



# 2021 Annual Meeting of Stockholders Corporate Presentation

**June 2021**



# Changes to the Ionis Board of Directors (1 of 2)

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## Departures

**Stanley T. Crooke, M.D., Ph.D.**

Ionis Founder and Executive Chairman  
30 Years of Ionis Leadership

**Breaux B. Castleman**

8 Year Board Member  
Audit Committee

# Changes to the Ionis Board of Directors (2 of 2)

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## **Joseph Loscalzo, M.D., Ph.D.**

Appointed Chairman  
Seven years Ionis Board Member

## **Allene M. Diaz**

New Board Member

## **Joseph H. Wender**

Lead Independent Director

Spencer R. Berthelsen, M.D.

Joan E. Herman

Joseph Klein, III

B. Lynne Parshall, Esq.

Brett P. Monia, Ph.D.

Frederick T. Muto, Esq.

Peter W. Reikes

Michael Hayden, C.M., O.B.C., M.B.,  
Ch.B., Ph.D., F.R.C.P.(C), F.R.S.C.

# Forward Looking Language Statement

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This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen) and Ionis' technologies and products in development. 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 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, 2020 and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available at [www.ionispharma.com](http://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 Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics® is a registered trademark of Akcea Therapeutics, Inc. TEGSEDI® is a trademark of Akcea Therapeutics, Inc. WAYLIVRA® is a registered trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.

# Ionis Today and the Future:

Continuing to Lead in the Discovery & Development of RNA-Targeted Therapeutics

**Built Upon  
30 Years  
of Innovation**

Launching a new business model;  
building our commercial capabilities;  
expanding our wholly owned pipeline

Expanding and enhancing the scope  
of our drug discovery capabilities

Expanding our mid/late-stage pipeline  
to deliver on our goal of  
12+ marketed medicines in 2026

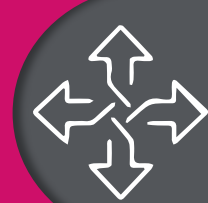
# Achieving Our Strategic Goals

## Evolving Business Model/ Excellence in Commercialization



- ✓ Reacquired Akcea
- ✓ Established distribution agreements w/Sobi for TEGSEDI & WAYLIVRA
- ✓ Building commercial capabilities & wholly owned pipeline
- ✓ Expanding R&D & manufacturing capacity

## Expanding and Enhancing the Scope of Our Drug Discovery Capabilities



- ✓ Strengthened genomics capabilities through new partnerships
- ✓ Strengthened targeted delivery (“LICA”) capabilities
- ✓ Launched additional initiatives to accelerate expansion of existing platform and creation of new complementary platforms

## 12+ Marketed Medicines in 2026



- 6 ongoing Phase 3 studies
- Tofersen Phase 3 read out Fall 2021
- More Phase 3 starts in 2H2021 and 2022
- $\geq 1$  Phase 3 readout each year through 2026

