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.

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Today’s Presenters

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

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

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

Richard Geary, Ph.D.
EVP, Development
Ionis Pharmaceuticals
### Today’s Agenda

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<td>- Medicines Targeting Triglyceride-driven Diseases</td>
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<td>All</td>
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</table>
Ionis – The Leader in RNA-targeted Drug Discovery and Development

Brett Monia
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
Delivering Medicines for Most Major Severe Diseases

NEUROLOGICAL

NEUROMUSCULAR

CARDIOVASCULAR

HEMATOLOGICAL

KIDNEY

OPHTHALMOLOGY

INFECTIOUS DISEASE

≥ 10 Marketing Applications through 2025
Delivering Medicines for Most Major Severe Diseases

NEUROLOGICAL

NEUROMUSCULAR

CARDIOVASCULAR

Ultra-rare to Common Diseases

HEMATOLOGICAL

KIDNEY

OPHTHALMOLOGY

INFECTIOUS DISEASE
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
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
All Medicines Targeting Cardiovascular Diseases Utilize Our LICA Technology

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>INDICATION</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
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<td>Pelacarsen\textsuperscript{1}</td>
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1. Previously AKCEA-APO\text{a}(a)-L\text{Rx}; 2. Previously AKCEA-ANGPTL3-L\text{Rx}
Ionis: Leading the Way in Targeting Cardiovascular Diseases

Sam Tsimikas
# Cardiovascular Disease Franchise Pipeline

<table>
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<tr>
<th>MEDICINE</th>
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1. Previously AKCEA-APO(a)-L<sub>Rx</sub>; 2. Previously AKCEA-ANGPTL3-L<sub>Rx</sub>
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1. Previously AKCEA-APO(a)-L<sub>Rx</sub>; 2. Previously AKCEA-ANGPTL3-L<sub>Rx</sub>
Apolipoprotein C-III (apoC-III)

Targeting apoC-III for patient diseases driven by high triglycerides
ApoC-III is a Genetically Validated Target for Triglyceride-driven Diseases

- 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

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

AKCEA-APOCIII-LRx

LICA medicine we designed to specifically target apoC-III for reduction of CVD risk
AKCEA-APOCIII-L_{Rx} Phase 2 Study Design

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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monthly equivalent dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg AKCEA-APOCIII-L_{Rx} or placebo Q4W</td>
<td>10</td>
</tr>
<tr>
<td>15 mg AKCEA-APOCIII-L_{Rx} or placebo Q2W</td>
<td>30</td>
</tr>
<tr>
<td>10 mg AKCEA-APOCIII-L_{Rx} or placebo QW</td>
<td>40</td>
</tr>
<tr>
<td>50 mg AKCEA-APOCIII-L_{Rx} or placebo Q4W</td>
<td>50</td>
</tr>
</tbody>
</table>

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

Screening and Diet Run-in
Up to 5 weeks

Treatment duration:
Min 6 months, max 12 months

Follow up
13 weeks

QW=every week
Q2W= every 2 weeks
Q4W=every 4 weeks
R-randomization
AKCEA-APOCIII-L\textsubscript{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\textsubscript{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.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of patients</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Pooled Placebo</td>
<td>4%</td>
<td>p&lt;0.2590</td>
</tr>
<tr>
<td>10 mg Q4W</td>
<td>14%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>15 mg Q2W</td>
<td>65%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>10 mg QW</td>
<td>76%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>50 mg Q4W</td>
<td>91%</td>
<td>p&lt;0.0001</td>
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</table>

Error bars denote the 95% CI P-values vs. pooled placebo QW=every week, Q4W=every 4 weeks TG=triglycerides
AKCEA-APOCIII-LRx 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)

*P=<0.05, **P=<0.01, *** P=<0.0001 versus placebo

*estimated using Martin’s equation, ultracentrifugation results pending

Martin SS et al, JAMA 2013;310:2061
AKCEA-APOCIII-L<sub>Rx</sub> Demonstrated a Favorable Safety and Tolerability Profile in Phase 2 Study

