Investor Day 2020

December 7, 2020

Forward Looking Language Statement

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, including the business of Akcea Therapeutics, Inc., Ionis' wholly owned subsidiary. 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

Frank Bennett, Ph.D.
Chief Scientific Officer

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

Onaiza Cadoret
EVP, Chief Development & Commercial Officer

Beth Hougen
Chief Financial Officer

Eric Swayze, Ph.D.
EVP, Research

Brett Monia, Ph.D.
Chief Executive Officer

Ionis 2020:
Where we are today

Today’s agenda

Ionis 2020: where we are today, *Brett Monia, Ph.D.*

Ionis pipeline: addressing major cardiovascular disease risk factors, *Sam Tsimikas, M.D.*

Ionis pipeline: addressing a broad range of neurological diseases, *Frank Bennett, Ph.D.*

Delivering on the significant market opportunity of the Ionis-owned pipeline, *Onaiza Cadoret*

Ionis’ commercial opportunities: driving substantial, sustained growth, *Beth Hougen*

Increasing our leadership position in RNA-targeted therapeutics, *Eric Swayze, Ph.D.*

2021 and beyond, *Brett Monia, Ph.D.*

Q&A

In 2020, we set a clear and aggressive set of goals…

- **Prioritize and expand the Ionis-owned pipeline while building our commercial strategy and capabilities**
- **Advance the pipeline to ensure a future rich in innovative first-in-class and/or best-in-class commercial medicines**
- **Advance our technology to expand our therapeutic scope**
- **Grow our leadership position in RNA-targeted therapeutics**

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In 2020, we set a clear and aggressive set of goals…

Prioritize and expand the Ionis-owned pipeline while building our commercial strategy and capabilities

Adv
first

Adv

Grow our leadership position in RNA-targeted therapeutics

…2020 Goals Achieved

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2020 Achievements…

- ✓ Invested in building our commercial capabilities
- ✓ Implemented our commercial strategy for Ionis-owned assets
- ✓ Expanded the Ionis-owned development pipeline
- ✓ Acquired Akcea to accelerate achievement of our key goals
- ✓ Initiated two more Phase 3 studies, now six ongoing
- ✓ Achieved multiple, key clinical proof of concept readouts
- ✓ Advanced our oral and pulmonary delivery platforms

…positioning us for our next stage of growth

- ✓ Stronger, more focused organization with Akcea integration
- ✓ Prioritizing Ionis-owned assets within our key franchises with greatest value-driving potential
- ✓ Build competitive advantage

POSITIONED FOR A STRONG 2021 & BEYOND

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Substantial Pipeline Performance Positioning Multiple Drugs to Achieve Next Key Stage in Development

2020 Goals	2020 Achievements
Grow from 4 to 6 Phase 3 studies	TTR-L, APOCIII-L Phase 3 studies underway
Report proof-of-concept data from multiple programs	Positive APOCIII-L, vupanorsen, ENAC-2.5, PKK-L, PCSK9, & AGT-L proof-of-concept data
Initiate at least 10 new mid-stage studies	13 Phase 2 starts across key franchises
Establish aerosol and oral proof-of-concept	Progress in aerosol and oral delivery

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Ionis Late-stage Programs: Several Multi-Billion Dollar Opportunities

Asset	Target Indication	Product Profile	Next Milestone(s)[1]	NDA[1]
TTR-L_{Rx}	TTR polyneuropathy TTR cardiomyopathy	LICA follow-on	Phase 3 data – 2023 (PN) Phase 3 data – 2024 (CM)	2023 2024
APOCIII-L_{Rx}	FCS 2nd Indication	First-in-class LICA follow-on	Phase 3 data – 2023 (FCS) 2nd Phase 3 start – 2021	2023 2024
Tofersen[2]	SOD1-ALS	First-in-class	Phase 3 data – 2021	2022 – 2024
Tominersen[3]	Huntington's disease	First-in-class	OLE/NH data – 2021 Phase 3 data – 2022	
Pelacarsen[4]	Lp(a) CVD Risk Reduction	First-in-class	Phase 3 data – 2024	

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1. Timings are approximate and subject to change; 2. Licensed to Biogen; 3. Licensed to Roche; 4. Licensed to Novartis

Potential Marketing Applications Through 2025

2021		2025	
			IONIS-AGT-L_{Rx} *Resistant hypertension (RHTN)*
		ION716 *Prion diseases*	ION449 (PCSK9) *CVD*
		AKCEA-APOCIII-L_{Rx} *TG-driven disease*	ION541 *Broad ALS*
		ION373 *Alexander disease*	IONIS-TMPRSS6-L_{Rx} *β-thalassemia*
	ION283 *Lafora disease*	IONIS-GHR-L_{Rx} *Acromegaly*	IONIS-HBV_{Rx} *Hepatitis B virus infection*
	AKCEA-APOCIII-L_{Rx} *FCS*	IONIS-$C9_{Rx}$ *C9-ALS*	Vupanorsen *sHTG/CVDRR*
	Tominersen *Huntington's disease*	IONIS-PKK-L_{Rx} *Hereditary angioedema (HAE)*	ION363 *FUS-ALS*
Tofersen *SOD1-ALS*	AKCEA-TTR-L_{Rx} *hATTR polyneuropathy*	AKCEA-TTR-L_{Rx} *ATTR cardiomyopathy*	Pelacarsen *Lp(a) CVDRR*

ALS, amyotrophic lateral sclerosis. FCS, familial chylomicronemia syndrome. hATTR, hereditary transthyretin amyloidosis. CVD, cardiovascular disease. sHTG, severe hypertriglyceridemia. CVDRR, cardiovascular disease risk reduction. TG, triglyceride.

Potential Marketing Applications for Ionis-owned Programs through 2025

Neurology Franchise	Cardiometabolic Franchise	Rare (non-neuro) Programs
AKCEA-TTR-L_{Rx} *hATTR polyneuropathy*	**AKCEA-TTR-L_{Rx}** *ATTR cardiomyopathy*	**IONIS-PKK-L_{Rx}** *Hereditary angioedema*
ION716 *Prion diseases*	**AKCEA-APOCIII-L_{Rx}** *TG-driven diseases*	**IONIS-TMPRSS6-L_{Rx}** *β-thalassemia*
ION283 *Lafora disease*	**IONIS-GHR-L_{Rx}** *Acromegaly*	
ION373 *Alexander disease*	**AKCEA-APOCIII-L_{Rx}** *FCS*	
ION363 *FUS-ALS*	**IONIS-AGT-L_{Rx}** *RHTN*	

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Potential Marketing Applications for Partnered Programs through 2025

Neurology Franchise	Cardiometabolic Franchise	Infectious Disease
Tominersen[1] ***Huntington's disease***	**Pelacarsen**[3] ***Lp(a) CVDRR***	**IONIS-HBV$_{Rx}$**[6] ***HBV infection***
ION541[2] ***Broad ALS***	**Vupanorsen**[4] ***sHTG/CVDRR***	
IONIS-C9$_{Rx}$[2] ***C9-ALS***	**ION449**[5] **(PCSK9)** ***CVD***	
Tofersen[2] ***SOD1-ALS***		

1. Licensed to Roche; 2. Licensed to Biogen; 3. Licensed to Novartis; 4. Licensed to Pfizer; 5. Licensed to AstraZeneca; 6. Licensed to GSK

Technology Advancements in 2020

EXPANDING OUR THERAPEUTIC SCOPE

Medicinal Chemistry

- **Extending duration of action in the CNS to support bi-annual or annual dosing**
- **New targeted-delivery strategies (i.e. LICA) to enable new organ systems**

Technology Advancements in 2020

EXPANDING OUR THERAPEUTIC SCOPE

Medicinal Chemistry

- Extending duration of action in the CNS to support bi-annual or annual dosing
- New targeted-delivery strategies (i.e. LICA) to enable new organ systems

New Routes of Delivery

- Expanding our pulmonary delivery pipeline
- Optimizing and expanding oral delivery platform

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Technology Advancements in 2020

EXPANDING OUR THERAPEUTIC SCOPE

Medicinal Chemistry

- Extending duration of action in the CNS to support bi-annual or annual dosing
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New Routes of Delivery

- Expanding our pulmonary delivery pipeline
- Optimizing and expanding oral delivery platform

Human Genomics

- Ensuring a rich pipeline of genetically validated drug discovery targets
- Targeting the root causes of human diseases

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Today's Focus:

Ionis-owned medicines

Commercial strategy

Pipeline value

Technology advancements

Positioned for substantial and sustained growth

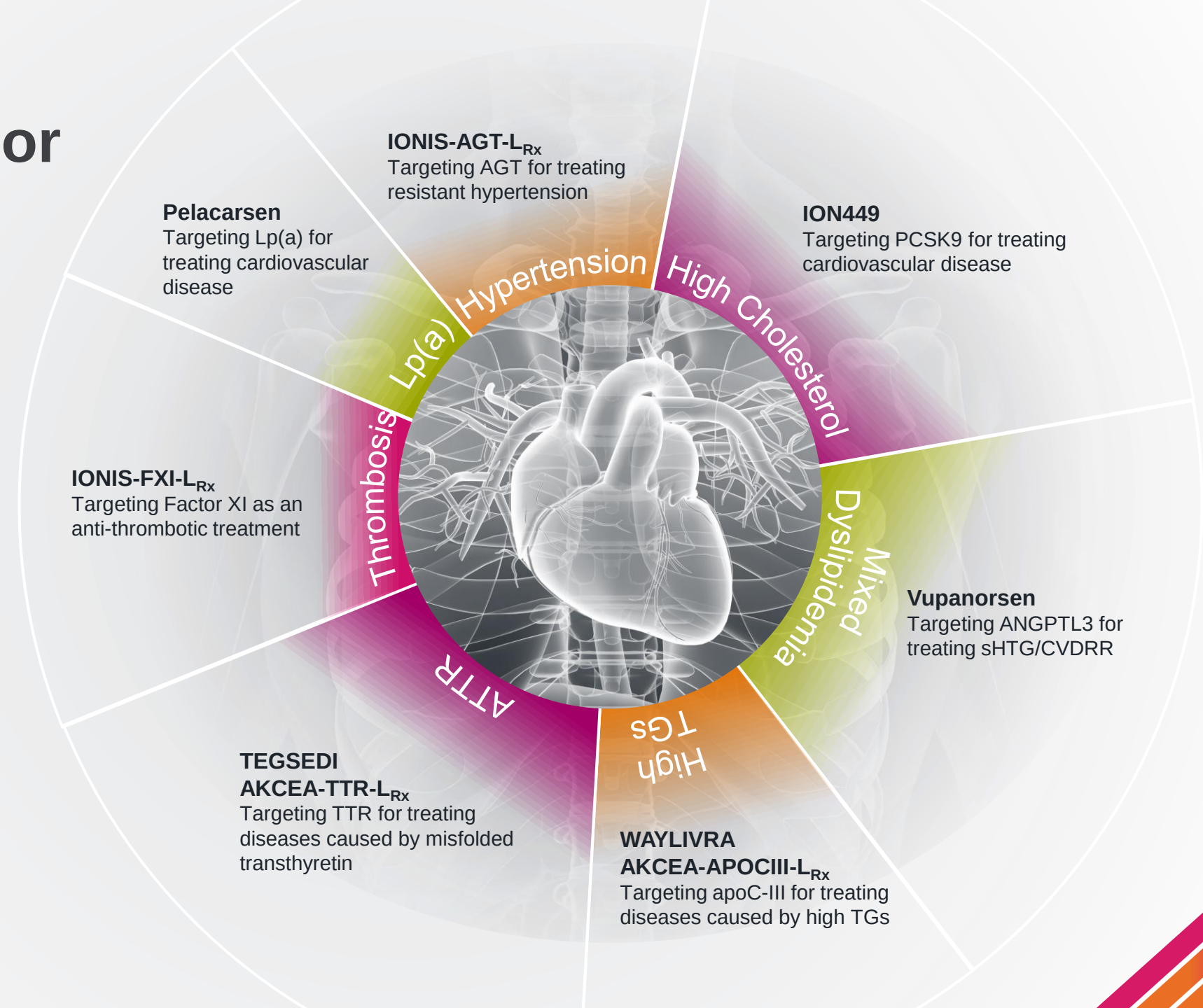
Ionis Pipeline: Addressing Major Cardiovascular Disease Risk Factors

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

CVD remains a leading cause of death in the U.S.

CVD is a key area of focus for Ionis

Addressing Major Cardiovascular Disease Risk Factors



IONIS-AGT-L_{Rx}
Targeting AGT for treating resistant hypertension

Pelacarsen
Targeting Lp(a) for treating cardiovascular disease

ION449
Targeting PCSK9 for treating cardiovascular disease

IONIS-FXI-L_{Rx}
Targeting Factor XI as an anti-thrombotic treatment

Vupanorsen
Targeting ANGPTL3 for treating sHTG/CVDRR

TEGSEDI
AKCEA-TTR-L_{Rx}
Targeting TTR for treating diseases caused by misfolded transthyretin

WAYLIVRA
AKCEA-APOCIII-L_{Rx}
Targeting apoC-III for treating diseases caused by high TGs

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ION449

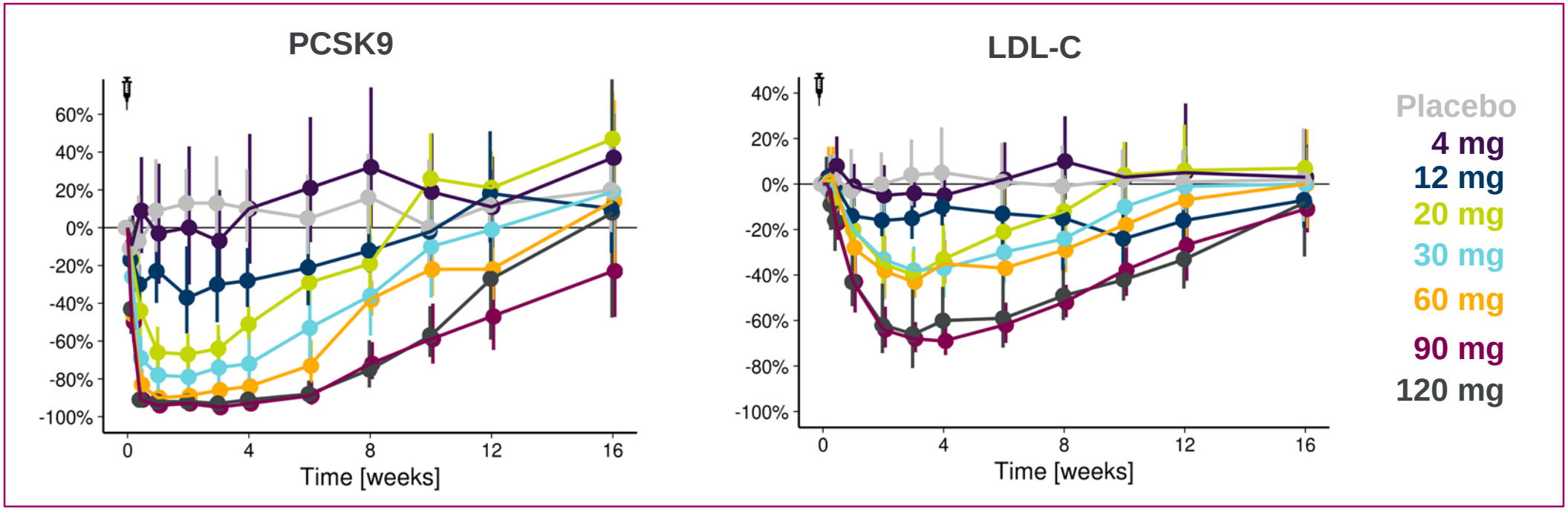
Designed to reduce plasma levels of proprotein convertase subtilisin/kexin type 9 (PCSK9)

ION449 has the potential for best-in-class reductions in PCSK9 and LDL-C

- **Substantial and durable reductions in PCSK9 and LDL** demonstrated in Phase 1 study
- **Favorable safety** and **tolerability** profile

Phase 1 Results for ION449 Demonstrate Best-in-Class Potential

- In a Phase 1 study, **single subcutaneous doses** of ION449 demonstrated **reductions** in **plasma PCSK9** protein and **LDL-C** levels up to **>90%** and up to **~70%** respectively
- **Favorable safety** and **tolerability** profile



Plots show geometric mean and SD of % change from baseline. n = 6 per AZD8233 cohort and n = 14 in placebo arm, PCSK9 measured as protein in plasma

ION449 Advancing in Clinical Development

- **Potential for best-in-class reductions in PCSK9 and LDL-C**
  - Potent, dose-dependent PCSK9 and LDL-C reductions of up to >90% and ~70%, respectively
- **Multiple ascending dose (MAD) cohort complete in Phase 1 study**
  - Safety and efficacy data continues to be favorable
- **Initiated Phase 2b study designed to enable rapid path to Phase 3**