# Two Leading Therapeutic Franchises

## Neurological

Addressing major neurological diseases

**3** ongoing Phase 3 studies

**11** medicines in clinical development

**3** wholly owned medicines in clinical development

 **SPINRAZA**  
(nusinersen) injection  
12 mg/5 mL

 **Tegsedi**  
(inotersen) injection  
284 mg/1.5 mL

**IONIS**<sup>TM</sup>

## Cardiometabolic

Addressing major cardiovascular disease risk factors

**3** ongoing Phase 3 studies

**14** medicines in clinical development

**6** wholly owned medicines in clinical development

 **waylivra**<sup>TM</sup>  
(volanesorsen sodium)  
Injection 300mg in 1.5mL

# Continued Blockbuster Performance with \$521M in Q1 2021 Sales

## \$60M in Q1'21 Royalties to Ionis

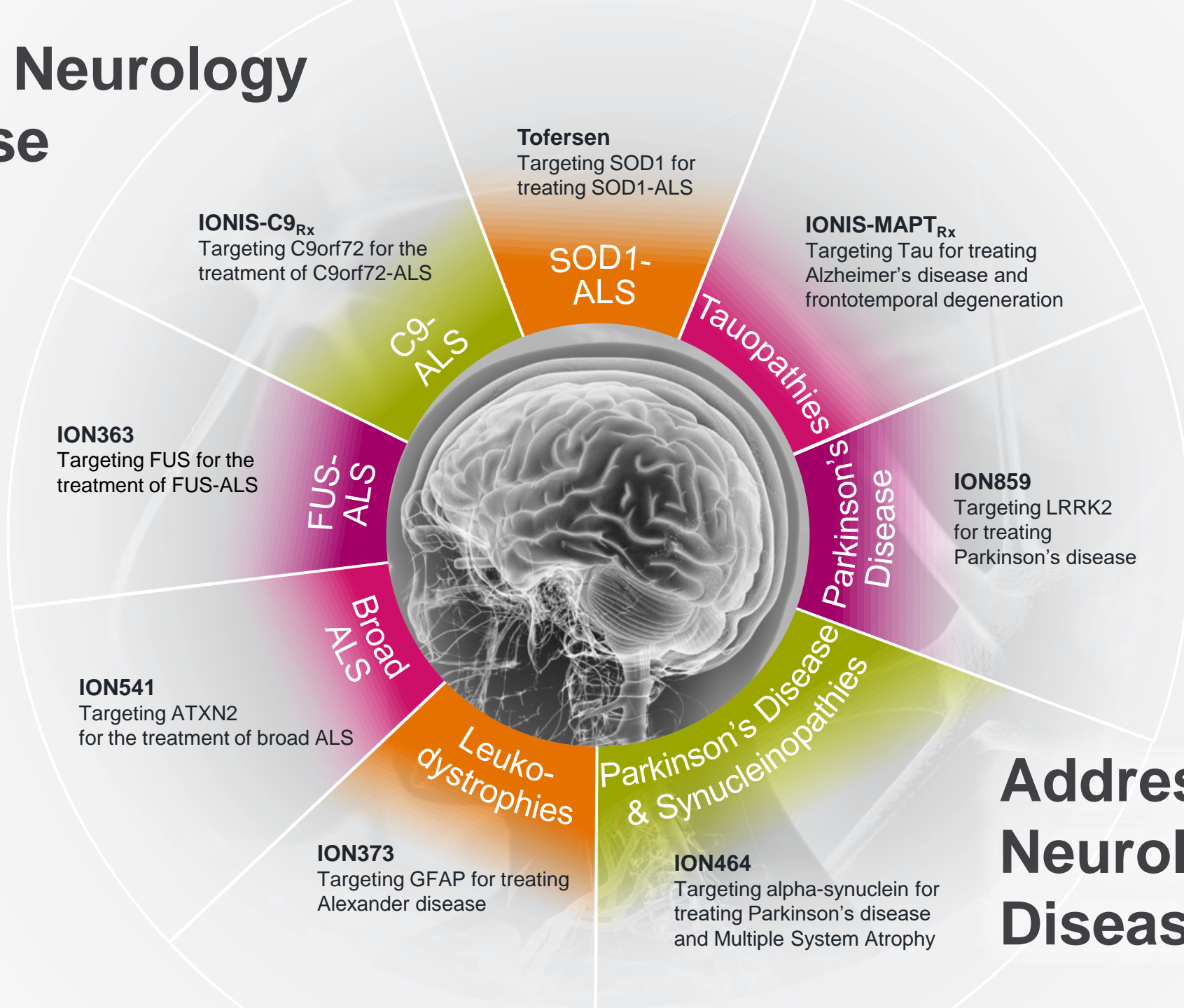


- >11,000 patients on SPINRAZA worldwide<sup>1,2</sup>
- >60,000 SMA patients in markets where Biogen has a commercial presence<sup>3</sup>
- Ongoing commitment to improving outcomes for SMA patients of all ages
  - **DEVOTE study:** designed to evaluate the potential for increased efficacy with higher dose SPINRAZA<sup>4</sup>
  - **RESPOND study:** dosing underway in SMA patients with suboptimal response to gene therapy<sup>5</sup>

Source: Biogen Q1 2021 Financial Results and Business Update; 1. Includes patients from post-marketing, EAP and clinical settings; 2. As of March 31, 2021; 3. Biogen estimate, data on file; 4. DEVOTE study: [clinicaltrials.org/NCT04089566](https://clinicaltrials.org/NCT04089566) 5. RESPOND study: [clinicaltrials.org/NCT04488133](https://clinicaltrials.org/NCT04488133);



