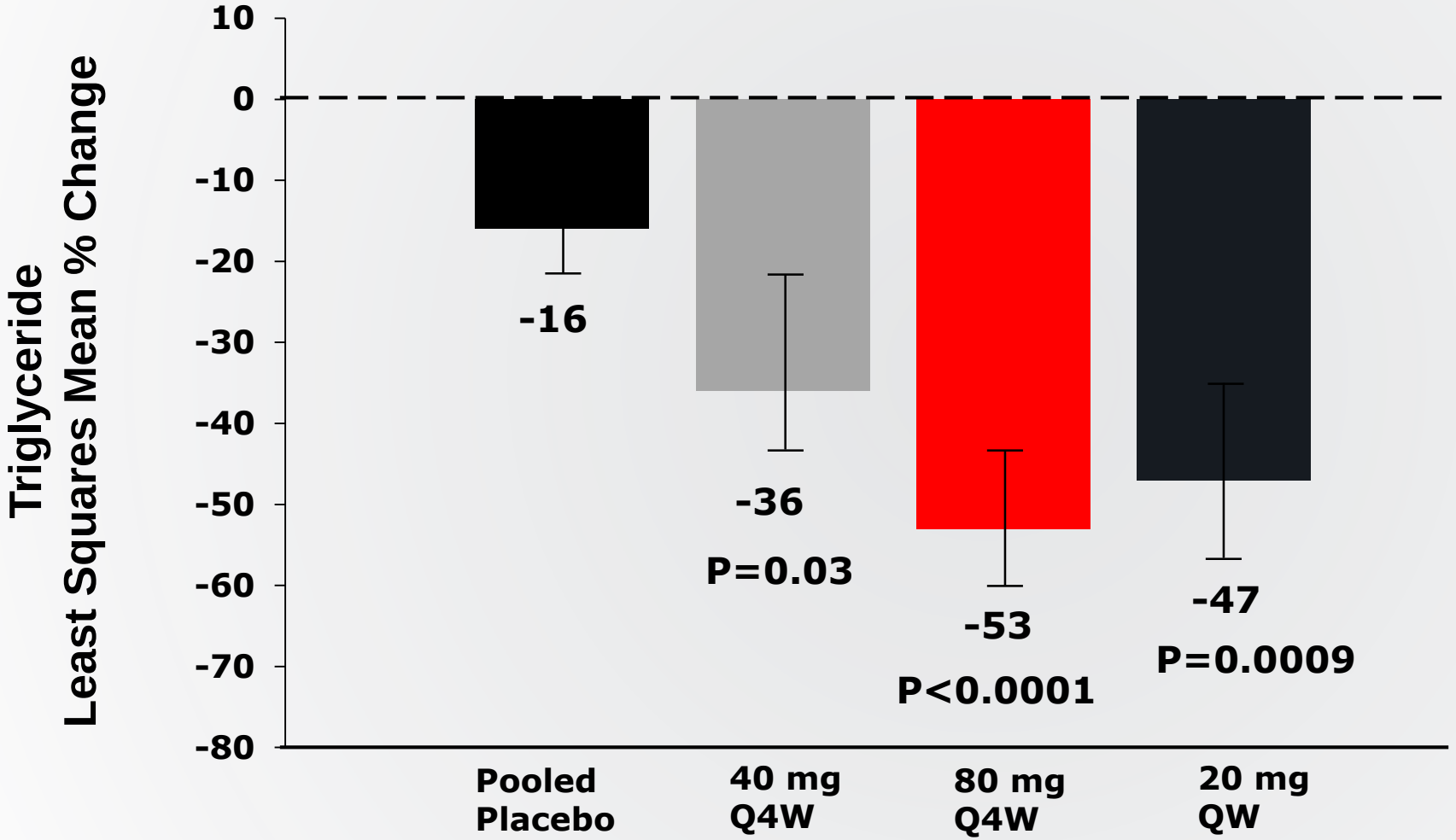
Secondary endpoints included change from baseline at the primary analysis timepoint in:

- ANGPTL3, TC, LDL-C, HDL-C, VLDL-C/remnant cholesterol, non–HDL-C, apo B, apoC-III, and FFAs
- Glycaemic parameters including HbA_{1c} and HOMA-IR
- Hepatic steatosis parameters including hepatic fat fraction (HFF, by MRI), and fatty liver index (FLI)

IONIS™

Vupanorsen Phase 2 Results

Met primary endpoint of significant triglyceride lowering



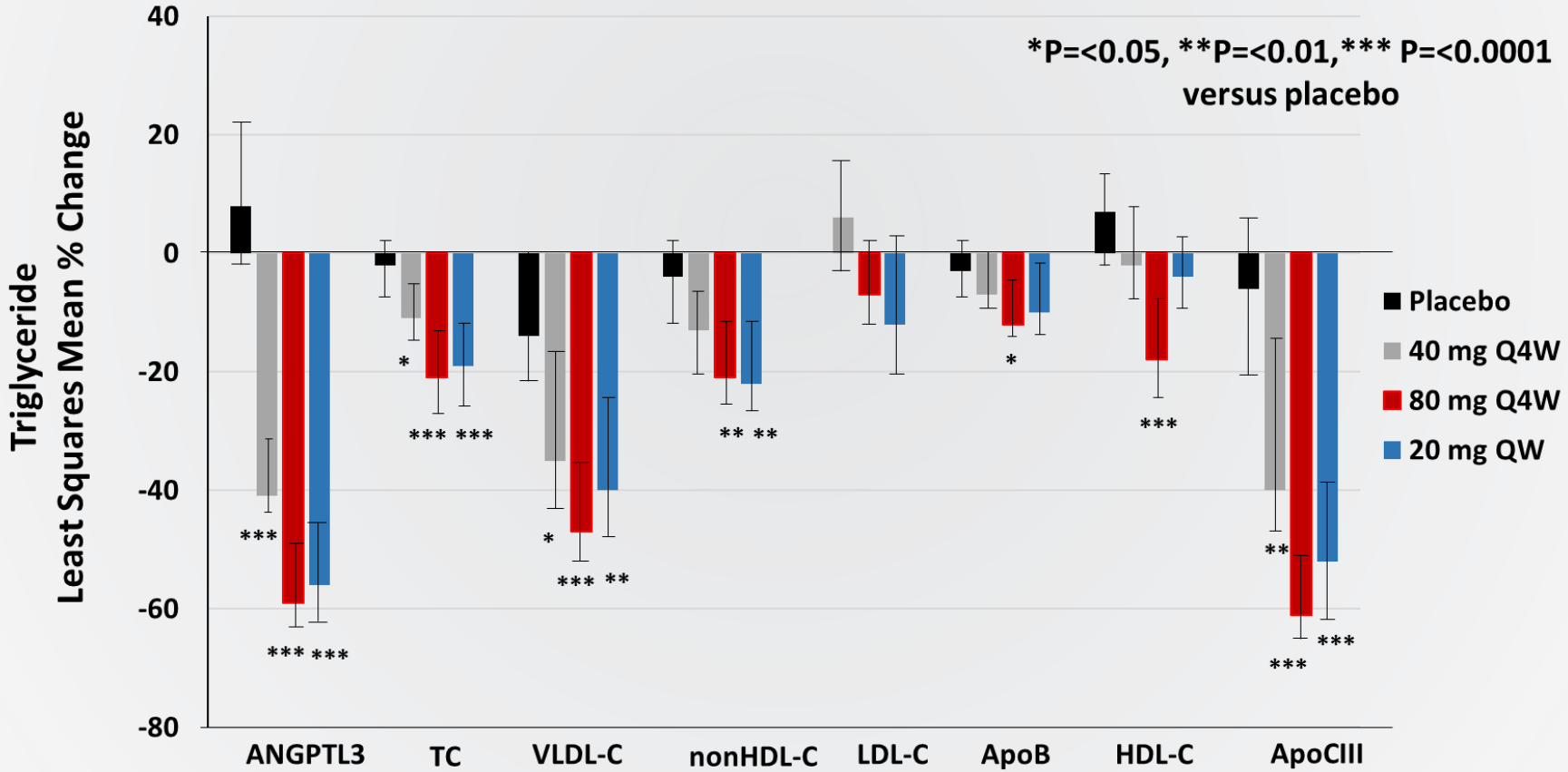
Primary Endpoint Analysis: Pairwise comparison between each vupanorsen group and pooled placebo group using an ANCOVA model, with treatment group as a fixed factor and log-transformed baseline triglycerides as a covariate.

Error bars denote the 95% CI, P-values vs pooled placebo
QW=every week, Q4W=every 4 weeks

IONIS™

Vupanorsen Phase 2 Met Multiple Secondary Endpoints

Dose-dependent reductions in ANGPTL3, apoC-III, VLDL-C, non-HDL-C and total cholesterol



Vupanorsen Demonstrated a Favorable Safety and Tolerability Profile in Phase 2 Study

	Placebo pooled N=27	Vupanorsen			
		40 mg Q4W N=26	80 mg Q4W N=26	20 mg QW N=26	Pooled N=78
Any TEAE*	16 (59.3%)	19 (73.1%)	23 (88.5)	23 (88.5)	65 (83.3%)
Serious TEAE**	0	0	0	1 (3.8%)	1 (1.3%)
TEAE leading to discontinuation***	0	1 (3.8%)	2 (7.7%)	3 (11.5%)	6 (7.7%)
TEAE leading to death	0	0	0	0	0

Treatment period: from the first dose through one dosing interval after the last dose

* The most frequent TEAEs : Injection site pruritus (14%) and Injection site erythema (12%) in pooled vupanorsen group

** Diverticulitis, moderate, not related to the study drug

*** TEAE at injection site (4 patients), elevated transaminases (1 patient), dehydration/acute pre-renal failure (1 patient)

IONIS™

Positive Vupanorsen (AKCEA-ANGPTL3-L_{Rx}) Phase 2 Results and Next Steps

- **Primary** and **multiple secondary endpoints** were **met** with significant reductions in triglyceride levels, additional lipid parameters and ANGPTL3
- **Favorable safety** and **tolerability** profile demonstrated in the study
- Pfizer to **initiate** a **Phase 2b** study this year in statin-treated patients with elevated non-HDL-C and triglycerides to determine the optimal dose for **Phase 3 cardiovascular outcomes** study
  - Multicenter, double-blind, placebo-controlled, dose-escalation study in 260 participants with elevated non-HDL-C and triglycerides that are receiving a stable dose of a statin
  - Three monthly (Q4W) cohorts: 80mg, 120mg, 160mg
  - Four bi-monthly (Q2W) cohorts: 60mg, 80mg, 120mg, 160mg
  - Primary endpoint: Percent change from baseline in non high density lipoprotein cholesterol at week 24