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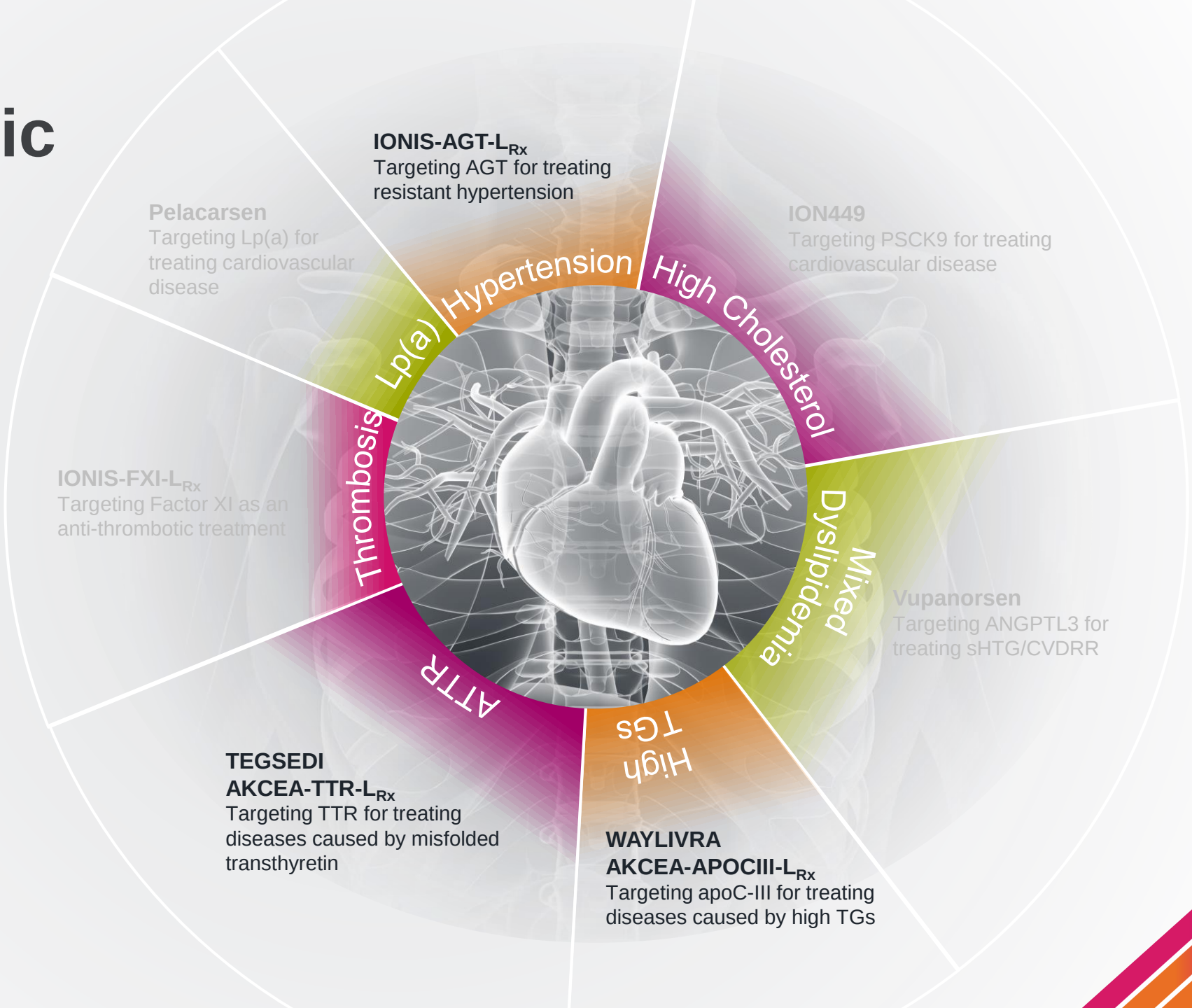
Ionis-owned Cardiometabolic Disease Programs



Justin and Naomi Providing a Message of Hope

AKCEA-APOCIII-L_{Rx}

Targeting apoC-III for the treatment of triglyceride-driven diseases

One product, multiple indications targeting elevated triglycerides

- **91% of patients achieved normal serum triglycerides** levels in Phase 2 study
- **Favorable safety** and **tolerability** profile
- **Phase 3** study **initiated** in FCS
- **Additional Phase 3 study** in second indication planned to start next year

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

- **Apolipoprotein C-III (apoC-III)**
  - Protein produced in the liver that regulates triglyceride metabolism in the blood
  - Independent cardiovascular risk factor
- **Elevated triglyceride levels associated with major medical issues**
  - Acute pancreatitis, which is associated with significant morbidity and mortality
  - Higher risk of cardiovascular disease

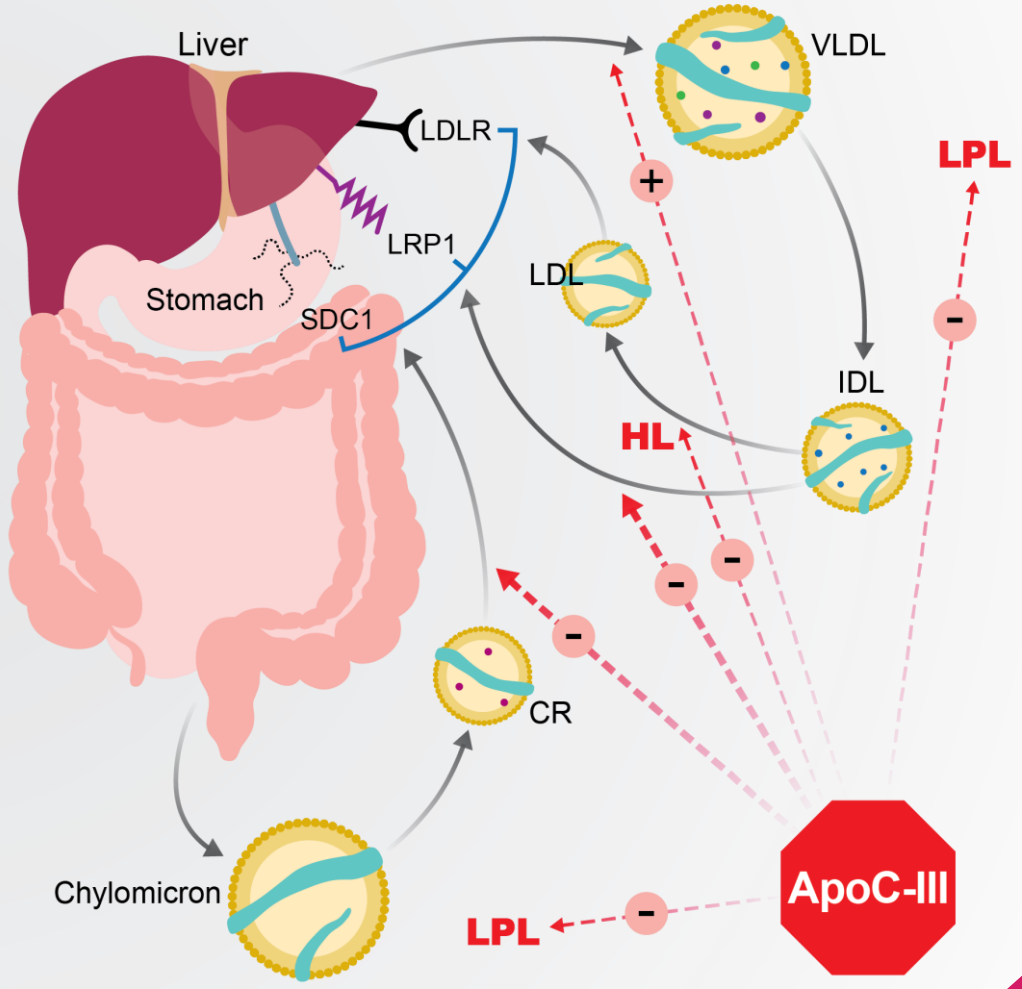


Image adapted from: Gordts PL, et al J Clin Invest. 2016;126:2855

AKCEA-APOCIII-L_{Rx}

One product, multiple indications targeting elevated triglycerides

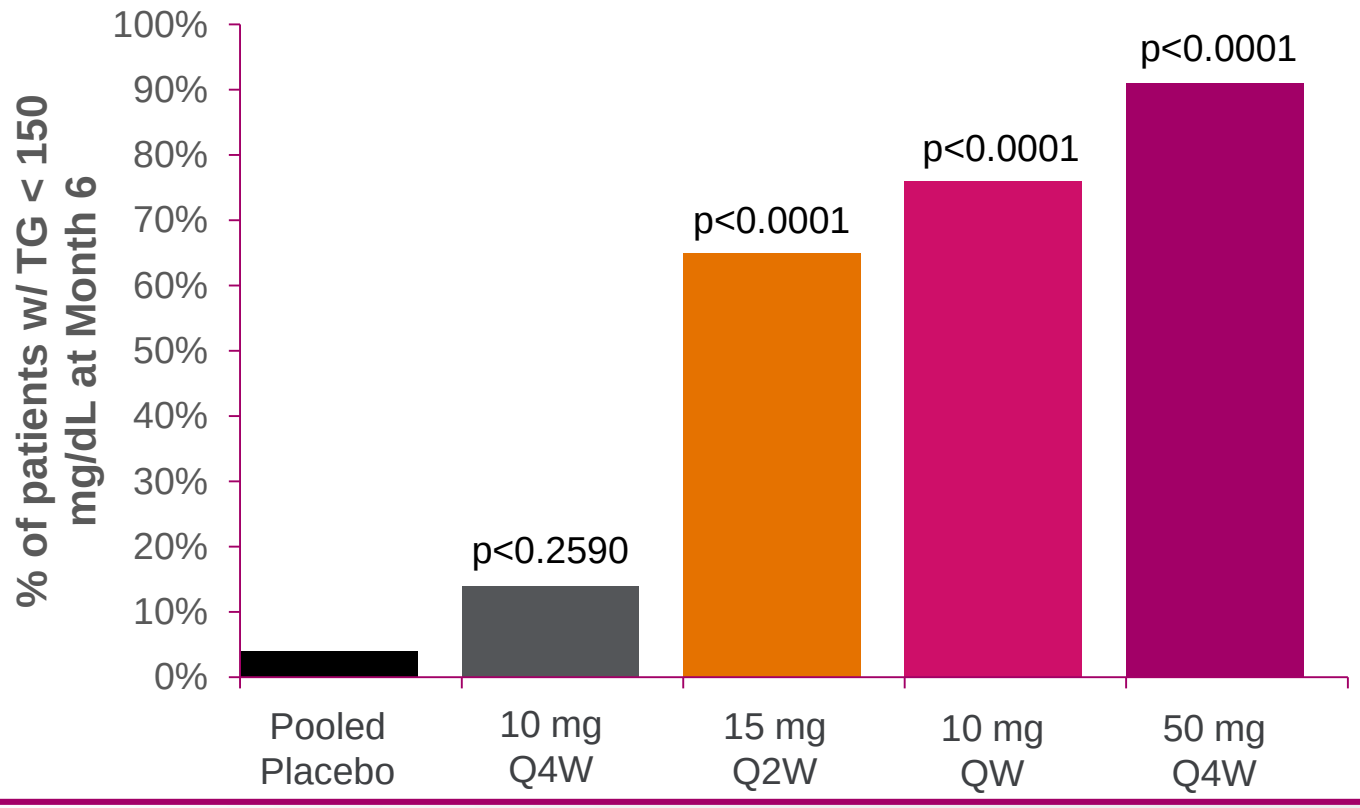
Familial Chylomicronemia Syndrome	Severe High Triglycerides (>500mg/dl)	High Triglycerides (150 – 500mg/dl)
~3-5K	**>10M**	**~50M**
patients globally[1]	**patients** globally[2]	**patients** globally[2]
	Leading cause of pancreatitis and increased risk for cardiometabolic diseases	Increased risk of CVD, including heart disease and stroke