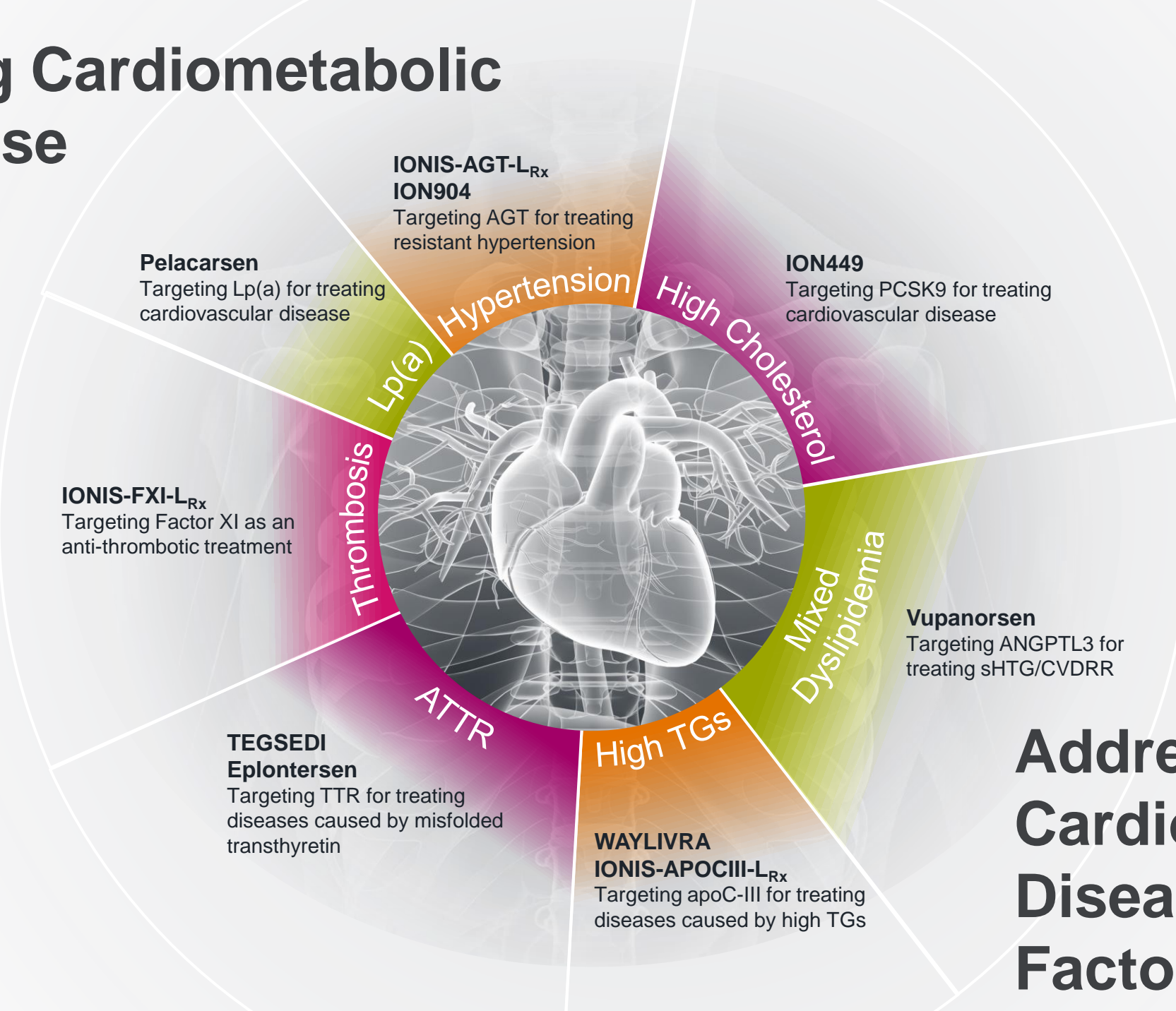
# Leading Neurology Franchise



## Addressing Major Neurological Diseases



# Leading Cardiometabolic Franchise



# Addressing Major Cardiovascular Disease Risk Factors



# Phase 3 Studies

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# Pioneering New Markets & Changing Standards of Care

## Advancing Phase 3 Pipeline



		Prevalence <sup>1</sup>	Phase 3 Data <sup>2</sup>
<b>Tofersen</b>	<b>SOD1-ALS</b> Biogen	~ 1.4K patients in G7 countries	Fall 2021
<b>ION363</b>	<b>FUS-ALS</b> Wholly owned	~ 350 patients in G7 countries	2024
<b>Eplontersen</b> (IONIS-TTR-L <sub>Rx</sub> )	<b>hATTR polyneuropathy</b> <b>ATTR cardiomyopathy</b> Wholly owned	> 250K patients worldwide	2022 (PN) 2024 (CM)
<b>IONIS-APOCIII-L<sub>Rx</sub></b>	<b>FCS</b> <b>sHTG</b> Wholly owned	~ 3-5K patients worldwide > 3M patients U.S.	2023 (FCS) 2024 (sHTG)
<b>Pelacarsen</b>	<b>Lp(a) CVDRR</b> Novartis	> 8M patients worldwide	2024



<sup>1</sup> Market data on file. <sup>2</sup> Data timing expectations are based on current estimates and are subject to change. Partnered program timelines are based on partners' most recent public disclosures.

ALS, amyotrophic lateral sclerosis. FCS, familial chylomicronemia syndrome. hATTR, hereditary transthyretin amyloidosis. CVDRR, cardiovascular disease risk reduction.



# Pioneering New Markets & Changing Standards of Care

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# Tofersen for the treatment of SOD1-ALS

*Pioneering New Markets*

**IONIS**

*Sonny, living with ALS*

# Amyotrophic Lateral Sclerosis

A fatal disease with a tremendous unmet medical need

- **Severe neuromuscular disease** characterized by motor neuron degeneration resulting in **functional decline, paralysis** and **respiratory deterioration**
- **Rapidly progressive** with average **survival** of **3-5 years** from symptom onset
- **Genetic** and **broad ALS** programs underway with Ionis and Biogen

**~ 55K**  
**patients in G7 countries<sup>1</sup>**

- Genetic ALS (e.g. SOD1, C9, FUS): ~15%
- ALS with no known genetic cause: ~85%

# SOD1-ALS: Molecular Pathology

Mutant SOD1 toxic gain of function

- **Mutant superoxide dismutase type 1** (SOD1) protein misfolds, aggregates and **causes** ALS through **toxic gain of function** in neurons and glia
- **2<sup>nd</sup>** most common **genetic** form of ALS
- **Over 100 mutations** have been identified in the SOD1 gene
  - Some mutations cause a rapidly progressing form of the disease
- **Tofersen targets** the **root cause** of SOD1 ALS