IONIS™

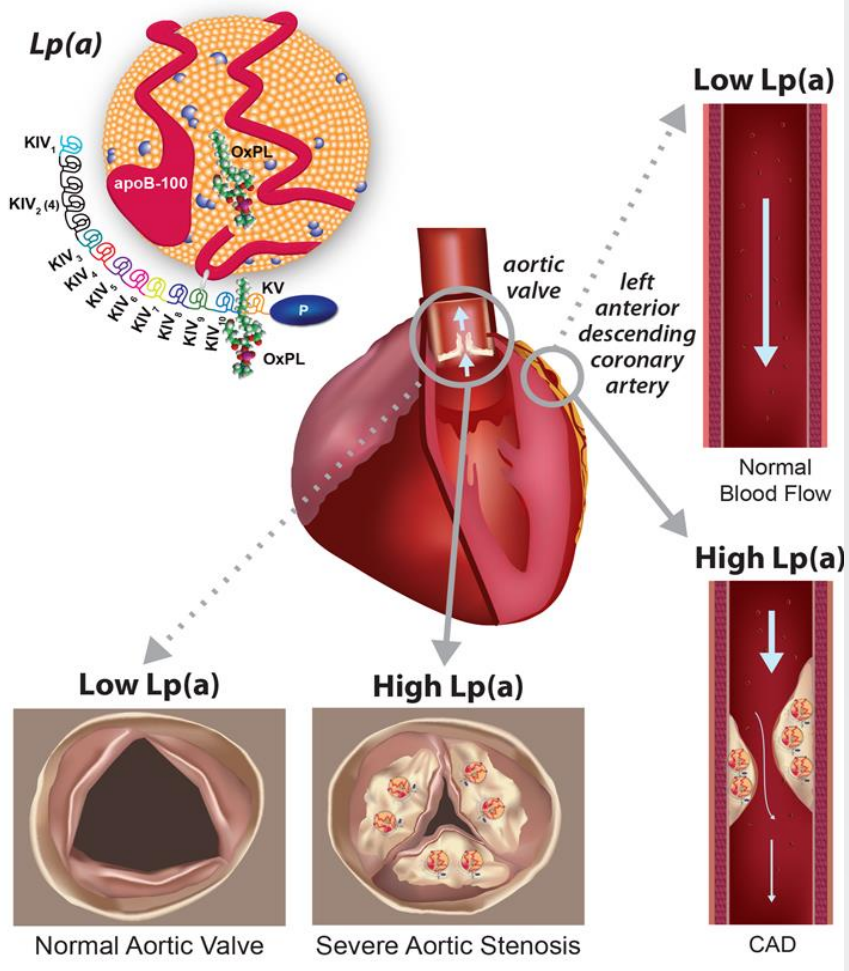
Lipoprotein(a)
Lp(a)

Elevated Lp(a), a major untreated cardiovascular disease risk factor

IONIS™

Lipoprotein(a)

A highly prevalent untreated risk factor for cardiovascular disease & aortic stenosis



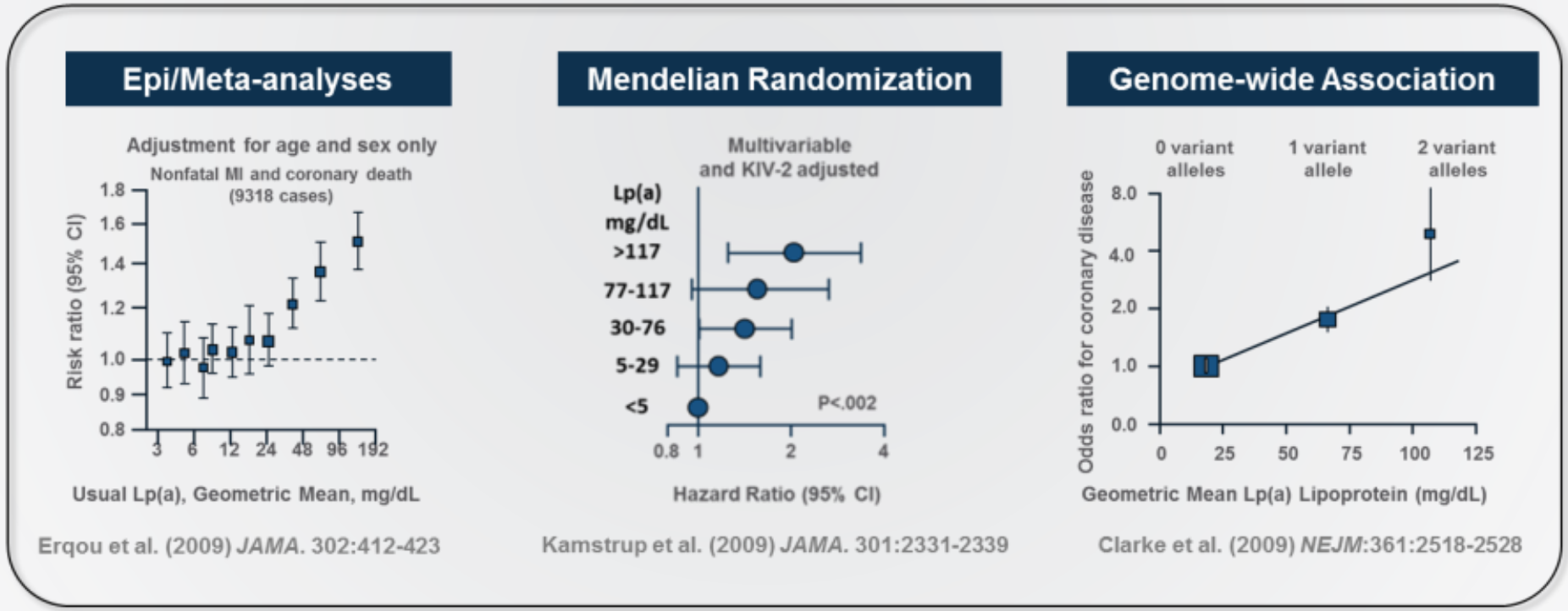
- Lp(a) levels are **genetically determined** at birth
- Elevated Lp(a) levels **cause cardiovascular disease** through multiple mechanisms
  - Atherogenicity through LDL moiety
  - Anti-fibrinolytic activity
  - Pro-inflammatory effects of oxidized phospholipids
- Elevated levels are recognized as a **major untreated cardiovascular risk factor**
- **> 8 million people worldwide** have Lp(a) driven CVD
- **No approved** pharmacological therapies

IONIS™

Only pelacarsen (TQJ230, AKCEA-APO(a)-L_{Rx}) has demonstrated the ability to selectively and robustly reduce Lp(a) levels in a clinical study

Strong Evidence Demonstrates Elevated Lp(a) Levels is a Key Driver of Cardiovascular Disease

- Linear relationship between Lp(a) levels and cardiovascular risk
  - Even modest increases in Lp(a) lead to meaningful cardiovascular risk
  - Similar to the risk associated with LDL-C and triglycerides



Pelacarsen*

LICA medicine we designed to specifically target Lp(a) for reduction of CVD risk

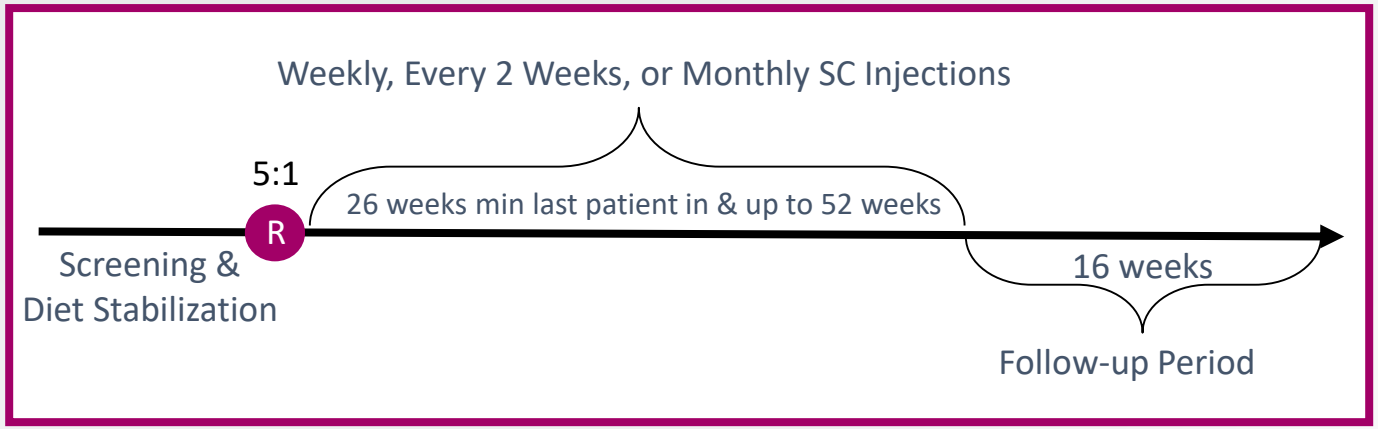
- Phase 3 Lp(a)HORIZON study of Lp(a)-driven cardiovascular disease is actively recruiting patients
- First-in-class medicine in development to selectively and robustly reduce Lp(a) levels
- Granted Fast Track Designation by the FDA

*Licensed to Novartis

Pelacarsen Phase 2 Study in Patients with Elevated Lp(a) and Established CVD (Completed)