1. Ionis data on file. 2. Ford, MD, MPH et al., Arch Intern Med. 2009;169(6):572-578

AKCEA-APOCIII-L_{Rx} Phase 2 Results

Setting a new standard for triglyceride management

91% of patients achieved normal serum triglycerides with 50 mg/month dose



Phase 2 Study

- Dose ranging, placebo-controlled study in 114 patients with CVD and TGs (200-500mg/dl)
- Primary endpoint: percentage change in fasting triglycerides at 6 months

Results

- Met primary endpoint of significant triglyceride lowering
- Favorable safety and tolerability profile

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AKCEA-APOCIII-L_{Rx}

Development strategy

Initiated	Phase 3 FCS study and pre-commercial activities
Planning to initiate	Phase 3 study in second, broader indication in 2021
Evaluating	Additional indications

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AKCEA-TTR-L_{Rx}

Targeting TTR for the treatment of ATTR cardiomyopathy

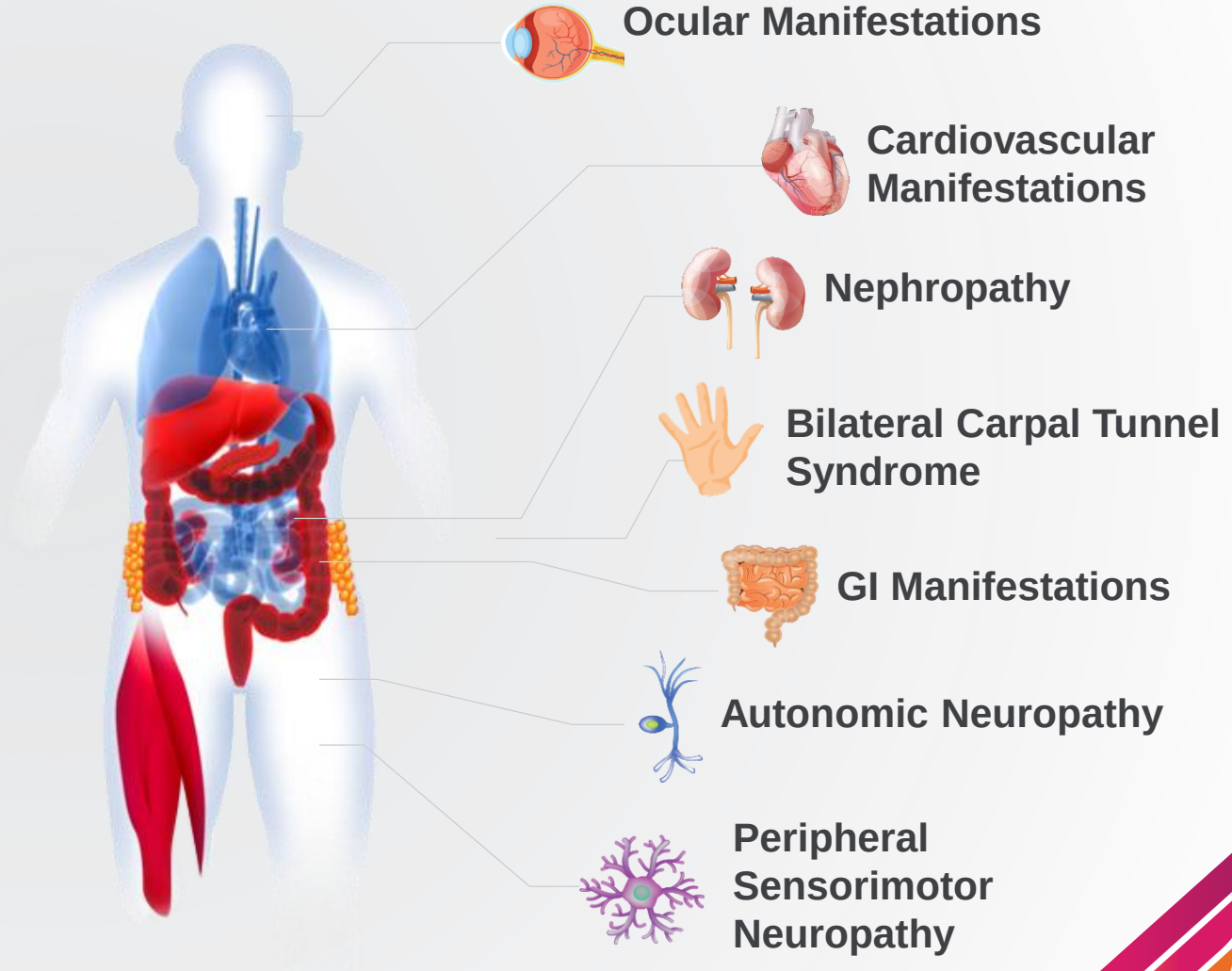
Expanding our ATTR franchise

- **Robust target reductions of >90%** demonstrated in Phase 1 study
- **Favorable safety** and **tolerability** profile
- **Flexibility** of at-home monthly self administration
- **Phase 3 CARDIO-TTRansform** study **underway**

TTR Amyloidosis (ATTR)

A devastating and fatal disease

- **Fatal disease** affecting over 250,000 patients worldwide[1,2]
- 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.

AKCEA-TTR-L_{Rx}

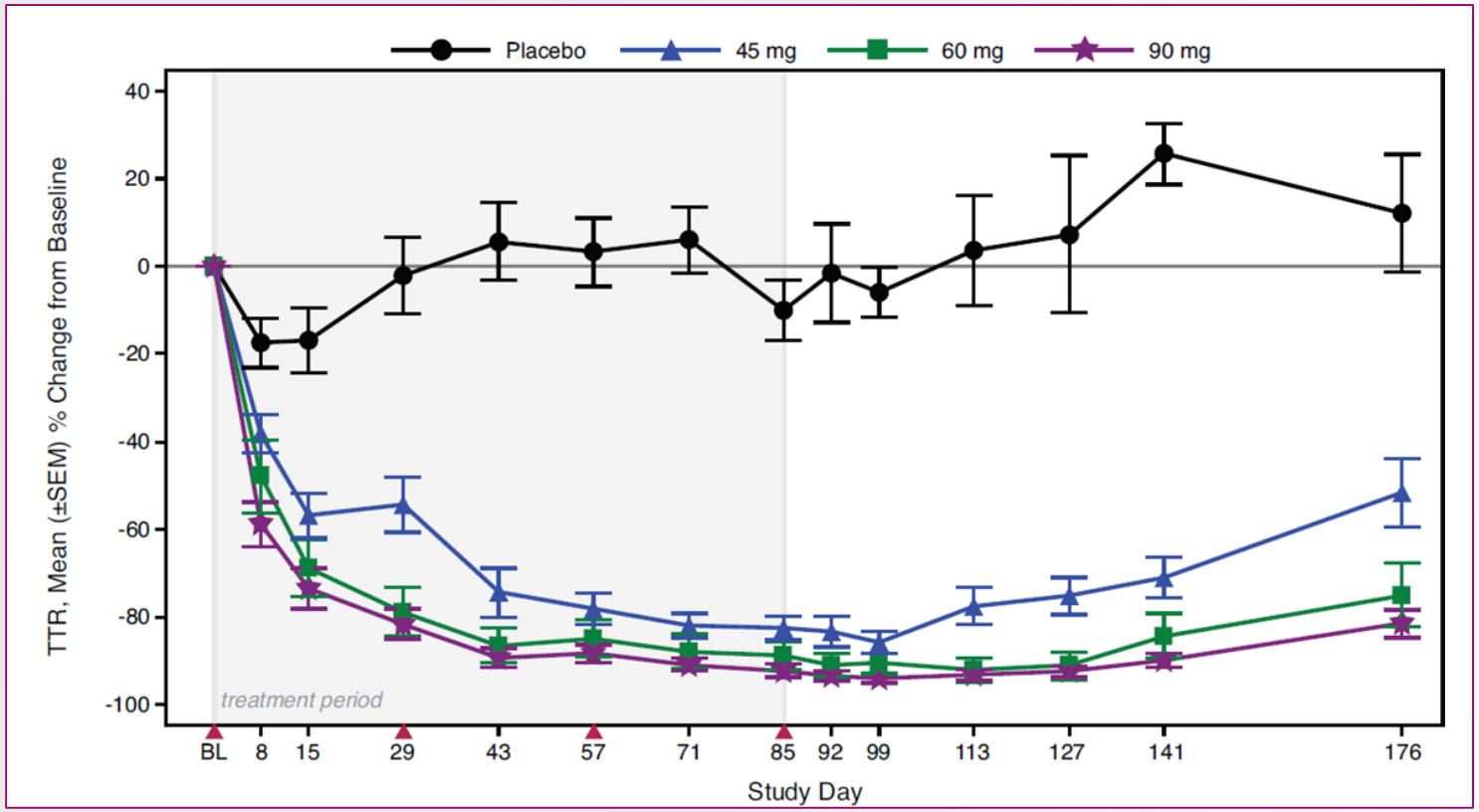
Dose-dependent reductions in TTR levels in healthy volunteers