# Tofersen for the Treatment of SOD1-ALS

First investigational medicine to demonstrate trends in slowing disease progression

## Prevalence

~ 1.4K

SOD1-ALS patients in G7 countries<sup>1</sup>

## High Unmet Need

Fatal

Severe motor neuron disease with no disease modifying treatments

## First In Class Product Profile Potential

Transformational

Demonstrated a slowing of decline of clinical function in Phase 1/2 study of tofersen

## Pioneering New Markets

# Tofersen<sup>1</sup>

*First of four medicines  
targeting ALS*

**Projected Phase 3 Data  
Fall 2021**

- **Targets the root cause** of SOD1-ALS, mutant superoxide dismutase type 1 protein
- Demonstrated **robust reductions** in SOD1 in patients with trends in **slowing disease** progression<sup>2</sup>
- **Next** potential **commercial medicine**
- Phase 3 **VALOR** study **fully enrolled**
- Phase 3 **ATLAS** study in **presymptomatic** SOD1-ALS patients underway

# ION363 for the treatment of FUS-ALS

*Pioneering New Markets*

*In honor of Jaci Hermstad*

# ION363 (FUS-ALS)

Caused by mutations in the Fused in Sarcoma (FUS) gene – no effective treatment

- **3<sup>rd</sup>** most common **genetic** form of ALS
  - ~25% incidence of SOD1-ALS
- **FUS-ALS** is a **fast-progressing** form of ALS
  - Good genotype-phenotype correlation
- **FUS mutations** cause motor **neuron degeneration** through a **toxic gain of function** mechanism
  - FUS is an RNA binding protein
  - Mutant FUS protein aggregates in the cytoplasm

## Pioneering New Markets

# ION363

*First wholly owned medicine  
in development for ALS*

**Projected Phase 3 Data  
2024**

- **Targets the root cause** of FUS-ALS, mutant FUS
- Prevented **motor neuron loss** in a mouse model of **FUS-ALS**
- Several FUS-ALS patients **previously treated** with **ION363** in an investigator sponsored compassionate use study
- **Innovative** pivotal study designed to achieve an **accelerated path** to the **market**
- Phase 3 study **underway**

# Committed to Treating All Forms of ALS

- Tofersen: **Phase 3 VALOR** study underway in SOD1-ALS (data expected Fall 2021)
- ION363: Phase 3 study with **Ionis-owned** program targeting **FUS** in FUS-ALS underway
- IONIS-C9<sub>Rx</sub>: **Phase 1/2 study ongoing** in **C9-ALS** (data expected 1H 2022)
- ION541: **Phase 1/2 study ongoing** targeting **ATXN2** in **broad ALS population**
- Additional programs advancing

## Multiple ALS Medicines in Development

MEDICINE	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	
Tofersen (IONIS-SOD1 <sub>Rx</sub> )	SOD1-ALS	[Progress bar]				
ION363 (FUS)	FUS-ALS	[Progress bar]				
IONIS-C9 <sub>Rx</sub> *	C9-ALS	[Progress bar]				
ION541* (ATXN2)	Broad ALS	[Progress bar]				
Additional medicines advancing into development		[Progress bar]				



\* Ionis categorizes patient studies to establish safety profile as Phase 1/2 and in healthy volunteers as Phase 1. Certain studies in this presentation that are categorized as Phase 1/2 may be categorized differently by outside parties.

# Pioneering New Markets & Changing Standards of Care

## Advancing Phase 3 Pipeline

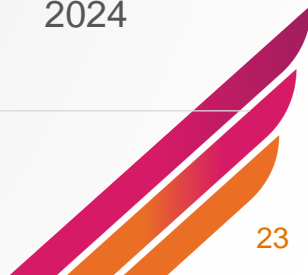


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# Pioneering New Markets & Changing Standards of Care

## Advancing Phase 3 Pipeline

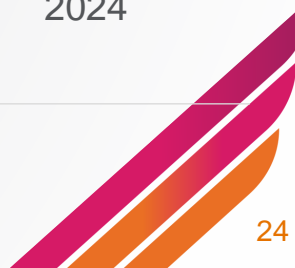


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# Eplontersen (IONIS-TTR-L<sub>Rx</sub>)