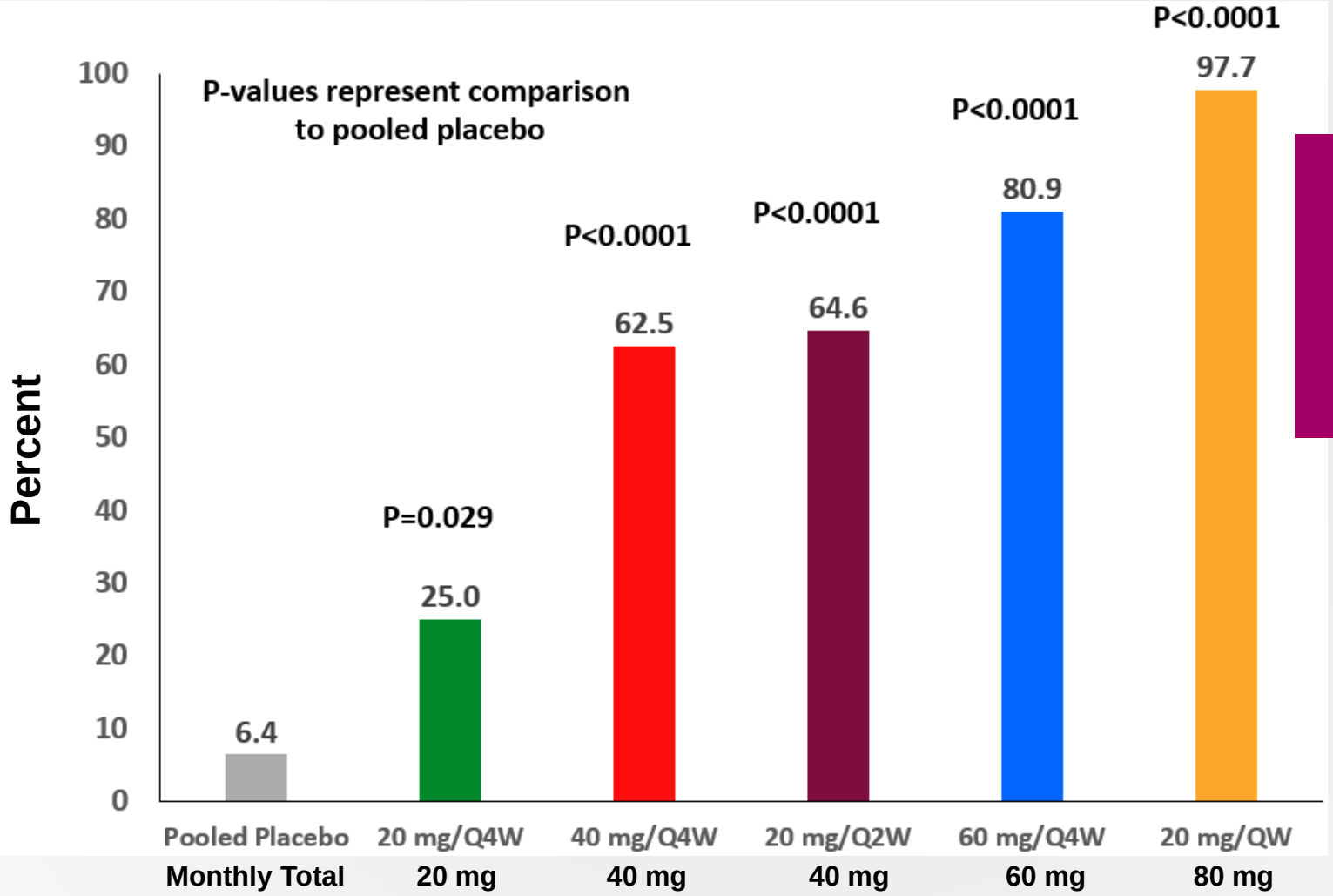
- Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study in 286 patients
- Primary objective:
  - Evaluate the safety and tolerability of different doses and dosing regimens of pelacarsen
  - Assess the efficacy of pelacarsen across different doses and dose regimens for reduction of Lp(a) levels
  - Weekly, bi-weekly and monthly dosing being explored in 5 dose cohorts from 20mg to 60mg
- Secondary objective:
  - Evaluate the efficacy of pelacarsen across different doses and dose regimens on serum levels of LDL-C, ApoB and Oxidized Phospholipid
  - Evaluate the pharmacokinetic profile of pelacarsen across different doses and dose regimen

Cohort	Frequency
20 mg	Weekly
20 mg	Bi-weekly
20 mg	Monthly
40 mg	Monthly
60 mg	Monthly



Pelacarsen Phase 2 Study: ~98% of Patients in the High Dose Group Achieved Lp(a) Levels Below 50 mg/dL

Percent of patients achieving Lp(a) ≤50 mg/dL (≤125 nmol/L)



≤50 mg/dL is considered below the threshold for risk of CVD events

QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks

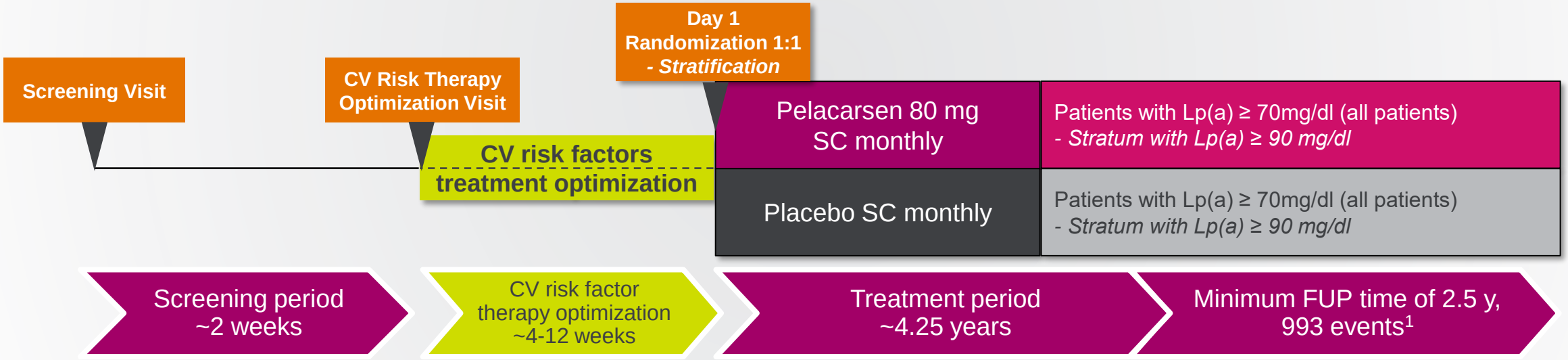
Pelacarsen Phase 2 Study

- **Largest, longest study** conducted in patients with Lp(a)-driven CVD
- **Robust, dose-dependent and durable reductions in Lp(a)** levels in patients treated for at least 6 months, with some patients treated for up to 1 year
- Reduced Lp(a) levels **below threshold of 50 mg/dL associated with CVD** in **98% of patients** on 20 mg weekly (equivalent to 80 mg monthly dose)
- Favorable **safety and tolerability** profile and **excellent compliance**
  - Comparable discontinuation between the active and placebo groups
- Convenient, **once monthly, low volume subcutaneous** dose

IONIS™

Pelacarsen Phase 3 Lp(a)HORIZON Study

- Multicenter, randomized, double-blind, placebo-controlled study in 7,680 patients with elevated Lp(a) levels (≥ 70 mg/dL) and history of CVD (myocardial infarction, ischemic stroke, peripheral artery disease)
- Co-Primary endpoints: 1) time to first major adverse cardiovascular event in patients with Lp(a) levels of ≥ 70 mg/dL or 2) patients with Lp(a) levels of ≥ 90 mg/dL. Significance of either endpoint will be considered a positive trial



Enrollment underway • Fast Track Designation
Data expected in 2024

1. A total sample size of 7,680 subjects is required to obtain 993 primary endpoint MACE events. CV: cardiovascular; SC: subcutaneous; MACE: major cardiovascular events

Factor XI

Sanjay Bhanot

Targeting Factor XI reduces thrombosis without an increase in bleeding

IONIS™

Thrombosis

Remains a leading cause of mortality with a high unmet medical need

- **Thrombosis** is the formation of **blood clots** inside blood vessels that can **lead** to **heart attacks**, **strokes**, and **pulmonary embolism**
- **Limitations** of **existing** anticoagulant **therapies**:
  - Although effective they cannot be safely administered in many patients
  - Risk of bleeding restricts ability to give effective treatment for high-risk patients
  - Discontinuation required prior to surgical procedure
  - Narrow therapeutic index makes it difficult to maintain patients within a defined anticoagulation range and some require routine monitoring
- There is a **significant need** for a **drug** that can provide **antithrombotic benefit** with **minimal bleeding risk**
- Because of its **novel mechanism** of action, IONIS-FXI-L_{Rx} has the potential to have a **benefit-to-risk** profile **superior** to existing **anticoagulants**
  - Potential to deliver value in a broader array of indications
  - Potential to be more effective than existing drugs in many indications