<table>
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<tr>
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<th>Placebo pooled N=24</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>10 mg Q4W N=22</td>
<td>15 mg Q2W N=23</td>
<td>10 mg QW N=26</td>
<td>50 mg Q4W N=22</td>
<td>Pooled N=90</td>
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<tr>
<td>Any TEAE&lt;sup&gt;*&lt;/sup&gt;</td>
<td>20 (83.3%)</td>
<td>17 (77.3%)</td>
<td>20 (87.0%)</td>
<td>22 (95.7%)</td>
<td>21 (95.5%)</td>
<td>80 (88.9%)</td>
</tr>
<tr>
<td>Serious TEAE&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1 (4.2%)</td>
<td>3 (13.6%)</td>
<td>3 (13%)</td>
<td>1 (4.3%)</td>
<td>2 (9.1%)</td>
<td>9 (10.0%)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation&lt;sup&gt;***&lt;/sup&gt;</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>1 (4.3%)</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>2 (2.2%)</td>
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<tr>
<td>TEAE leading to death&lt;sup&gt;****&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>0</td>
<td>1 (1.1%)</td>
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</table>

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<sub>Rx</sub> 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)
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
Angiopoietin-like 3 (ANGPTL3)

Targeting ANGPTL3 for patient diseases driven by high triglycerides and cholesterol
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
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
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

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 HbA₁c and HOMA-IR
- Hepatic steatosis parameters including hepatic fat fraction (HFF, by MRI), and fatty liver index (FLI)
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
Vupanorsen Phase 2 Met Multiple Secondary Endpoints

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

*P<0.05, **P<0.01, *** P<0.0001 versus placebo
Vupanorsen Demonstrated a Favorable Safety and Tolerability Profile in Phase 2 Study

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<td>40 mg Q4W</td>
<td>80 mg Q4W</td>
<td>20 mg QW</td>
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<td>N=26</td>
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<td>N=26</td>
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<tr>
<td>Any TEAE*</td>
<td>16 (59.3%)</td>
<td>19 (73.1%)</td>
<td>23 (88.5)</td>
<td>23 (88.5)</td>
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<td>Serious TEAE**</td>
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<td>0</td>
<td>0</td>
<td>1 (3.8%)</td>
<td>1 (1.3%)</td>
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<tr>
<td>TEAE leading to</td>
<td>0</td>
<td>1 (3.8%)</td>
<td>2 (7.7%)</td>
<td>3 (11.5%)</td>
<td>6 (7.7%)</td>
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<td>discontinuation***</td>
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<tr>
<td>TEAE leading to death</td>
<td>0</td>
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</table>

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)
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
Lipoprotein(a) 
Lp(a)

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

Only pelacarsen (TQJ230, AKCEA-APO(a)-LRx) 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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>Weekly</td>
</tr>
<tr>
<td>20 mg</td>
<td>Bi-weekly</td>
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<tr>
<td>20 mg</td>
<td>Monthly</td>
</tr>
<tr>
<td>40 mg</td>
<td>Monthly</td>
</tr>
<tr>
<td>60 mg</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

Weekly, Every 2 Weeks, or Monthly SC Injections

Screening & Diet Stabilization

26 weeks min last patient in & up to 52 weeks

Follow-up Period

16 weeks
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)

<table>
<thead>
<tr>
<th>Monthly Total</th>
<th>20 mg/Q4W</th>
<th>40 mg/Q4W</th>
<th>60 mg/Q4W</th>
<th>20 mg/Q2W</th>
<th>40 mg/Q2W</th>
<th>60 mg/Q2W</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled Placebo</td>
<td>6.4</td>
<td>25.0</td>
<td>62.5</td>
<td>64.6</td>
<td>80.9</td>
<td>97.7</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>20 mg</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

≤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**
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
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\textsubscript{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
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\(^6,7\)