*Changing the Standard of Care*

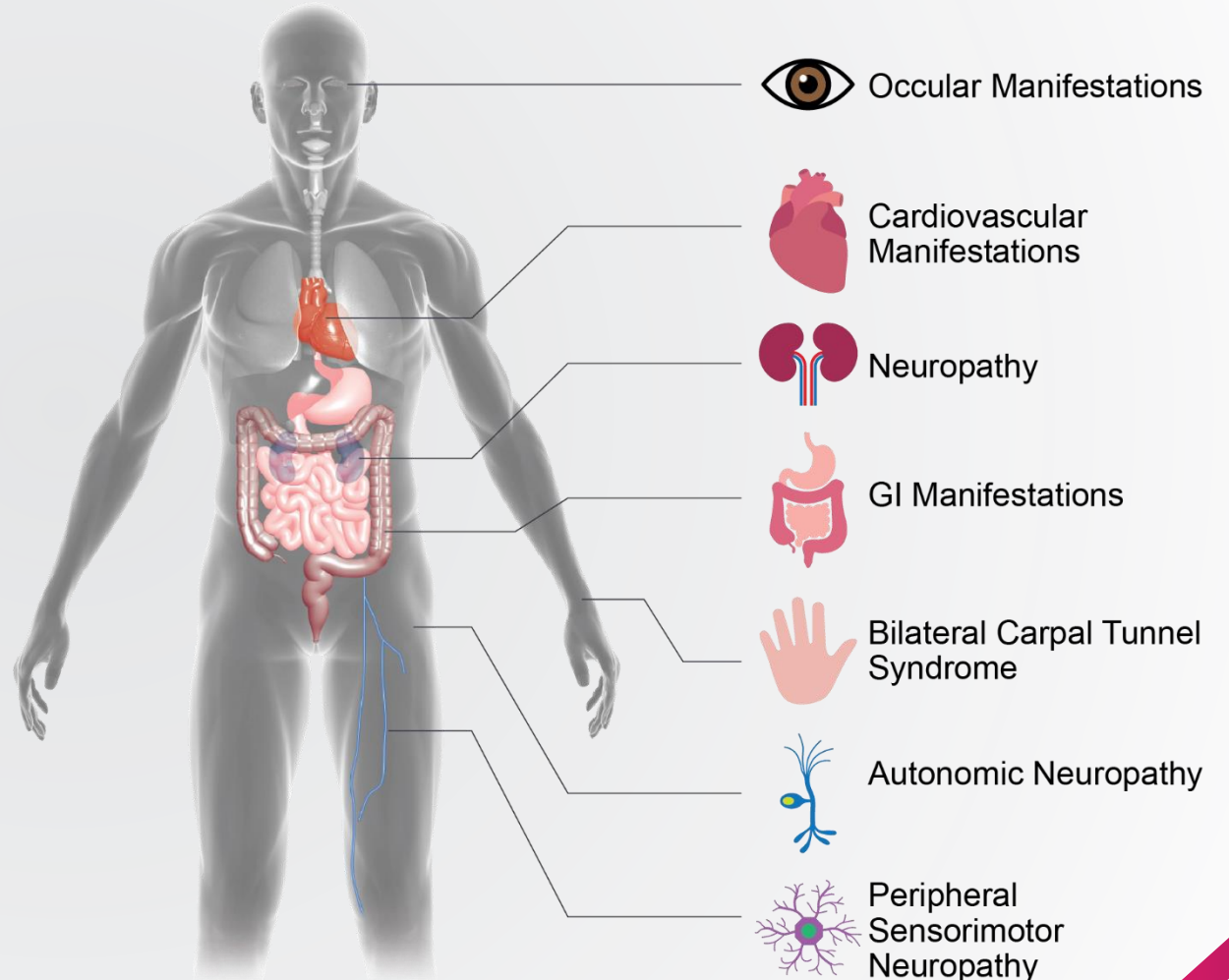
*Clay, living with ATTR*

**IONIS**

# TTR Amyloidosis (ATTR)

A devastating and fatal disease

- Characterized by the formation of **TTR amyloid deposits** leading to multi-organ failure<sup>1,2</sup>
- Patients suffer from multi-organ failure, dominated by progressive **polyneuropathy** and **cardiomyopathy**
- Progressive disease resulting in a **rapid decline in quality of life and death**
  - 3-15 year life expectancy for polyneuropathy<sup>3</sup> patients
  - 2-5 year life expectancy for cardiomyopathy<sup>4</sup> patients



# Eplontersen

Potentially changing the standard of care for all forms of amyloidosis

## Prevalence

**> 250K**

ATTR patients globally<sup>1</sup>

## High Unmet Need

**Often Fatal**

Progressive disease resulting in a rapid decline in quality of life

## Product Profile Potential to Change the Standard of Care

**Transformational**

Largest CM outcomes trial in TTR amyloidosis

# Eplontersen

Expanding our ATTR franchise

- Eplontersen utilizes our highly advanced **LICA** chemistry, providing high **potency** with attractive **convenience** and **tolerability**
- **Targets** TTR: **the root cause** of TTR amyloidosis
- **Robust** target **reduction** and **positive safety** profile demonstrated in healthy volunteers
  - > 90% demonstrated in Phase 1 healthy volunteer study
  - **Favorable safety** and **tolerability** observed

## Changing Standards of Care

# Eplontersen

*Potential foundational therapy  
for hATTR polyneuropathy and  
ATTR cardiomyopathy*

**Projected Phase 3 Data**  
2022 polyneuropathy  
2024 cardiomyopathy

- **Targets the root cause** of TTR amyloidosis, mutant TTR protein
- An Ionis next-generation **high-potency LICA medicine**
- **Robust target reductions** demonstrated in Phase 1 study
- Two ongoing Phase 3 studies actively recruiting: **NEURO-TTRansform** and **CARDIO-TTRansform** outcome study