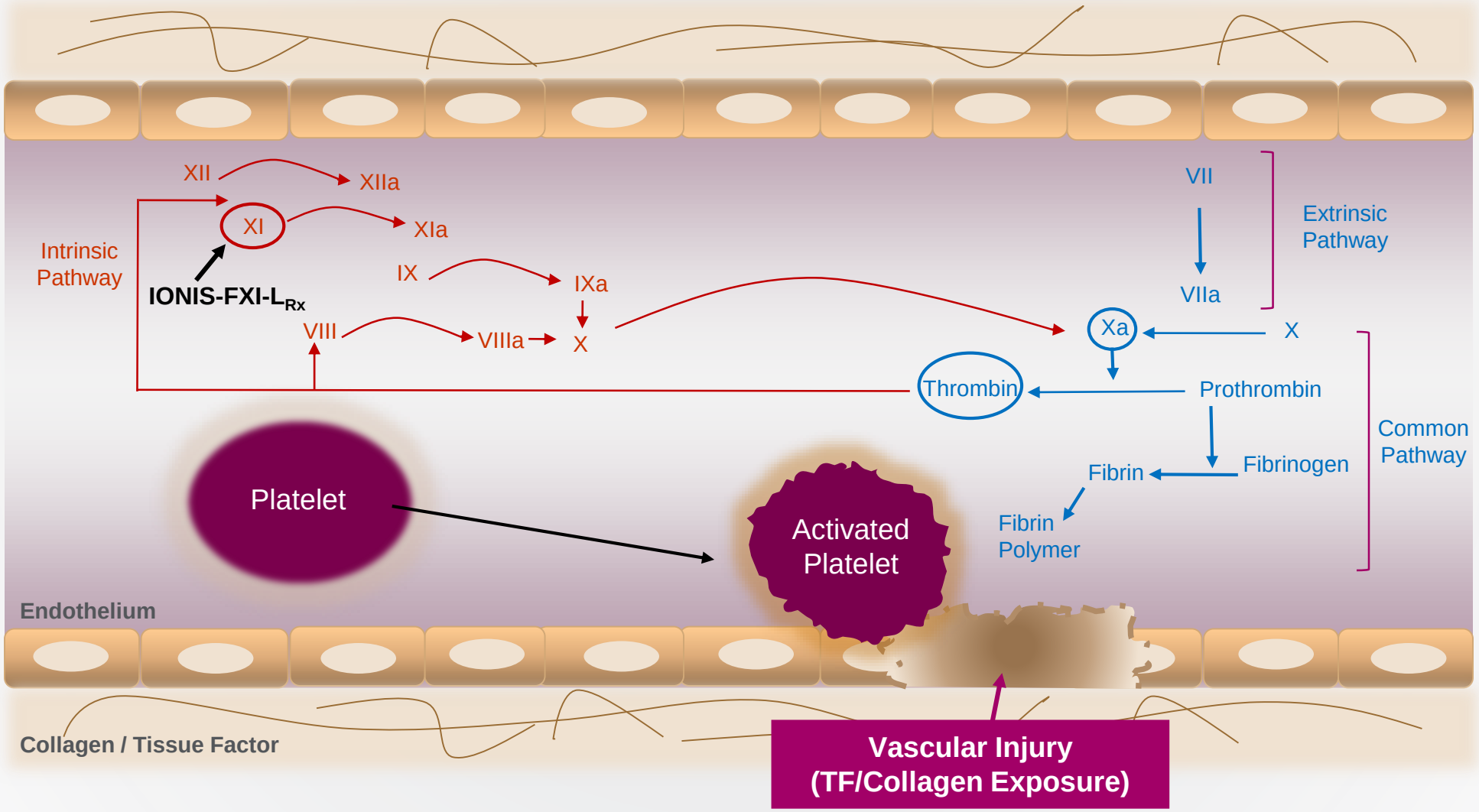
IONIS™

Factor XI (FXI) is a Genetically Validated Target

- **Factor XI** contributes to **thrombosis**:
  - Elevated Factor XI levels lead to increased risk of venous (vein) and arterial (artery) thrombosis and higher incidence of stroke[1,2,3]
  - Lower Factor XI levels are associated with a reduced incidence of venous thrombosis[4]
- **Factor XI deficiency** is **not associated** with **spontaneous bleeding**[5]
- **Inhibition** of **Factor XI** may provide the **ability** to **dissociate** the **antithrombotic effect** of a medicine from **bleeding risk**
- Preclinical data has demonstrated that **Factor XI reduction** is associated with **decreased thrombosis without increased bleeding**[6,7]

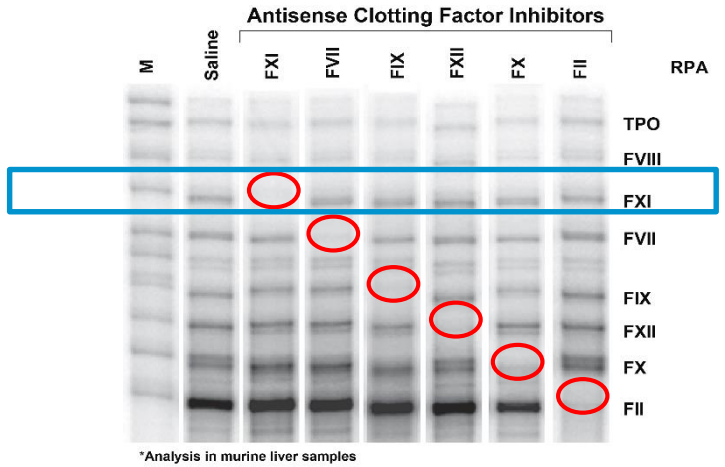
1. Meijers et al. (2000) NEJM. 342,696-701. 2. Doggen et al. (2006) Blood. 108, 4045-4051. 3. Siegerink et al. (2014) J Thromb Haemost. 12, 606-613. 4.Salomon et al. (2011) J Thromb Haemost. 105, 269-273. 5. Duga, S. & Salomon, O. (2013) Semin Thromb Hemost. 39, 621-631. 6. van Montfoort et al. (2014) Arterioscler Thromb Vasc Biol. 34, 1668-1673. 7. Zhang et al. (2010) Blood. 116, 4684-4692.

Inhibiting Factor XI Activity Reduces Clot Propagation, but *NOT* Clot Initiation - Therefore Risk of Bleeding is Low

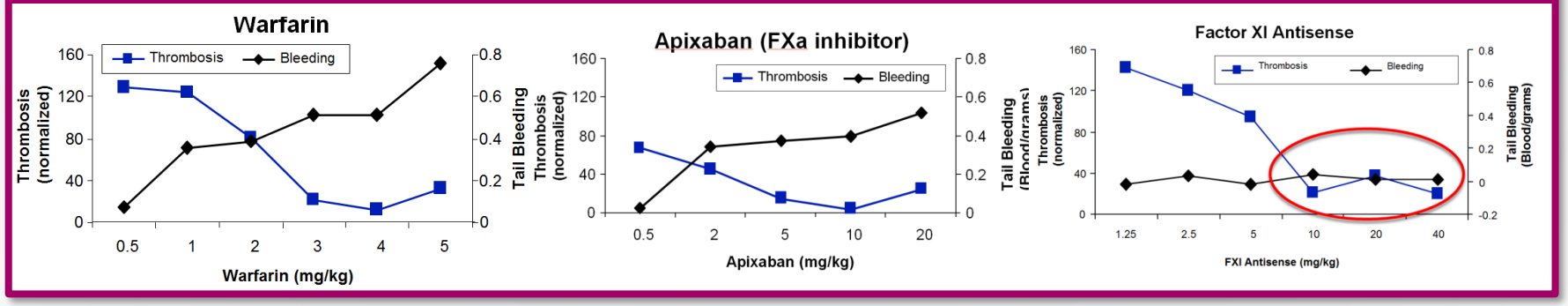


Selective Antisense Reduction of Factor XI Reduced Thrombosis Without Increased Bleeding

Selective Reduction Clotting Factors



Inhibition of Factor XI in Mice: Reduction in Thrombosis Without Increased Bleeding



Phase 2 Data with IONIS-FXI$_{Rx}$ (parent) in Patients Undergoing Total Knee Replacement

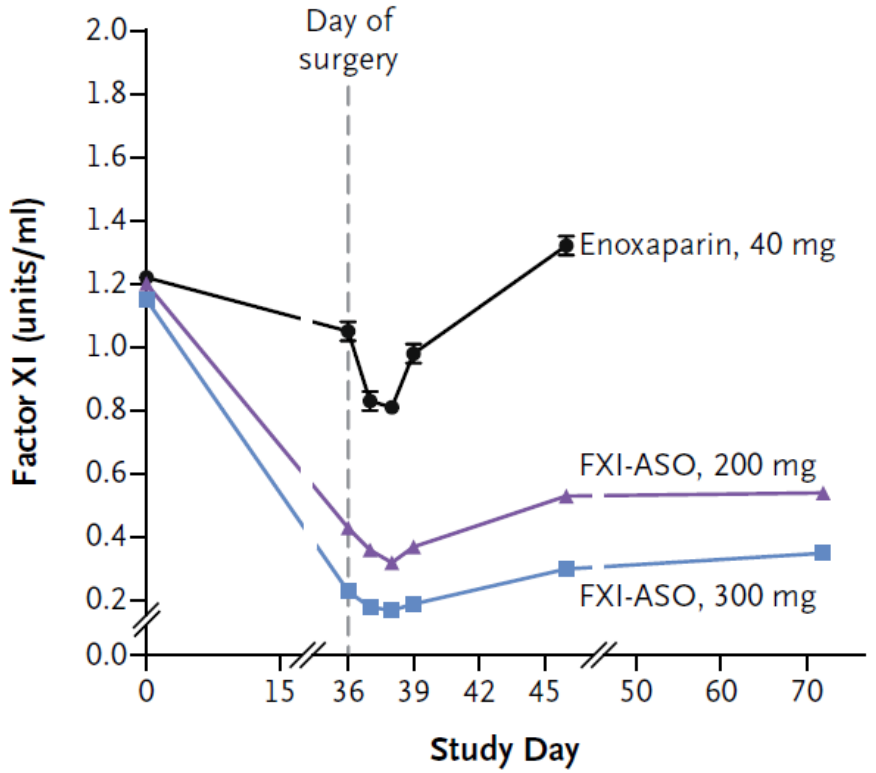
Factor XI validated as an attractive anti-thrombotic target

The NEW ENGLAND JOURNAL of MEDICINE

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D., David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D., Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D., for the FXI-ASO TKA Investigators*

Dose-dependent and Sustained Reductions in FXI Activity



IONIS™

IONIS-FXI$_{Rx}$ Phase 2 Study in Patients Undergoing Total Knee Replacement – Key Findings

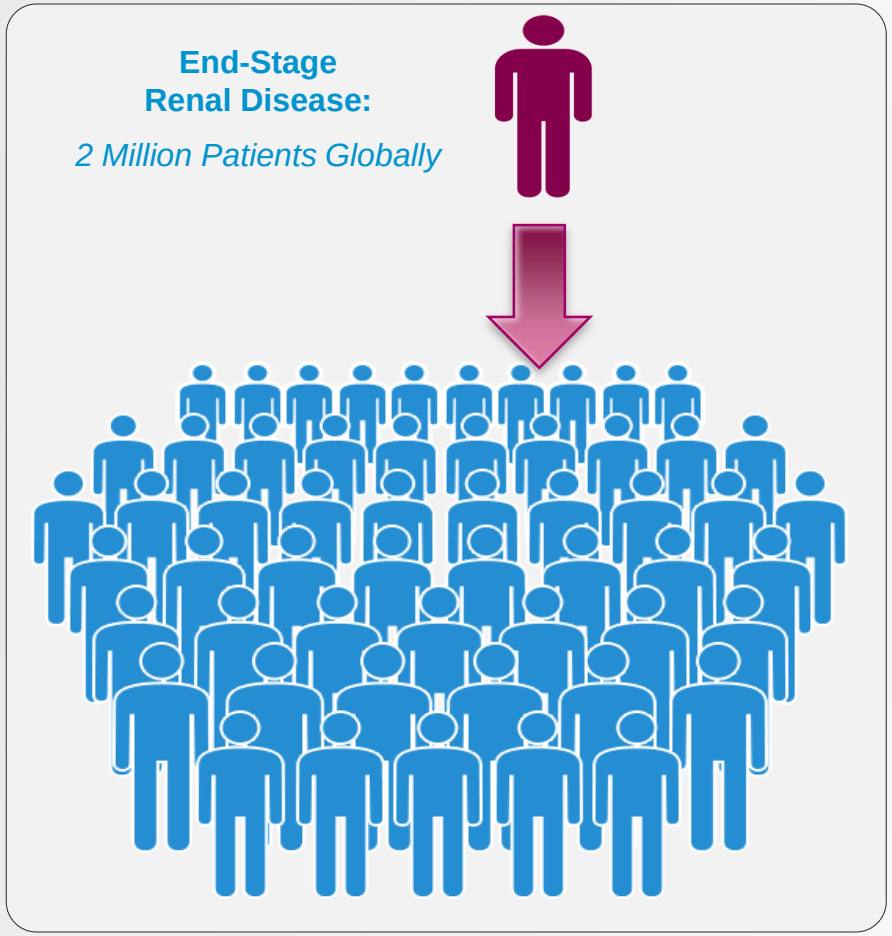
- Patients treated with **IONIS-FXI$_{Rx}$** had **robust** and **sustained decrease** in **Factor XI** activity
- **Substantial reduction in incidence** of **VTE** in postoperative TKA patients treated with **IONIS-FXI$_{Rx}$** compared with enoxaparin treatment
  - 7-fold lower incidence of VTE in patients treated with 300 mg IONIS-FXI$_{Rx}$ compared with enoxaparin-treated patients
- Patients treated with **IONIS-FXI$_{Rx}$** experienced numerically **fewer bleeding events** than with enoxaparin treatment
  - Dissociation between thrombosis and bleeding
- **Favorable safety** and **tolerability** profile supported continued clinical development