Phase 1 Study

- Dose escalation, placebo-controlled study in 47 healthy volunteers
- Objectives: Safety and pharmacokinetics, pharmacodynamics and change in TTR levels

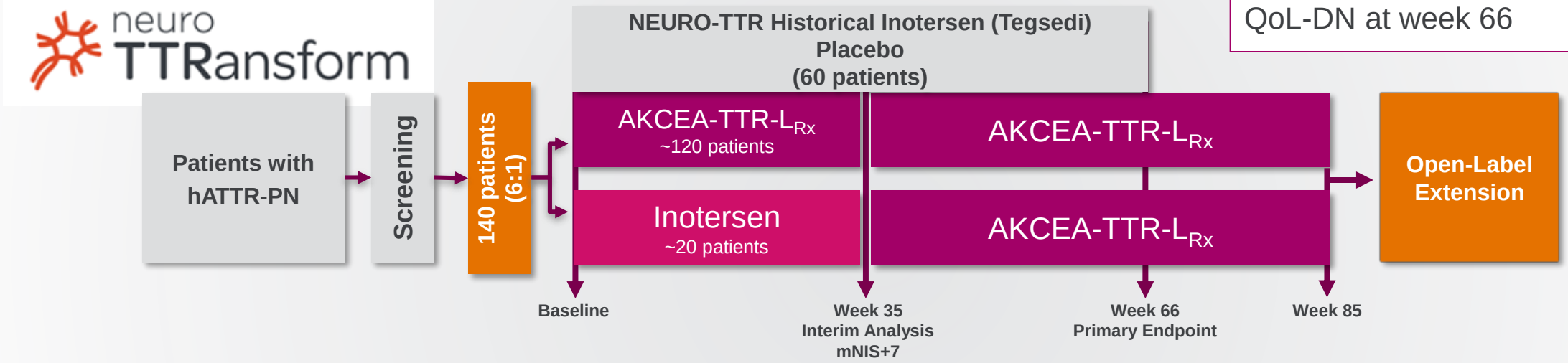
Results

- Achieved a mean reduction in TTR levels of 94%
- Favorable safety and tolerability profile

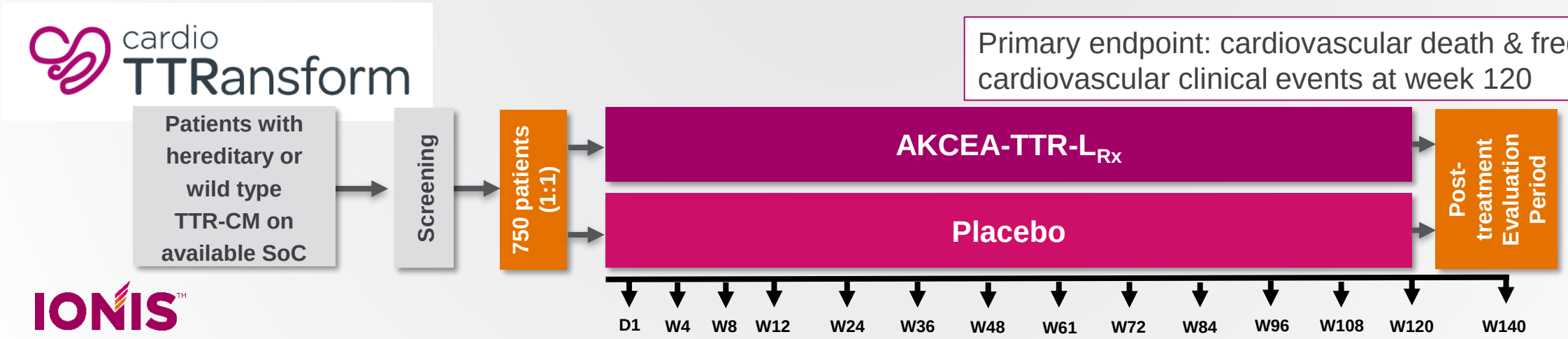


AKCEA-TTR-L_{Rx} NEURO-TTRansform and CARDIO-TTRansform Phase 3 Studies Underway

Co-primary endpoints: mNIS+7 and QoL-DN at week 66



Primary endpoint: cardiovascular death & frequency of cardiovascular clinical events at week 120



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IONIS-AGT-L_{Rx}

Targeting AGT for the treatment of resistant hypertension

Hypertension is one of the most important risk factors for cardiovascular disease (CVD), the leading cause of mortality[1,2]

1. He et al., Am Heart J 1999; 138 (3 Pt 2):211–219; 2. Stamler et al., Arch Intern Med 1993; 153:598–615.

IONIS-AGT-L_{Rx} Market Opportunity

Large unmet need in patients with treatment-resistant hypertension

WW Prevalence

>140M

patients

>14% of 1.1B people with hypertension are uncontrolled with three or more medicines[1]

U.S. Prevalence[2]

~10M

patients

Disease Burden

Up to a 3-fold

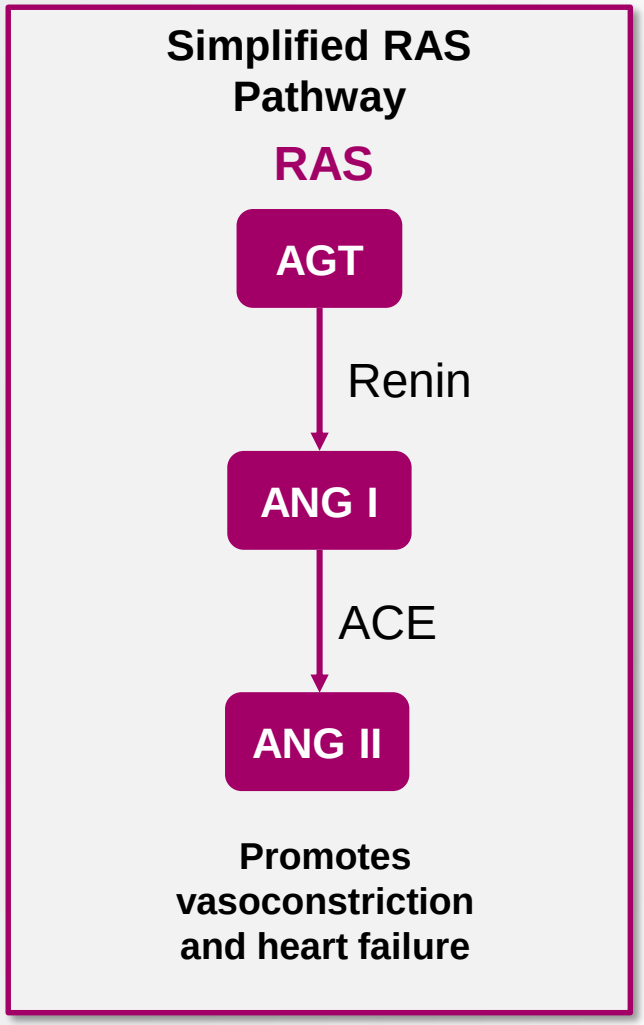
increased risk of having cardiovascular events[3]

1. Achelrod et al., Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. Am J Hypertens 2015;28:355-61; 2. Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens. 2014 Aug;28(8):463-8. 3. Zhang et al., J Hypertens. 2018 Jan;36(1):93-100.

IONIS-AGT-L_{Rx} is a Potential Treatment to Lower Blood Pressure in Treatment Resistant Hypertension Patients

- **IONIS-AGT-L_{Rx} targets AGT** (angiotensinogen), the most **upstream** substrate in renin-angiotensin system **(RAS)**, which is a well-established pathway involved in **hypertension (HTN)** and **complications** of **HTN**

- **Two Phase 2** clinical studies conducted in:
  - Patients with **mild HTN**
  - Patients with **uncontrolled HTN** who are on 2-3 antihypertensive medications, including Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs)



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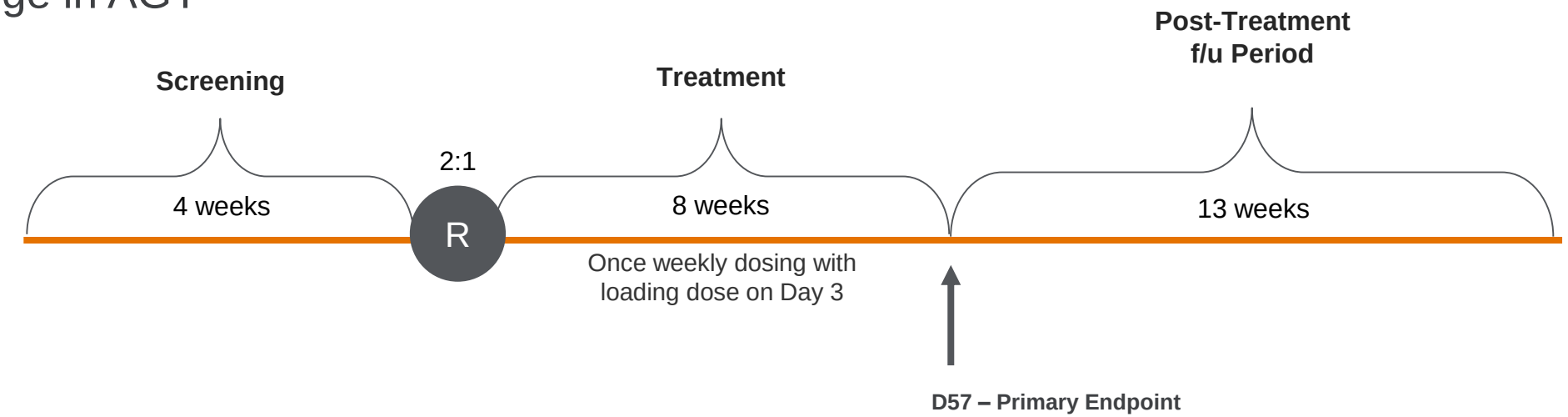
IONIS-AGT-L_{Rx} Phase 2 Study in Patients with Treatment Resistant Hypertension