# IONIS-APOCIII-L<sub>Rx</sub>

*Changing the Standard of Care*

**IONIS**<sup>™</sup>

*Fred, living with FCS*

# Severe Diseases Driven by Elevated Triglycerides

- **Elevated triglyceride levels are associated with major medical issues**
  - Increased CVD risk
  - Acute, potentially fatal pancreatitis
- **Apolipoprotein C-III (apoC-III)**
  - Key regulator of triglycerides
  - Independent cardiovascular risk factor
- **Potential best-in-class mechanism for TG-related cardiometabolic disease management**

**Familial Chylomicronemia Syndrome (FCS)**  
(> 1,000 mg/dl)

**~ 3-5K**  
patients globally<sup>1</sup>

**Severe High Triglycerides (sHTG)**  
(> 500 mg/dl)

**> 3M**  
patients In the U.S.<sup>2</sup>

**High Triglycerides**  
(150 – 500 mg/dl)

**~ 50M**  
patients globally<sup>2</sup>

# IONIS-APOCIII-L<sub>Rx</sub>

One product, multiple indications targeting elevated triglycerides

## Prevalence

~ **3-5K**

FCS patients globally<sup>1</sup>

> **3M**

sHTG patients in the U.S.<sup>1</sup>

## High Unmet Need

**FCS**

High risk of unpredictable & potentially fatal acute pancreatitis

**sHTG**

High risk of CVD & type 2 diabetes

## Best In Class Product Profile Potential

**Transformational**

Potential best in class TG reductions with patient-friendly monthly SC administration



## Changing Standards of Care

# IONIS-APOCIII-L<sub>Rx</sub>

*One product, multiple indications  
targeting elevated triglycerides*

Projected Phase 3 Data  
2023 (FCS)  
2024 (sHTG)

- **Robust triglyceride reductions** demonstrated in Phase 2 study
- Phase 3 **FCS BALANCE** study actively recruiting
- Phase 3 **severe hypertriglyceridemia** (sHTG) study start planned for 2H 2021

*Michael, living with Lp(a) driven  
Cardiovascular Disease*

# **Pelacarsen** (IONIS-APO(a)-L<sub>Rx</sub>)

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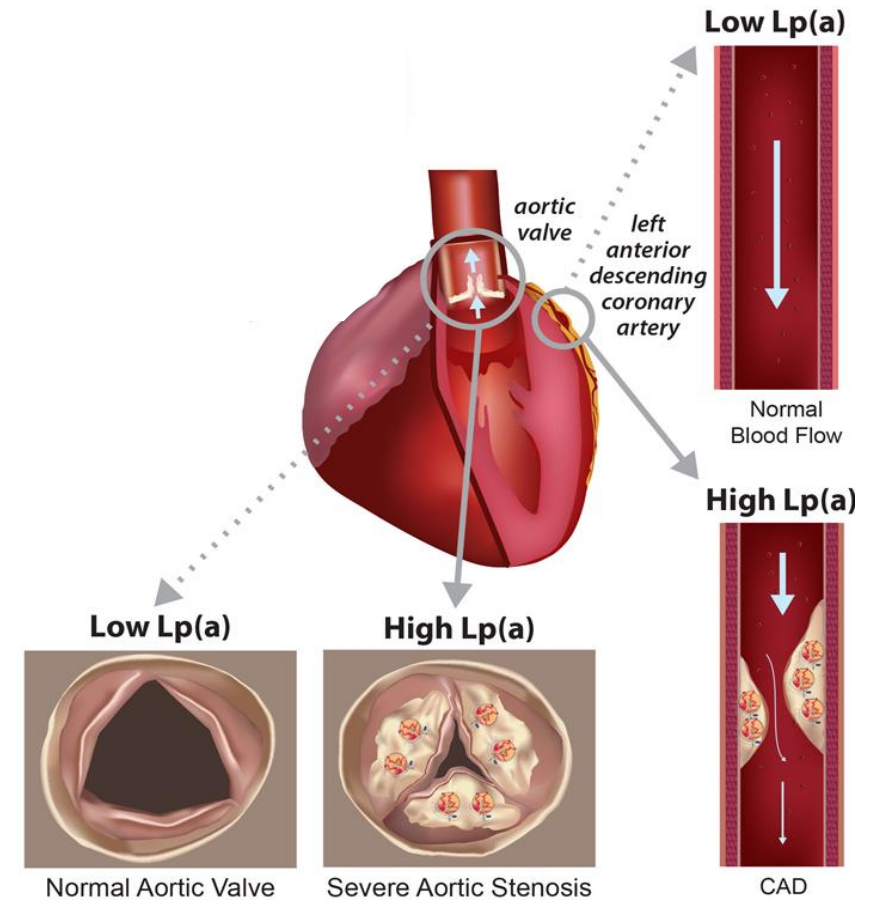
*Pioneering New Markets*

**IONIS**

# Lipoprotein(a)

A highly prevalent untreated risk factor for cardiovascular disease

- Lp(a) levels are **genetically determined** at birth
- Elevated Lp(a) levels **cause cardiovascular disease** through multiple mechanisms
- Elevated levels are recognized as a **major untreated cardiovascular risk factor**
- **No approved** pharmacological therapies