IONIS™

Evaluation of IONIS-FXI$_{Rx}$ in Patients with End Stage Renal Disease on Hemodialysis

- ~2 million patients receive dialysis for end stage renal disease (ESRD) globally[1]
  - Prevalence is increasing rapidly

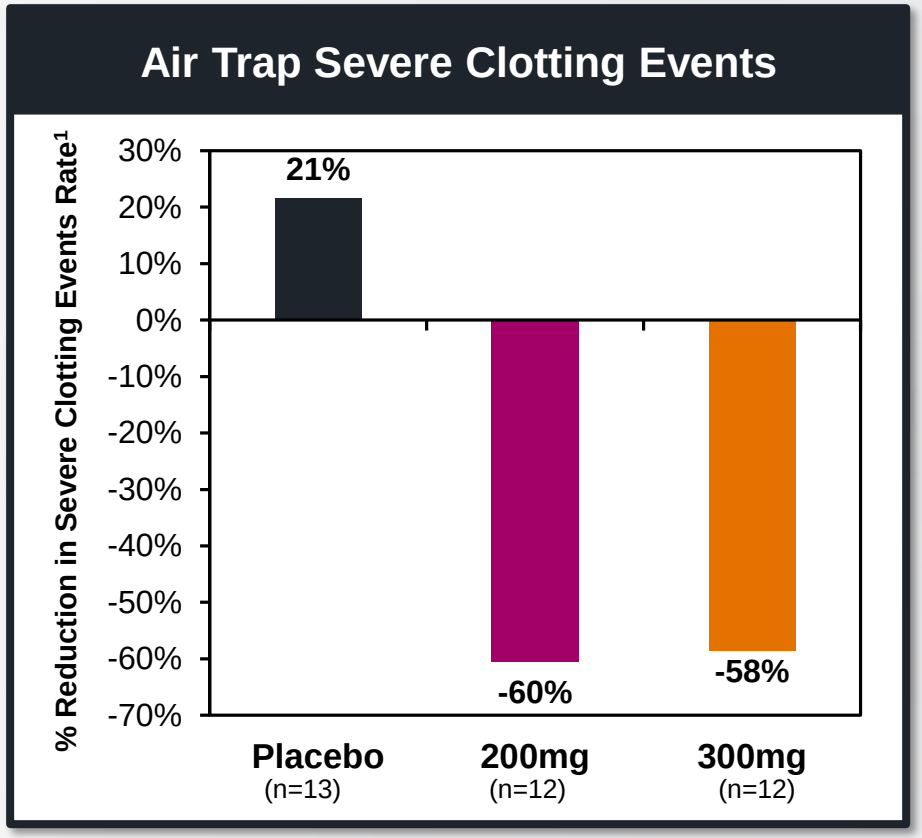
- ESRD patients suffer from numerous thrombotic and bleeding events
  - Risk of stroke is 10x higher than the general population[2]
  - 1 out of every 7 patients will be hospitalized for bleeding within 3 years of starting dialysis[3]

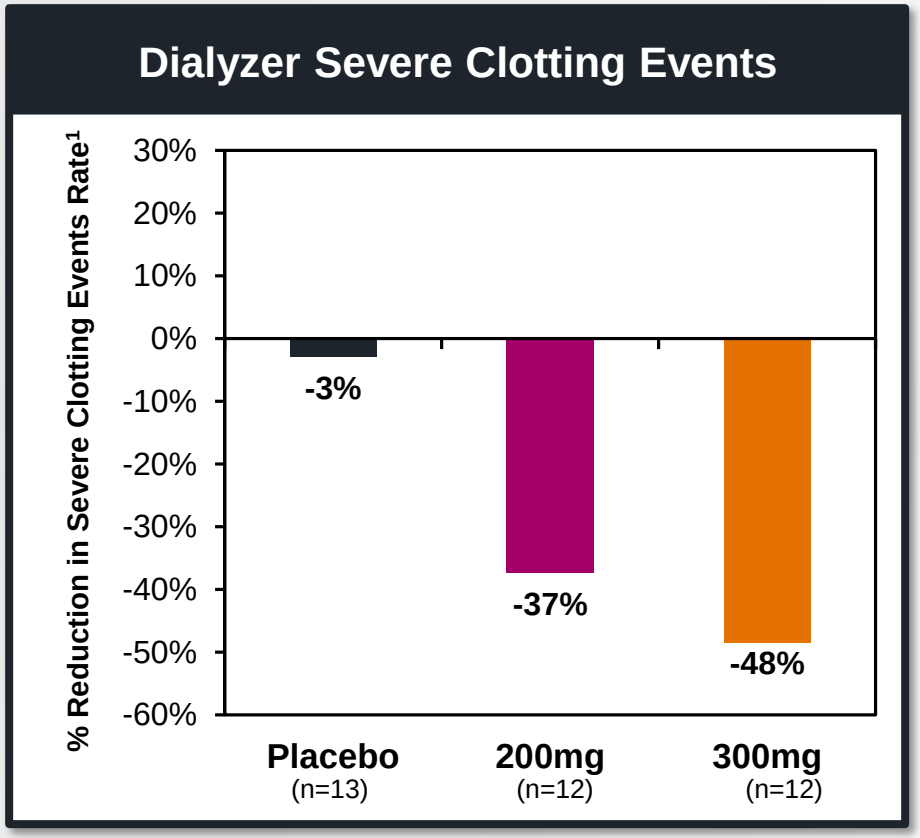


IONIS™

1. National Kidney Foundation. 2. Power, Blood Purif 2013;36:179–183. 3. Sood, et al. Can J Kidney Health Dis. 2014; 1: 21

IONIS-FXI$_{Rx}$ Dose-dependent Reductions in Factor XI Activity Observed in Phase 2 Study in Patients with ESRD





No treatment related major bleedings observed

1. Clotting events measured between week 6 and week 13 inclusive compared to all post-baseline clotting events prior to week 6.

IONIS-FXI$_{Rx}$ Validated FXI as an Anti-thrombotic Target:

Provides support to move forward rapidly with LICA

- **Safety of IONIS-FXI$_{Rx}$ demonstrated** across multiple studies
  - Phase 1 study: No increase in spontaneous bleeding events
  - Phase 2 TKA study: Substantial reduction in postoperative thrombosis without increased bleeding events compared to standard of care in patients undergoing knee surgery
  - Phase 2 ESRD study: No major bleeding events and results similar to Phase 2 TKA study
- **Efficacy of IONIS-FXI$_{Rx}$ in phase 2 studies**
  - Reduction in postoperative thrombotic events
  - Reduction in dialysis circuit clotting events beyond heparin use in ESRD patients
  - FXI activity reduced by 70% or more in all studies
- **Data support moving forward** with the more potent **FXI LICA** medicine

IONIS™

Image source: https://gl.wikipedia.org/wiki/Factor_XI

IONIS-FXI-L_{Rx}

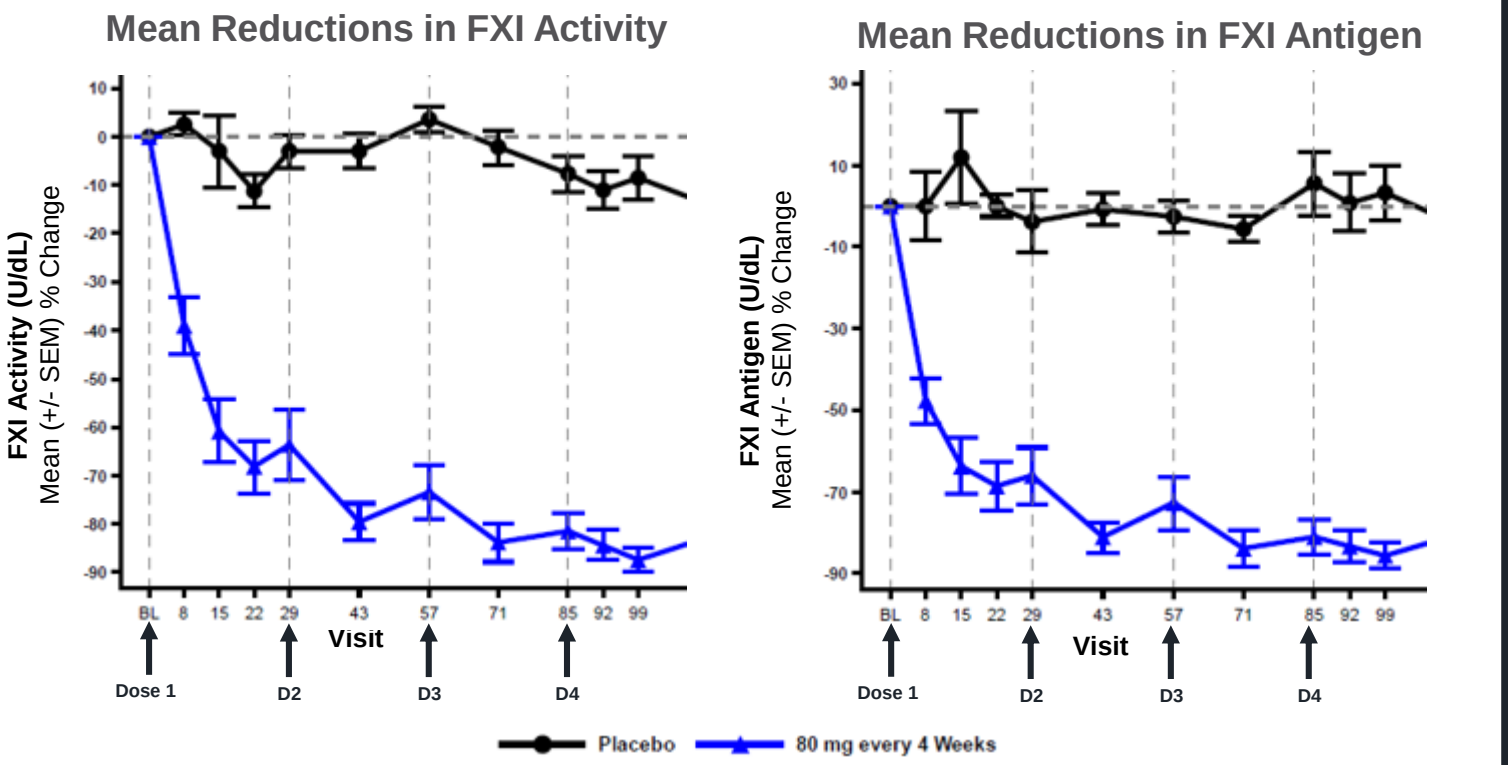
LICA medicine we designed to specifically target Factor XI (FXI) for the treatment of thrombosis