Patient Population

- 26 hypertensive patients **uncontrolled with 2-3 antihypertensive medications**, including an ACE or ARB

Key Outcome Measures

- Change in systolic blood pressure (SBP)
- Change in AGT



Substantial Blood Pressure Reductions Demonstrated in Patients with Uncontrolled Hypertension

- **Positive** Phase 2 study in **uncontrolled HTN** patients on 2-3 HTN meds, including an ACE inhibitor or an ARB (65% on 2 HTN meds, 35% on 3 HTN meds)

Key Parameters	IONIS-AGT-L_{Rx}
Mean Change SBP mmHg	**-12**
Mean Change DBP mmHg	**-6**
% of Patients Reaching Goal SBP ≤140	**50%**

- **Favorable safety** and **tolerability** profile
  - No hypotension, no hyperkalemia and no acute renal failures
- Plan to **present** detailed **results** at upcoming medical **conference**

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Advancing the Ionis-owned Hypertension Portfolio

Broadening market opportunity through life cycle management

Planning to initiate multiple studies with our AGT program

- **Phase 2b in uncontrolled hypertension (3+ medications)**
- **Phase 2 study in patients with heart failure with reduced ejection fraction (HFrEF)**
- **Phase 1 study of ION904 (AGT-2.5-L_{Rx}) with the potential for less frequent SC & oral administration**

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Ionis Leads the Discovery and Development of Medicines to Treat Cardiometabolic Diseases

- Multiple medicines targeting major cardiovascular risk factors
- Broad cardiometabolic pipeline spanning rare to common diseases
- Extensive pipeline representing substantial commercial opportunity

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Ionis Pipeline: Addressing a Broad Range of Neurological Diseases

Clinically and commercially validated platform

Targeting all major brain regions and CNS cell types

Continued technology advancement increases leadership advantage

Frank Bennett, Ph.D.
Chief Scientific Officer

Ionis' Neurological Pipeline Addresses Broad Range of Diseases in All Major Brain Regions and CNS Cell Types

Tominersen
Huntington's Disease

ION373
Alexander Disease

ION716
Prion Diseases

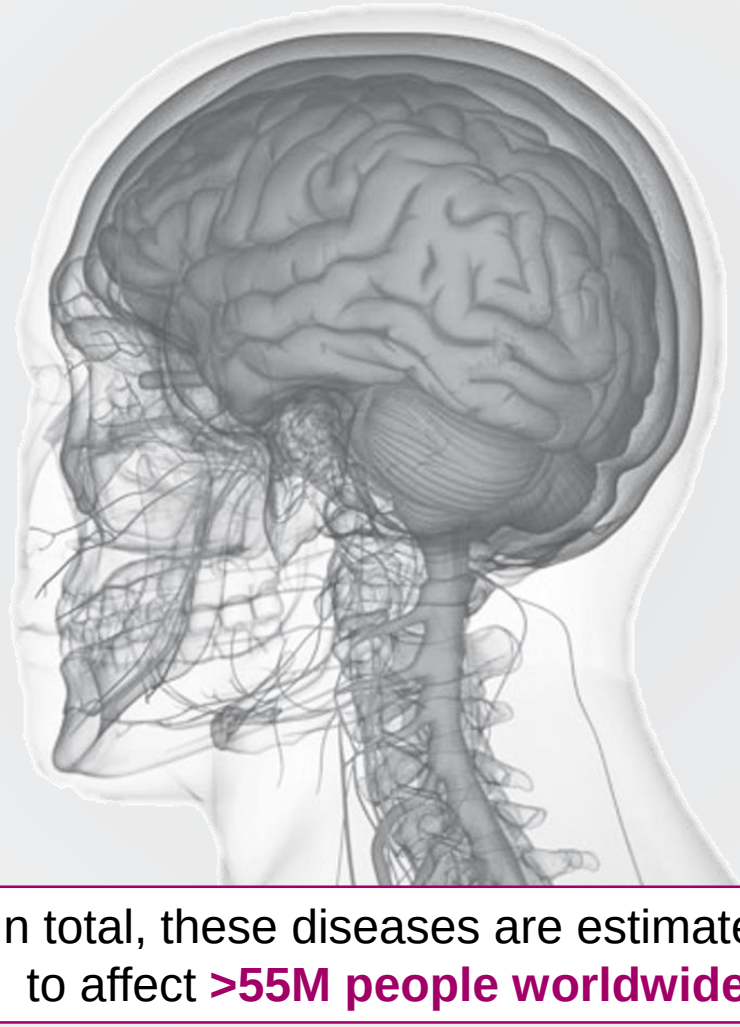
ION283
Lafora Disease

Tofersen
SOD1-ALS

IONIS-C9$_{Rx}$
C9-ALS

ION541
Sporadic-ALS

ION363
FUS-ALS



SPINRAZA® (nusinersen) injection 12 mg/5 mL
Spinal muscular atrophy

IONIS-MAPT$_{Rx}$
Alzheimer's Disease and Tauopathies

ION859
Parkinson's Disease

ION260
Undisclosed

ION464
Parkinson's Disease and synucleinopathies

ION582
Angelman syndrome

In total, these diseases are estimated to affect **>55M people worldwide**

And many more in research stage

Phase 3
Phase 1/2†
Preclinical

† 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.

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Advancing a Substantial and Growing Ionis-owned Neurological Pipeline

ATTR amyloidosis

TEGSEDI for hATTR polyneuropathy
AKCEA-TTR-L_{Rx} for all major forms

Alexander disease

ION373

Lafora disease

ION283

Amyotrophic Lateral Sclerosis

ION363 (FUS)

Prion diseases

ION716

Advancing a Substantial and Growing Ionis-owned Neurological Pipeline

ATTR amyloidosis

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AKCEA-TTR-L_{Rx} for all major forms

Alexander disease

ION373

Lafora disease

ION283

Prion diseases

ION716

Amyotrophic Lateral Sclerosis

ION363 (FUS)

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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
- **~55,000 patients diagnosed** (to date) in the G7 countries[1]
  - Genetic ALS (e.g. SOD1, C9, FUS): ~15%
  - ALS with no known genetic cause ALS: ~85%
- **Genetic** and **broad ALS** programs underway with Ionis and Biogen

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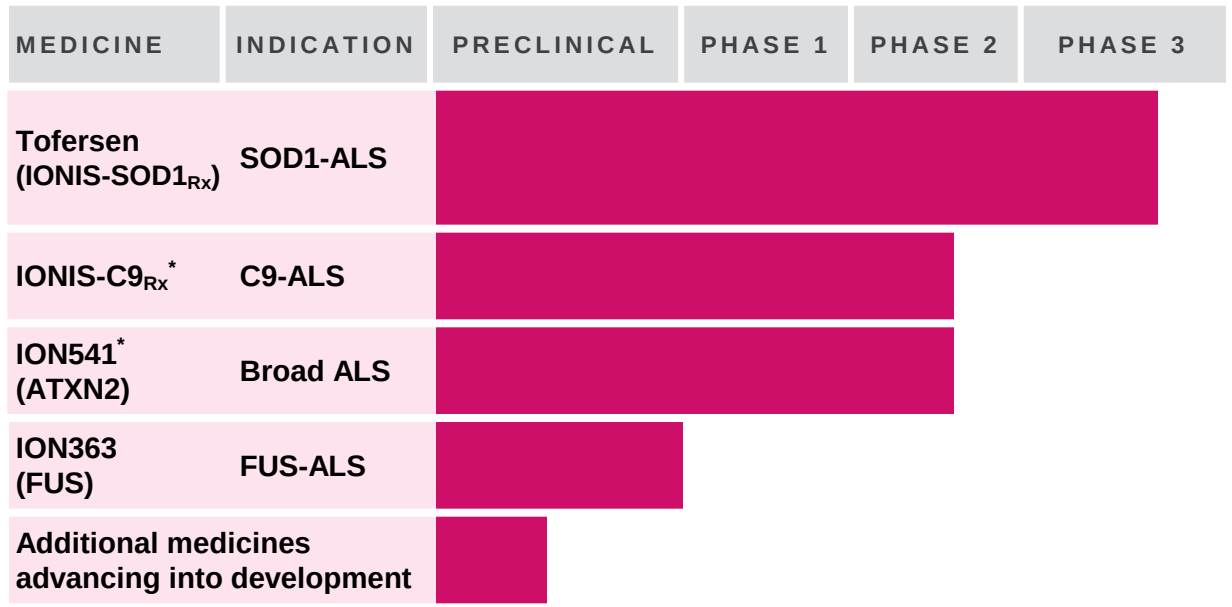
1. Biogen data on file; G7 countries include the U.S., Germany, the U.K., France, Italy, Spain, and Japan.