# Pelacarsen

Potential first in class profile for Lp(a) driven cardiovascular disease

## Prevalence

**> 8M**

People worldwide with Lp(a)  
driven CVD<sup>1</sup>

## High Unmet Need

**Often Fatal**

Genetic cause of coronary artery  
disease, heart attack, stroke and  
peripheral arterial disease

## First In Class Product Profile Potential

**Transformational**

Expected to be first disease  
modifying treatment for Lp(a)  
driven CVD

## Pioneering New Markets

# Pelacarsen<sup>1</sup>

*Expected to be first disease modifying treatment for Lp(a) driven cardiovascular disease*

**Projected Phase 3 Data  
2024**

- **Targets the root cause** of Lp(a)-driven cardiovascular disease
- **98% of patients** achieved Lp(a) levels below CVD risk threshold in Phase 2 study<sup>2,3</sup>
- Granted **Fast Track** Designation by the FDA
- Phase 3 **Lp(a)HORIZON** cardiovascular outcome study actively enrolling

# IONIS-PKK-L<sub>Rx</sub>

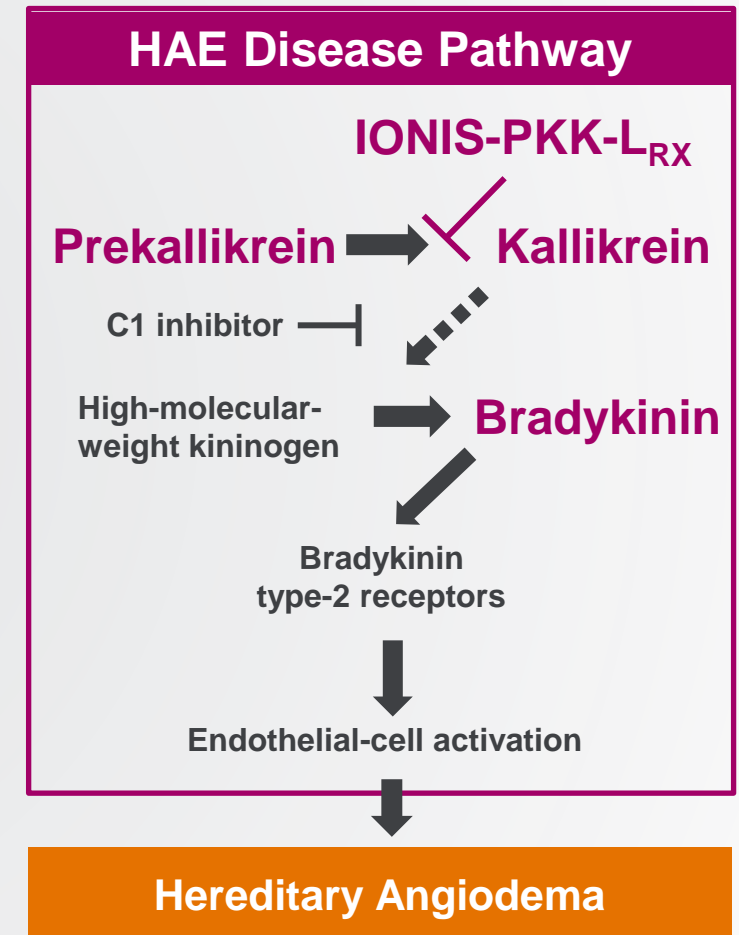
*Changing the Standard of Care*

# Hereditary Angioedema is Characterized by Unpredictable and Painful Attacks that are Potentially Fatal

- Hereditary Angioedema (HAE) is a rare autosomal dominant disease caused by **insufficient or dysfunctional C1-Inhibitor** that results in dysregulation of the Prekallikrein-Bradykinin pathway
- **HAE symptoms**
  - Severe swelling of the arms, legs, face, intestinal track and throat
  - Significant anxiety is common due to unpredictable disease pattern
  - Swelling of the throat can cause suffocation
- **Approved prophylactic therapies require frequent administration** (daily, weekly or bi-weekly) that can negatively impact patient compliance
- Patients **still experience breakthrough attacks** with currently marketed products
- Continued **need** for a **prophylactic treatment** offering HAE patients **greater efficacy, safety and tolerability**
- Patients seek to **regain their freedom** from the disease and **improve their quality of life**

# Hereditary Angioedema is a Rare, Severe Disease Driven by Overactivity of the Prekallikrein Pathway

- Hereditary Angioedema (HAE) is caused by **insufficient or dysfunctional C1-Inhibitor** resulting in:
  - Overactivity of the Prekallikrain (PKK) pathway
  - Excessive bradykinin production
  - Severe swelling, characteristic of HAE
- **IONIS-PKK-L<sub>RX</sub>** is a LICA-medicine designed to **block the production of PKK**, thereby reducing production of bradykinin – the cause of HAE



Lumry (2103) Am. J. Manag. Care. 19:S103-S110



# IONIS-PKK-L<sub>Rx</sub>

Potential to change standard of care for the treatment of HAE

## Prevalence

**> 20K**

Patients in the United States and Europe suffering from HAE<sup>1</sup>

## High Unmet Need

**Potentially Fatal**

Significant need for safe, better tolerated, and more convenient therapy for prevention of potentially fatal HAE attacks