- LICA technology enables more potent, specific reduction in plasma FXI activity without affecting other coagulation factors
- Same sequence as IONIS-FXI_{Rx} (parent FXI compound)
- Phase 1 study completed
- Phase 2b study in patients with End Stage Renal Disease on hemodialysis expected to initiate this year
- Licensed to Bayer

IONIS™

IONIS-FXI-L_{Rx} Demonstrated Robust Reductions in FXI Activity & FXI Antigen with No Spontaneous Bleeding in Phase 1 Study

Greater than 80% Reduction in FXI Sustained Through Four Month Treatment Period



- **Robust** and **sustained FXI reductions** at **all doses** and **regimens**; greater than 80% reductions achieved at 80mg monthly dose
- **Supports monthly dosing** for Phase 2/3 study
- **Well tolerated** at all doses and dose regimens
  - No SAEs reported
  - All AEs were mild or moderate

Advancing Thrombosis Program

- Bayer is expected to **initiate a Phase 2b** study with IONIS-FXI-L_{Rx} in patients with **End Stage Renal Disease** (ESRD) on hemodialysis in 2020
  - Randomized, double-blind, placebo-controlled, dose-escalation study in ~300 ESRD patients
  - Primary objective is to evaluate safety, including bleeding events
  - Additional objectives: evaluate PK and PD
- **Additional anti-thrombotic targets in development**

IONIS™

TTR Cardiomyopathy and Treatment Resistant Hypertension

Richard Geary

IONIS™

TTR Cardiomyopathy

Richard Geary

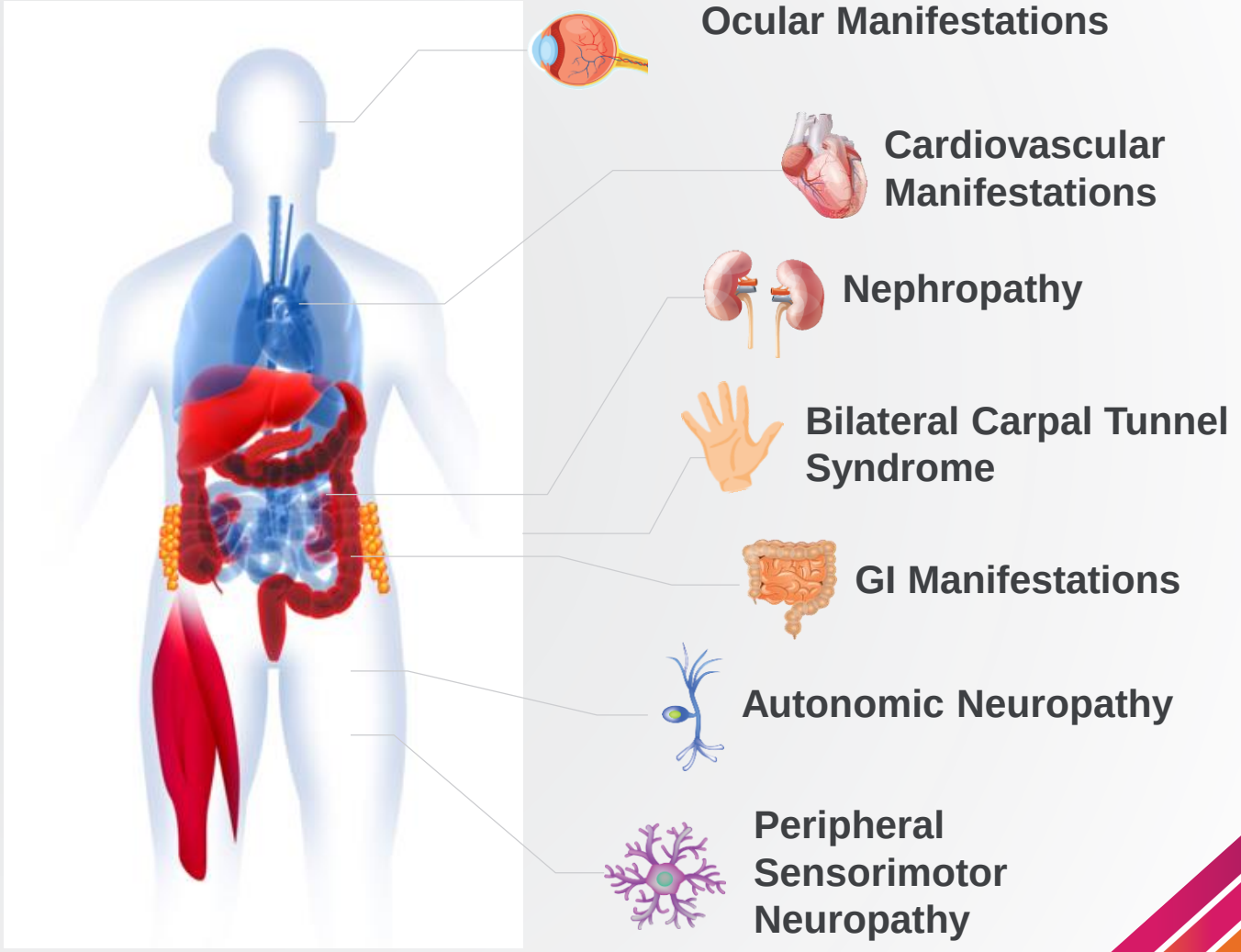
- Fatal disease affecting over 240,000 patients worldwide[1,2]
- Phase 3 CARDIO-TTRansform study of LICA medicine in patients with TTR-Cardiomyopathy underway

1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31.

TTR Amyloidosis (ATTR)

A devastating and fatal disease

- Characterized by the formation of **TTR amyloid deposits** leading to multi-organ failure[1,2]
- Patients suffer from progressive **neuropathy**, **cardiac disease**, **nephropathy** and **gastrointestinal symptoms**
- Progressive disease resulting in a **rapid decline** in **quality of life** and a 3-15 year life expectancy[3] and 2-5 years with cardiac involvement[4]



GI, gastrointestinal. 1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31. 3. Gertz MA. *Am J Manag Care*. 2017;23:S107-S112. 4. Maurer MS et al. *Circulation*. 2017;135:1357-1377.

Multiple Ongoing Investigator Initiated Studies Evaluating Inotersen in ATTR Cardiomyopathy Patients

- **Dr. Rodney Falk study at Brigham and Women's Hospital**
  - Up to 50 patients
  - Open-label up to 2 years, initiated 2019
  - Objectives
    - Safety and tolerability
    - Efficacy vs. patient history and disease natural history
- **Benson & Dasgupta Study at the Indiana University School of Medicine**
  - Up to 45 patients
  - Open-label up to 5 years, initiated 2014
  - Objectives
    - Safety and tolerability
    - Efficacy vs. disease natural history

IONIS™

Inotersen in Patients with TTR Cardiomyopathy

Benson & Dasgupta Investigator Initiated Study (Indiana University School of Medicine)

- **Compassionate** use **trial** started in **August 2014** to evaluate the safety and tolerability of inotersen in patients with TTR cardiomyopathy
- **Long-term experience**
  - 27 actively enrolled patients (February 2020) with five patients on treatment for more than 5 years
- **Favorable safety** and **tolerability** profile
  - No severe thrombocytopenia or drug-related renal adverse events
- **Demonstrated efficacy at 3 years** compared to natural history
  - Improved 6-minute walk distance
  - Reduced left ventricular mass
  - Decrease in mean BNP compared to baseline

IONIS™

Noel R. Dasgupta, Stacy M. Rissing, Jessica Smith, Jeesun Jung & Merrill D. Benson (2020) Inotersen therapy of transthyretin amyloid cardiomyopathy, Amyloid, 27:1, 52-58, DOI: 10.1080/13506129.2019.1685487

AKCEA-TTR-L_{Rx}

LICA medicine we designed to specifically target TTR for the treatment of ATTR-Cardiomyopathy

- Phase 3 CARDIO-TTRansform of LICA medicine in patients with ATTR-cardiomyopathy underway
- Robust target reduction demonstrated in Phase 1 study
- Data expected in 2023