Committed to Treating All Forms of ALS

- Tofersen: **Phase 3 VALOR** study underway in SOD1-ALS (data expected 2021)
- IONIS-$C9_{Rx}$: **Phase 1/2 study ongoing** in **C9-ALS** (data expected 2021)
- ION363: **Ionis-owned** targeting **FUS** on track to initiate a pivotal clinical study in FUS-ALS in 2021
- ION541: **Phase 1/2 study ongoing** targeting **ATXN2** in **broad ALS population**
- Additional programs advancing

Multiple ALS Medicines in Development



* 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.

ION363

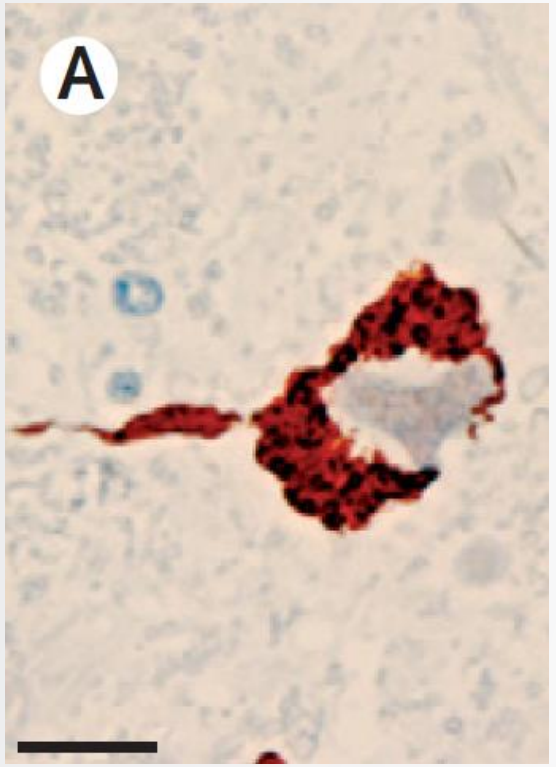
Targeting FUS-ALS

First medicine in development to specifically target FUS-ALS

- Potential treatment for a **rare, rapidly progressing form of ALS**
- On track to **initiate a pivotal study** in **2021**

FUS-ALS: Fast Progressing form of ALS with No Effective Treatment

- Caused by mutations in the Fused in Sarcoma (FUS) gene
- FUS-ALS is generally a fast-progressing form of ALS which follows a predictable pattern of disease progression
  - 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 forms aggregates in the cytoplasm



MacKenzie et al., Lancet Neurology 2010.

IONIS™

ION363: Designed to Selectively Reduce the Expression of Human FUS

- Antisense-mediated reduction of mutant FUS protein in a FUS-ALS mouse model **prevents motor neuron loss**
- **ION363** has been used by a collaborator to **treat several ALS patients** with FUS mutations under a compassionate use IND
- Initiation of a **pivotal study** in **FUS-ALS patients** on track for **early 2021**
- Potential for a **rapid path** to the market

IONIS™

ION716

Targeting prion diseases

Potential treatment for all forms of prion disease

- ION716 is designed to **reduce the production** of **prion protein** (PRNP), the **root cause** of prion disease
- **Pursuing two indications**
  - Pre-symptomatic (genetic carriers)
  - Symptomatic (genetic and sporadic)
- **2,000 patients** in the U.S.
- Planning to start **clinical studies in 2021**

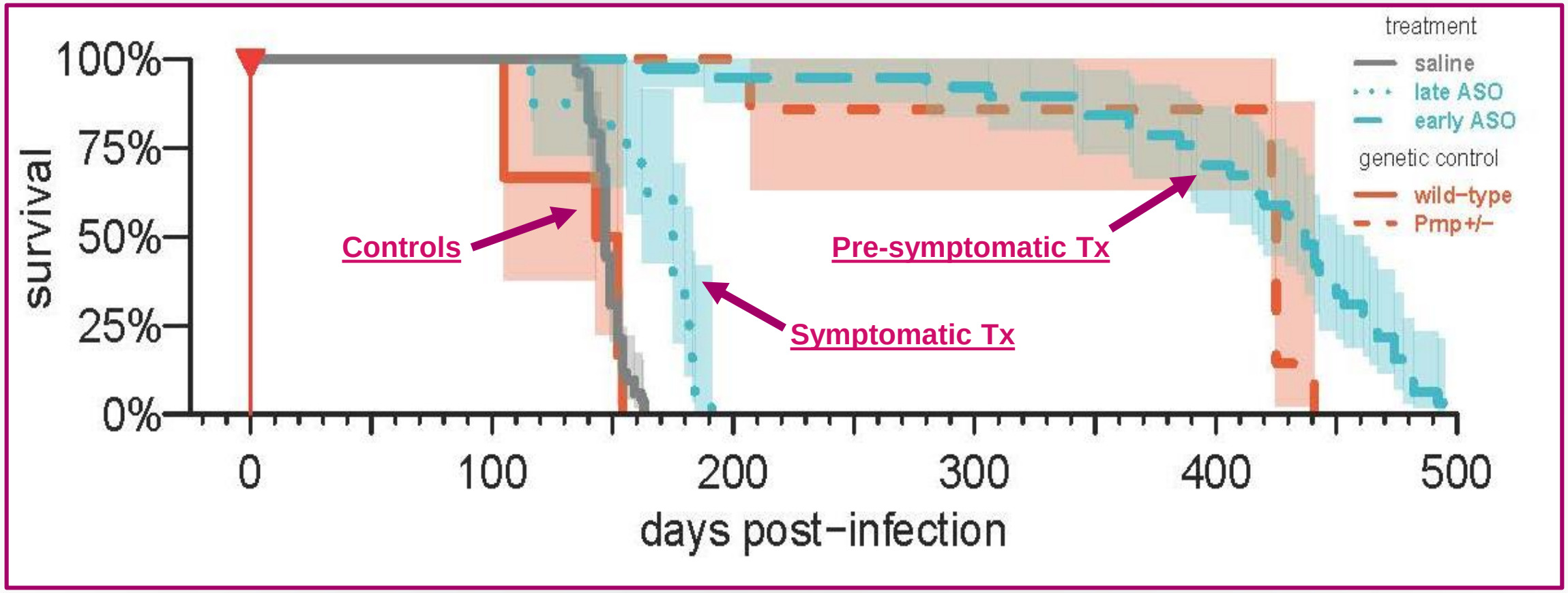
ION716 Targets the PRNP RNA for the Treatment of All Forms of Prion Disease[1]

- **Prion** diseases are **neurodegenerative** diseases caused by **misfolding** of the cellular **prion** protein (PrP^{C}) into misfolded, proteinaceous scrapie PrP^{Sc}
- **Rare**, **rapidly progressing** and **fatal** neurological diseases
- **Symptoms** include difficulty walking, speaking and **rapidly developing dementia**
- **No cure** or effective treatment
- ION716 **reduces** the **production** of **prion protein** (PRNP), the **root cause** of the **disease**

IONIS™

1. Raymond et al., JCII 2019

Antisense-mediated Suppression of PRNP can Dramatically Delay Disease in Rodent Models of Prion Disease



*Treatment initiation early at –7 to 78 days post-infection or late at 105 to 120 days post-infection
**Genetic control Prion disease models included for reference

IONIS™

1. Minikel et al., Nucleic Acids Research (2020). Prion protein lowering is a disease-modifying therapy across prion disease stages, strains and endpoints

Ionis Leads the Discovery and Development of Medicines to Treat Neurological Diseases

Ionis pioneered RNA therapeutics for neurological diseases

- Well-validated technology platform for addressing targets in multiple brain regions and all major cell types
- Clinically and commercially validated modality
- Broad neurological disease pipeline that spans from rare to common diseases
- The RNA-targeting antisense mechanism of action provides direct and rapid translation of genetic information to investigational medicine
- Antisense medicines offer the opportunity to treat patients with genetic mutations prior to symptom onset

IONIS™

Dr. Robert Henry: An Accomplished Researcher, Inspiring Teacher and Proud Grandfather of Five

Delivering Life-changing Medicines

Delivering on the Significant Market Opportunity of the Ionis-Owned Pipeline

Onaiza Cadoret-Manier

Chief Corp. Development Officer & Commercial Officer

Driving value for patients, providers & shareholders

Ionis Commercial Priorities

Focus

- Rare to Broad Rare
- Neurology and Cardiology

Pioneer new markets and **create** new standards-of-care

Rapidly bring **medicines** to patients

- Potential for multiple product launches through 2026

Ionis' Commercial Strategy

Maximizing the value of the Ionis-owned pipeline

Large, diverse portfolio of rare disease medicines

Addressing significant need

High probability of success from a well-established platform technology

Potential for 6+ product launches in next 5 years

Durable franchises in neurology and cardiovascular

Emerging products in hematology, endocrinology, and pulmonology

IONIS™

Growing in Neurology and Cardiology

Expanding beyond rare diseases opportunistically

Today

Rare Diseases

Neurology	Cardio/ metabolic
	
hATTR-PN	FCS

Growing in Neurology and Cardiology

Expanding beyond rare diseases opportunistically

Today

Rare Diseases

Neurology

hATTR-PN

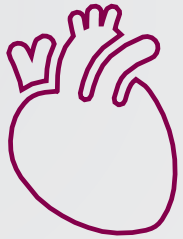
Cardio/ metabolic

FCS

Future

Broad Rare Diseases

hATTR-PN
Prion
FUS-ALS
Alexander



FCS
ATTR-CM

Growing in Neurology and Cardiology

Expanding beyond rare diseases opportunistically

Today

Rare Diseases

Neurology

hATTR-PN

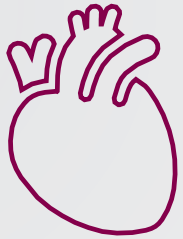
Cardio/ metabolic

FCS

Future

Expand

hATTR-PN
Prion
FUS-ALS
Alexander



FCS
ATTR-CM

Endocrinology

Acromegaly

Pulmonary

CF
HAE

Hematology

β-thal

IONIS™

Growing in Neurology and Cardiology

Expanding beyond rare diseases opportunistically

Today

Rare Diseases

Neurology

hATTR-PN

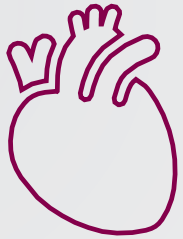
Cardio/ metabolic

FCS

Future

Expand

hATTR-PN
Prion
FUS-ALS
Alexander



FCS
ATTR-CM
HTG
RHTN

Endocrinology

Acromegaly

Pulmonary

CF
HAE
COPD

Hematology

β-thal

IONIS™

Pioneering New Markets

Prioritizing diseases with no approved treatment options

Meaningfully impacting patients, their families and HCPs while reducing the burden on the healthcare system