## Best In Class Product Profile Potential

**Transformational**

Potential best in class reductions in HAE related attacks with monthly SC administration

# IONIS-PKK-L<sub>Rx</sub> Demonstrated Significant Reductions in HAE Attack Rate in Phase 2 Study

- Potential **best in class** prophylactic treatment for patients with HAE
- **Favorable safety** and **tolerability** profile

**90%**

Mean reduction in  
monthly HAE attacks  
vs. placebo  
(weeks 1-17)

**97%**

Mean reduction in  
monthly HAE attacks  
vs. placebo  
(weeks 5-17)

**92%**

Treated patients were  
attack-free vs. **0%** patients  
on placebo  
(weeks 5-17)

**Phase 3 planning underway**

## Changing Standard of Care

# IONIS-PKK-L<sub>Rx</sub>

*Potential best in class medicine  
for prevention of HAE attacks*

**Phase 3  
Planning Underway**

- **Targets** the pathway at the **root cause of HAE**
- Designed as a convenient **prophylactic treatment** for prevention of HAE attacks
- Utilizes Ionis' next-generation **LICA chemistry with high potency, attractive tolerability and convenience**
- Phase 2 profile supports a potential **Best-In-Class medicine** for HAE



# 2021 Planned Pipeline Events

# Key 2021 Pipeline Events

DATA READOUTS <sup>1</sup>			H1	H2
PKK-L <sub>Rx</sub>	Phase 2	Hereditary Angioedema (top-line data)	✓	
AGT-L <sub>Rx</sub>	Phase 2	Hypertension	✓	
Tominersen <sup>2</sup>	Phase 3	Huntington's disease	✓	
ENAC-2.5 <sub>Rx</sub>	Phase 2	Cystic Fibrosis	✓	
GHR-L <sub>Rx</sub>	Phase 2 + OLE	Acromegaly		●
PKK-L <sub>Rx</sub>	Phase 2	Hereditary Angioedema (full data)		●
MAPT <sub>Rx</sub>	Phase 1/2	Alzheimer's Disease		●
Vupanorsen	Phase 2b	sHTG/CVD risk reduction		●
Tofersen	VALOR Phase 3	SOD1-ALS		●
KEY STUDY INITIATIONS <sup>1</sup>			H1	H2
SPINRAZA	RESPOND Phase 4	SMA, Suboptimal gene therapy response	✓	
Tofersen	ATLAS Phase 3	Presymptomatic SOD1-ALS	✓	
ION363	Phase 3	FUS-ALS	✓	
AGT-L <sub>Rx</sub>	Phase 2b	Resistant hypertension	✓	
AGT-L <sub>Rx</sub>	Phase 2	Heart failure with reduced ejection fraction	✓	
ION373	Phase 2/3	Alexander disease	✓	
ION224	Phase 2b	NASH	●	
APOCIII-L <sub>Rx</sub>	Phase 3	Second TG indication (sHTG)		●
ION582	Phase 1/2	Angelman syndrome		●

1. Timing of partnered program catalysts based on partners' most recent publicly available disclosures

2. Dosing stopped in Phase 3 GENERATION HD1 Study, paused in GEN-EXTEND OLE study. GEN-PEAK and Roche HD Natural History study continuing

# 12+ Marketed Medicines Projected in 2026

 **SPINRAZA**  
(nusinersen) injection  
12 mg/5 mL

 **Tegsedi**  
(inotersen) injection  
284 mg/1.5 mL

 **waylivra**  
(volanesorsen) injection  
285 mg/1.5 mL

## Wholly owned Neuro

Eplontersen (hATTR-PN)  
ION716 (Prion)  
ION373 (Alexander)  
ION363 (FUS-ALS)  
ION283 (Lafora)

## Partnered Neuro

Tofersen (SOD1-ALS)  
C9<sub>Rx</sub> (C9-ALS)  
ION541 (Broad ALS)

## Wholly owned Cardio

Eplontersen (ATTR-CM)  
APOCIII-L<sub>Rx</sub> (FCS)  
APOCIII-L<sub>Rx</sub> (sHTG)  
AGT-L<sub>Rx</sub> (RHTN)

## Partnered Cardio

Pelacarsen (Lp(a) CVDRR)  
Vupanorsen (sHTG/CVDRR)  
FXI-L<sub>Rx</sub> (ESRD)  
ION449 (PCSK9)

## Wholly owned Other

TMPRSS6-L<sub>Rx</sub> ( $\beta$ -thal)  
PKK-L<sub>Rx</sub> (HAE)  
GHR-L<sub>Rx</sub> (Acromegaly)

## Partnered Other

HBV<sub>Rx</sub> (Hep B)

# Well Positioned for Accelerated Growth

**Advancing**  
pipeline  
&  
technology

**Pioneering** new  
markets  
&  
**Changing**  
standards of care

**Financial**  
**strength**  
to invest in areas  
with the greatest  
**value-driving**  
**potential**



**IONIS™**

**A force for life**



# Q&A

Please standby as we compile your questions. Thanks for your patience.