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

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*
IONIS-FXI\textsubscript{Rx} Phase 2 Study in Patients Undergoing Total Knee Replacement – Key Findings

• Patients treated with IONIS-FXI\textsubscript{Rx} had robust and sustained decrease in Factor XI activity

• Substantial reduction in incidence of VTE in postoperative TKA patients treated with IONIS-FXI\textsubscript{Rx} compared with enoxaparin treatment
  • 7-fold lower incidence of VTE in patients treated with 300 mg IONIS-FXI\textsubscript{Rx} compared with enoxaparin-treated patients

• Patients treated with IONIS-FXI\textsubscript{Rx} experienced numerically fewer bleeding events than with enoxaparin treatment
  • Dissociation between thrombosis and bleeding

• Favorable safety and tolerability profile supported continued clinical development
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-FXI<sub>Rx</sub> 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<sub>Rx</sub> Validated FXI as an Anti-thrombotic Target:**
Provides support to move forward rapidly with LICA

- **Safety of IONIS-FXI<sub>Rx</sub> 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<sub>Rx</sub> 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

Image source: https://en.wikipedia.org/wiki/Factor_XI
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-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
TTR Cardiomyopathy and Treatment Resistant Hypertension

Richard Geary
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

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\(^4\)

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
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

• 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
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
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%
  - Favorable safety and tolerability observed
- Enrolling Phase 3 studies in patients with all forms of ATTR.

![Phase 1 Studies Graph]

- 30x Increased Potency

- TTR-L_{Rx} observed
- Tegsedi observed

<table>
<thead>
<tr>
<th>Dose (mg/week)</th>
<th>TTR Target Reduction (%Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>120</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>1000</td>
<td>40</td>
</tr>
</tbody>
</table>
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

Patients with hereditary or wild type TTR-CM on available SoC

Enrollment underway • Data expected in 2023
Treatment Resistant Hypertension

A leading cause of cardiovascular disease
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 of **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.

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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-AGT-L\textsubscript{Rx}: Designed to Reduce Angiotensinogen to Decrease Blood Pressure in TRH Patients

- IONIS-AGT-L\textsubscript{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\textsubscript{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’ 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.
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 to ACE inhibitor or ARB$^1$

- Data from both Phase 2 studies expected this year

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Ionis: Leading the way in targeting cardiovascular diseases

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

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

Anticipated marketing applications for cardiovascular disease medicines through 2025 and beyond

- **Tofersen (IONIS-SOD1_Rx)**
  - *SOD1-ALS*

- **ION363**
  - *FUS-ALS*

- **AKCEA-APOCIII-L_Rx**
  - *Severe hypertriglyceridemia*

- **ION373**
  - *Alexander disease*

- **IONIS-GHR-L_Rx**
  - *Acromegaly*

- **IONIS-C9_Rx**
  - *C9-ALS*

- **ION541**
  - *Sporadic ALS*

- **IONIS-TMPRSS6-L_Rx**
  - *β-thalassemia*

- **ION716**
  - *Prion diseases*

- **Vupanorsen (AKCEA-ANGPTL3-L_Rx)**
  - *CV/metabolic disease*

- **IONIS-HBV_Rx**
  - *Hepatitis B virus infection*

- **AKCEA-TTR-L_Rx**
  - *hATTR polyneuropathy*

- **AKCEA-TTR-L_Rx**
  - *ATTR cardiomyopathy*

- **IONIS-FXI-L_Rx**
  - *ESRD*

- **AKCEA-PKK-L_Rx**
  - *Hereditary angioedema*

- **IONIS-APOL1-L_Rx**
  - *Severe hypertriglyceridemia*

- **IONIS-ANGPTL3-L_Rx**
  - *CV/metabolic disease*

- **Pelacarsen (AKCEA-APO(a)-L_Rx)**
  - *Cardiovascular disease*
Investor Day 2020

Ionis to host Investor Day 2020 in early December
Q&A Session
A commitment to science, to medicine and to patients