IONIS™

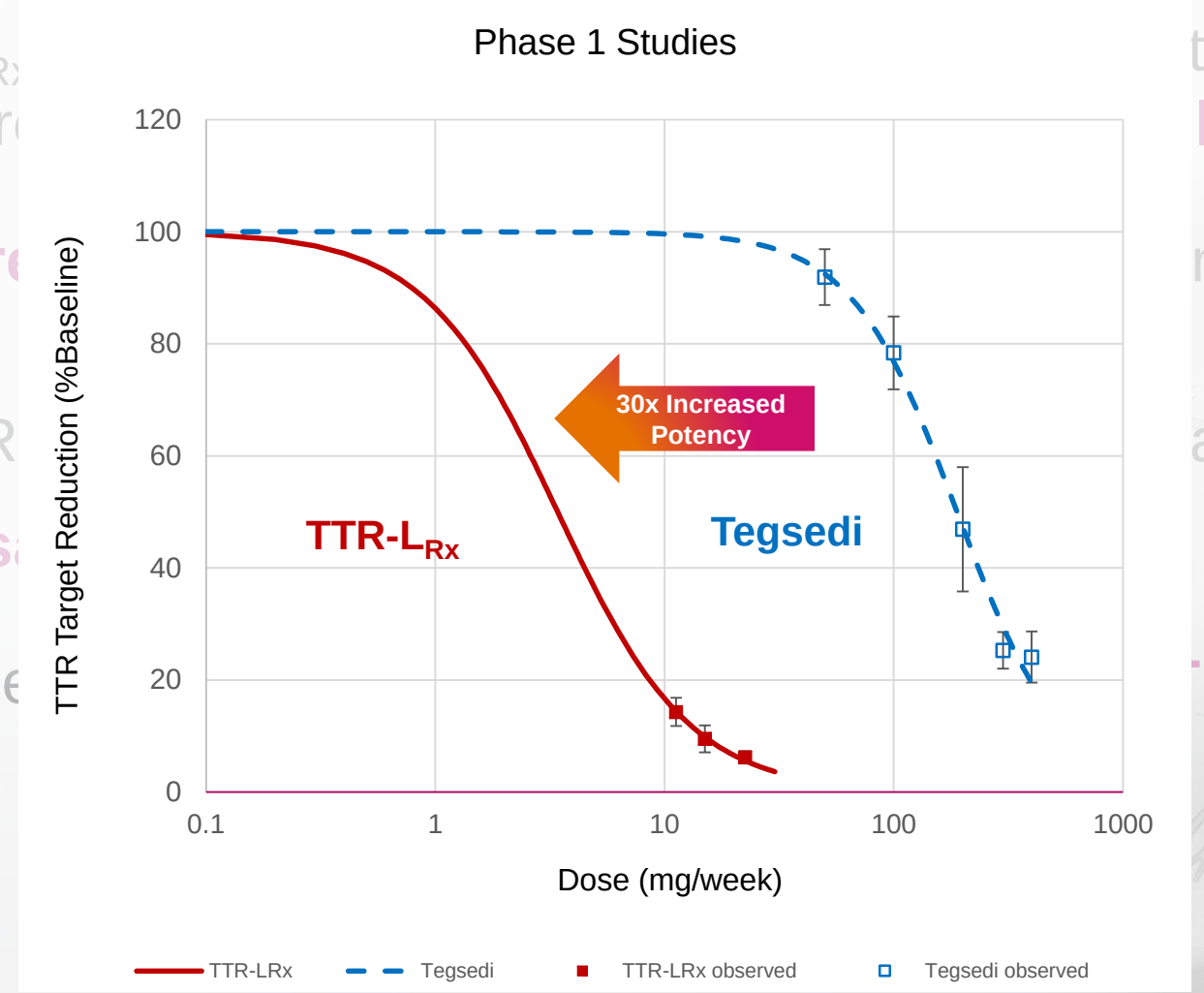
AKCEA-TTR-L_{Rx}: A Follow-On Medicine to TEGSEDI that Expands Our ATTR Franchise

- AKCEA-TTR-L_{Rx} utilizes our highly advanced **LICA** chemistry, providing high **potency** with greatly **improved convenience** and **tolerability**
- **Robust** target **reduction** and **positive safety** profile demonstrated in healthy volunteers
  - **Robust** TTR **reductions** of greater than **90%** demonstrated
  - **Favorable safety** and **tolerability** observed
- **Enrolling** Phase 3 studies in patients with all **forms** of **ATTR**

IONIS™

AKCEA-TTR-L_{Rx}: A Follow-On Medicine to TEGSEDI that Expands Our ATTR Franchise

- AKCEA-TTR-L_{Rx} **potency** with gr try, providing high lity
- **Robust** target re nstrated in healthy volunteers
  - **Robust** TTR ated
  - **Favorable** sa
- **Enrolling** Phase TR

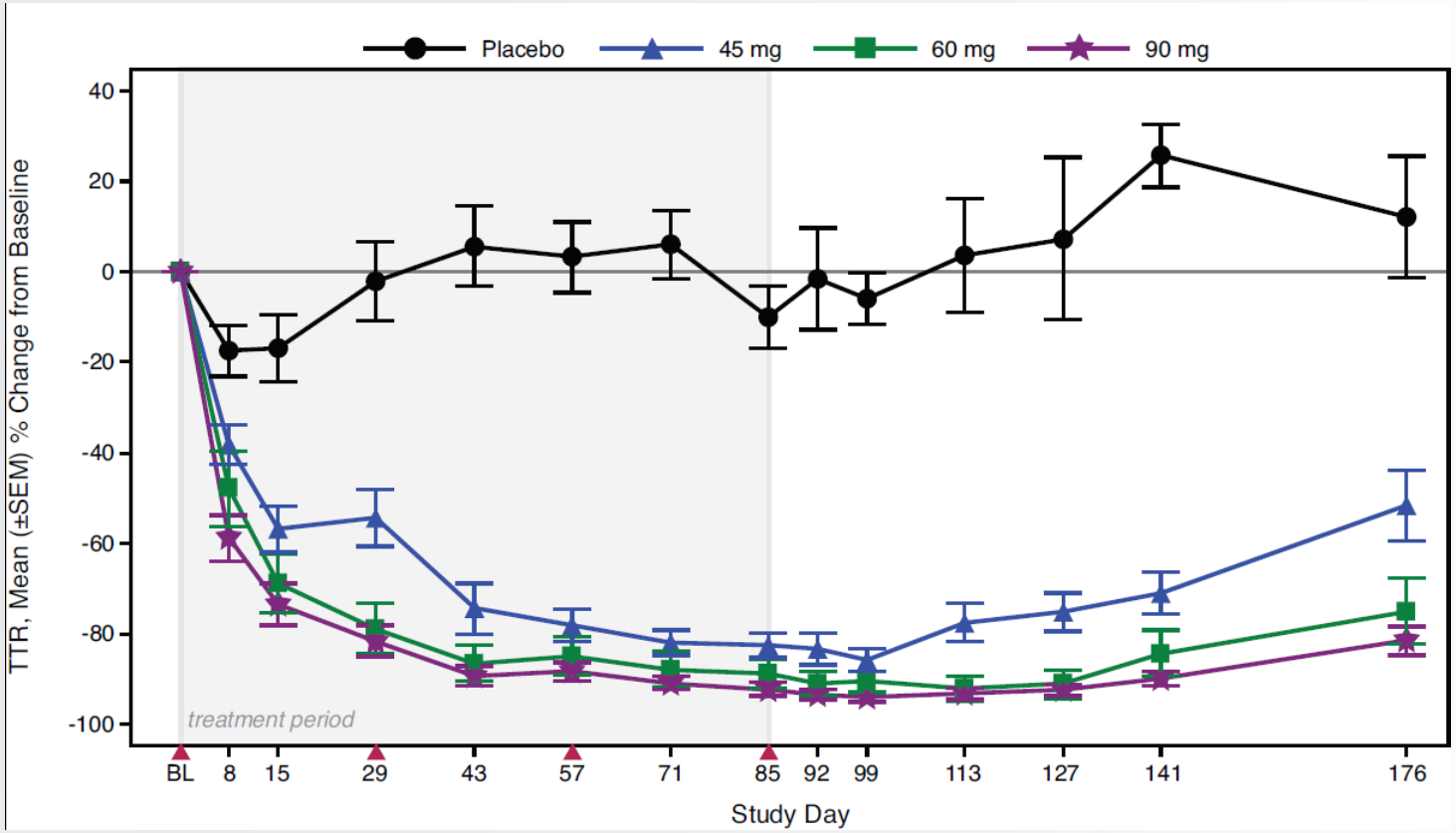


AKCEA-TTR-L_{Rx}

Dose-dependent reductions in TTR levels in healthy volunteers

Phase 1 Study in Healthy Volunteers

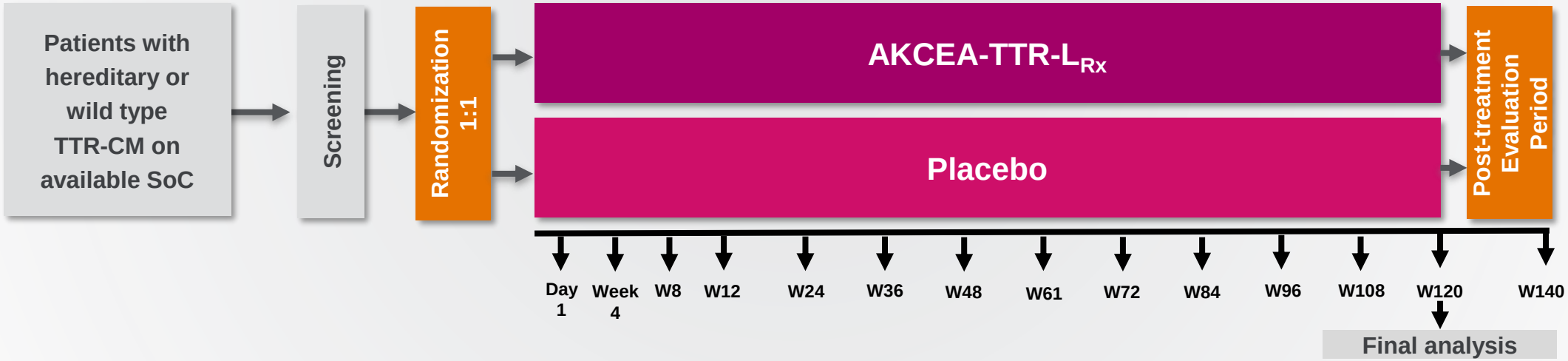
- Achieved a mean reduction in TTR levels of 94% in highest dose group
- Adverse events (AEs) were mild
- No AEs led to an interruption in dosing
- There were no severe adverse events in patients treated with AKCEA-TTR-L_{Rx}



AKCEA-TTR-L_{Rx} CARDIO-TTRansform

Phase 3 study in patients with ATTR-cardiomyopathy underway

- A global, randomized, double-blind, placebo-controlled study in up to 750 patients with hereditary or wild-type TTR amyloid cardiomyopathy receiving monthly subcutaneous AKCEA-TTR-L_{Rx} or placebo
- Primary endpoint: Cardiovascular death and frequency of cardiovascular clinical events at week 120
- Secondary endpoints:
  - Change from baseline at 120 weeks: 6MWT, patient-reported outcomes (KCCQ), rate of CV death and clinical events
  - Exploratory endpoints: Echo, biomarkers



Enrollment underway • Data expected in 2023

Treatment Resistant Hypertension

A leading cause of cardiovascular disease

IONIS™

Treatment-Resistant Hypertension is a Major Contributor to Cardiovascular Disease

- **Hypertension** is defined as blood pressure (BP) >140/90 (systolic/diastolic) and if **untreated** can increase the **risk fatal** and **non-fatal cardiovascular events** (death, heart disease, stroke)
- **TRH** is defined as BP >140/90 **despite** the use of **3 or more** different antihypertensive medications of different mechanisms[1]
- ~75 million adults in the U.S. have hypertension, of which, **~5 million** have treatment resistant hypertension (TRH)
- People with **TRH** have up to a **3-fold increased risk** of having **fatal** and **non-fatal cardiovascular events** relative to those with controlled hypertension

IONIS™

1. Vemulapalli et al, Proceedings from Duke Resistant HTN Think Tank AHJ 2014. Judd E, Calhoun DA.

IONIS-AGT-L_{Rx}

LICA medicine we designed to specifically target AGT for the treatment of people with treatment resistant hypertension

- LICA medicine to inhibit the production of angiotensinogen to decrease blood pressure
- Superior efficacy and tolerability compared to ACE & ARB demonstrated in preclinical studies
- Results from two Phase 2 studies in patients with hypertension expected in 2020

IONIS™

IONIS-AGT-L_{Rx}: Designed to Reduce Angiotensinogen to Decrease Blood Pressure in TRH Patients

- **IONIS-AGT-L_{Rx} targets AGT** in the liver in the most **upstream** substrate in renin-angiotensin-aldosterone system (**RAAS**), which is a well-established pathway of **treating hypertension** and **complications** of **hypertension**
  - AGT is upstream of angiotensin converting enzyme (ACE) and angiotensin receptor blockers (ARBs) in the RAAS pathway
- IONIS-AGT-L_{Rx} is designed to **reduce hepatic AGT**, while **maintaining renal compensatory mechanisms** by minimizing inhibition on renal ANGII
  - The therapeutic index of inhibitors targeting downstream components of RAAS that act in the kidney is limited due to their propensity to hyperkalemia and acute renal failure (ARF) in some patients
  - A liver-targeting approach is predicted to have a superior therapeutic index

IONIS™

Ionis' Robust Development Program Targeting Treatment Resistant Hypertension

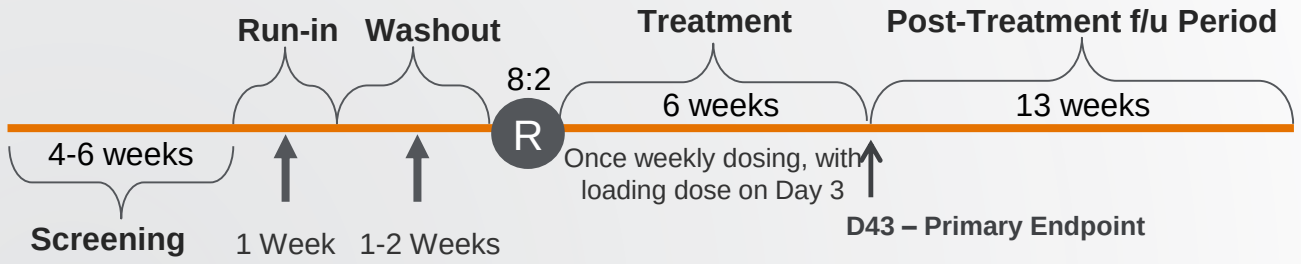
- In a **pre-clinical** model of a hypertensive rat, we saw **robust blood pressure lowering** and **up to 90% reductions** in **AGT**
- Evaluating **IONIS-AGT-L_{Rx}** in **two Phase 2 studies** with data expected in 2020
  - Mild hypertension: 25 patients with controlled HTN on 2 medications, one of which is an ACE inhibitor or ARB
  - Uncontrolled hypertension: Up to 30 patients with uncontrolled HTN on 2-3 medications, one of which is an ACE inhibitor or ARB

IONIS™

Evaluating IONIS-AGT-L_{Rx} in Two Phase 2 Clinical Studies with Data Expected in 2020

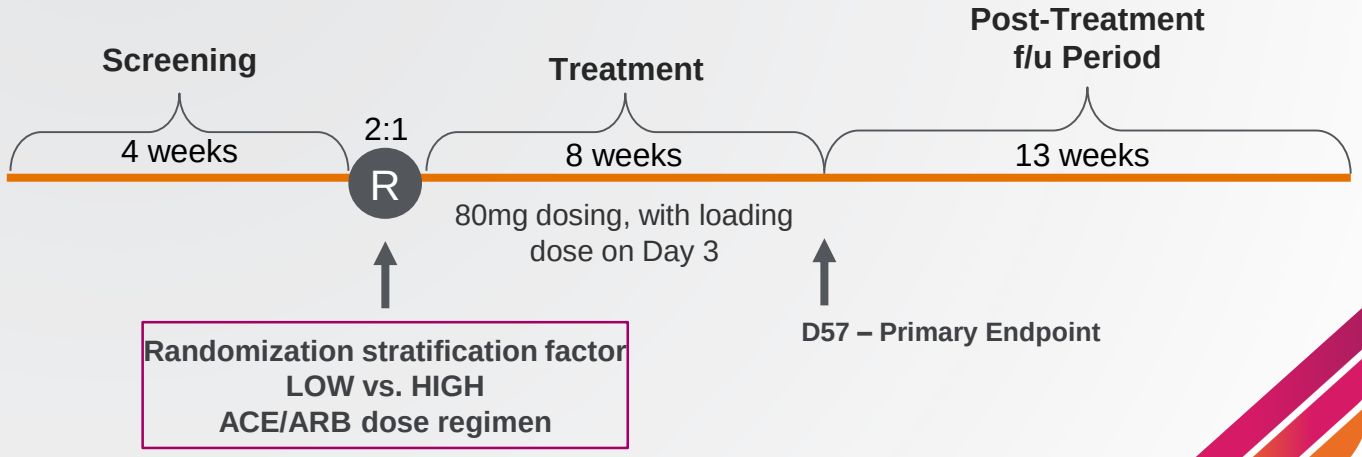
Phase 2 study in patients with mild HTN

- 25 patients with controlled HTN on 2 medications, one of which is an ACE or ARB, washed out and treated with 80 mg/wk IONIS-AGT-L_{Rx} or placebo subcutaneous injections
- **Objectives**: AGT lowering, SBP lowering, safety and tolerability (hyperkalemia, hypotension, ARF)
- **Exploratory**: Evaluate pharmacokinetics and RAAS analytes



Phase 2 study in patients with uncontrolled HTN

- Up to 30 patients with uncontrolled HTN on 2-3 medications, one of which is an ACE or ARB, treated with 80 mg/wk IONIS-AGT-L_{Rx} or placebo subcutaneous injections
- **Objectives**: AGT lowering, SBP lowering, safety and tolerability (hyperkalemia, hypotension, ARF)
- **Exploratory**: Evaluate pharmacokinetics and RAAS analytes



IONIS-AGT-L_{Rx} Program Summary and Next Steps

- In **pre-clinical** studies, **reduction** of **AGT** by IONIS-AGT-L_{Rx} results in **superior efficacy** & **tolerability** compared ACE inhibitor or ARB[1]
- **Data** from both Phase 2 studies **expected this year**

IONIS™

1. Mullick, et al. BP Lowering and Safety Improvements with Liver Angiotensinogen Inhibition in Models of Hypertension and Kidney Injury. Hypertension 2017

Ionis: Leading the way in targeting cardiovascular diseases

Brett Monia

IONIS

Investing in All Aspects of our Technology to Further Increase our Impact on the Treatment of Human Diseases

INVESTMENTS	IMPACT
Improved Drug Candidate Selection Processes	• Improved drug discovery efficiency • Improved overall drug performance
Human Genomics Investments	• Novel target identification • Improved drug discovery efficiency (e.g. patient selection, biomarkers, disease natural history) • Increased probability for clinical success
New Routes of Delivery	• Even more patient convenience (e.g. oral) • Opens up new target organs/cell types (e.g. pulmonary, ocular)
Medicinal Chemistry (e.g. LICA)	• Even more patient convenience (e.g. monthly, quarterly dosing) • Opens up new target organs/cell types (e.g. cardiac, muscle, immune) • Enhanced overall safety and efficacy performance

Next Wave of Potential Commercial Products

Anticipated marketing applications for cardiovascular disease medicines through 2025 and beyond

2021			2025 and beyond
		ION363 *FUS-ALS*	**IONIS-FXI-L$_{Rx}$** *ESRD*
		AKCEA-APOCIII-L$_{Rx}$ *Severe hypertriglyceridemia*	**ION541** *Sporadic ALS*
		ION373 *Alexander disease*	**IONIS-TMPRSS6-L$_{Rx}$** *β-thalassemia*
		IONIS-GHR-L$_{Rx}$ *Acromegaly*	**IONIS-HBV$_{Rx}$** *Hepatitis B virus infection*
	AKCEA-APOCIII-L$_{Rx}$ *FCS*	**IONIS-C9$_{Rx}$** *C9-ALS*	**Vupanorsen** (AKCEA-ANGPTL3-L$_{Rx}$) *CV/metabolic disease*
	Tominersen (IONIS-HTT$_{Rx}$) *Huntington's disease*	**IONIS-PKK-L$_{Rx}$** *Hereditary angioedema*	**ION716** *Prion diseases*
Tofersen (IONIS-SOD1$_{Rx}$) *SOD1-ALS*	**AKCEA-TTR-L$_{Rx}$** *hATTR polyneuropathy*	**AKCEA-TTR-L$_{Rx}$** *ATTR cardiomyopathy*	**Pelacarsen** (AKCEA-APO(a)-L$_{Rx}$) *Cardiovascular disease*

IONIS™

Investor Day 2020

Ionis to host Investor Day 2020
in early December

IONIS™

Q&A Session

IONIS

IONIS™

A commitment
to **science,**
to **medicine**
and to **patients**