- **Alexander Disease**
- **Prion Diseases**
- **FCS**
- **FUS-ALS**
- **Spinocerebellar ataxia (SCA) diseases**

IONIS™

Leading Innovation in Neurological Diseases

Positioned to launch multiple Ionis-owned medicines through 2026

ATTR amyloidosis

TEGSEDI for hATTR polyneuropathy
AKCEA-TTR-L_{Rx} for all major forms

Alexander disease

ION373

Lafora disease

ION283

Prion diseases

ION716

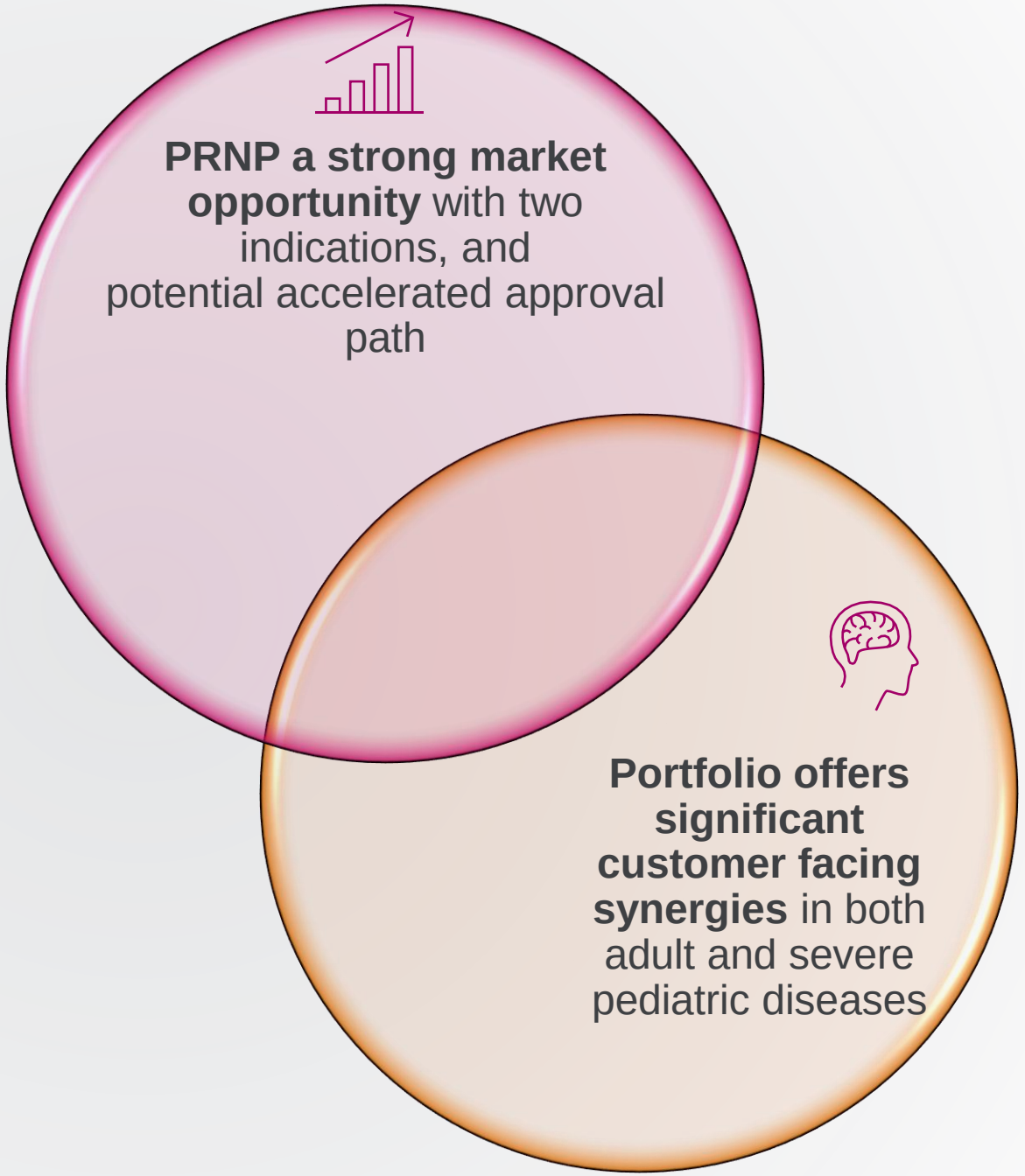
Amyotrophic Lateral Sclerosis

ION363 (FUS)

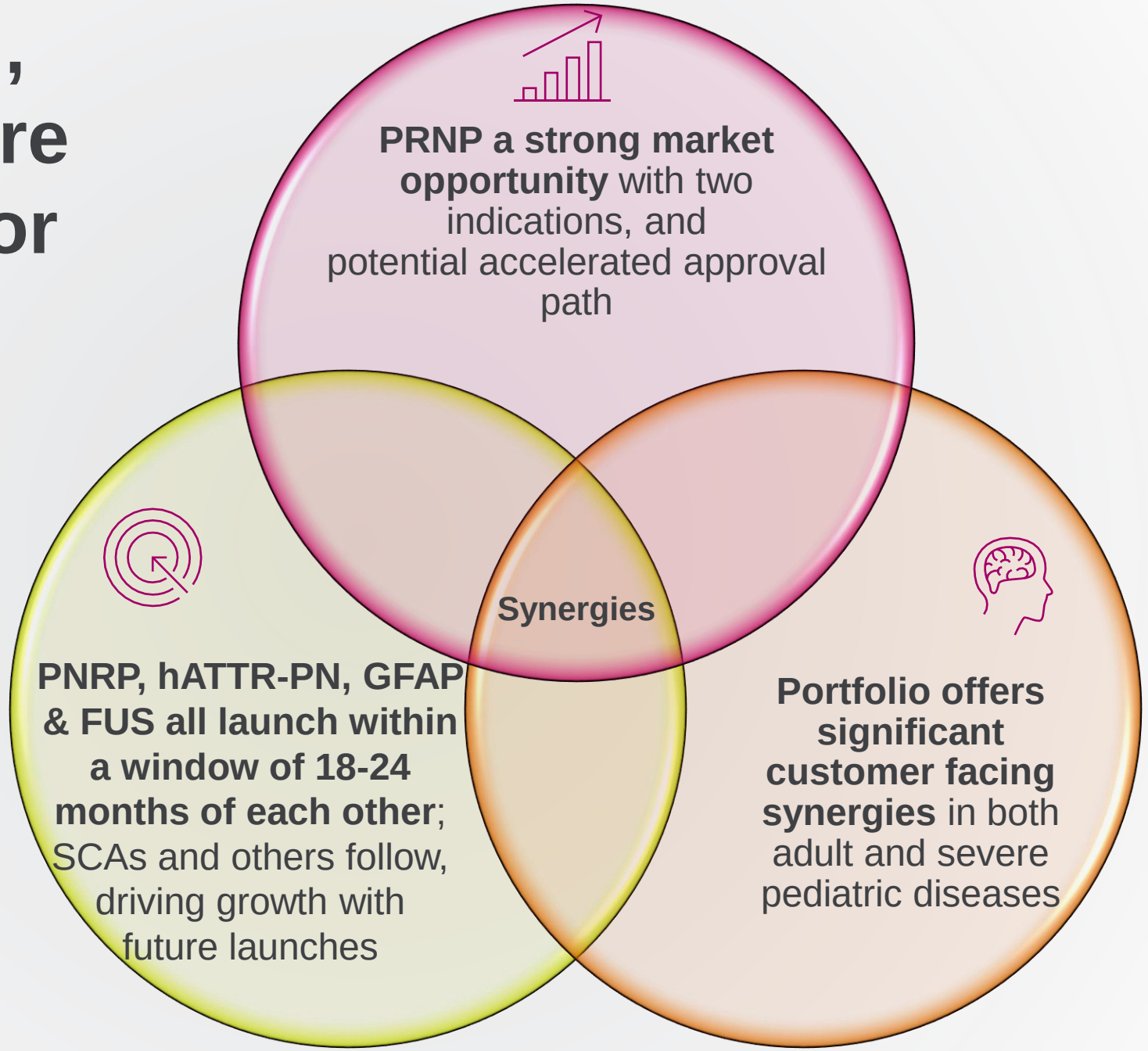
And many more in research stage

PRNP, hATTR-PN, GFAP, and FUS are the Foundation for our Neurology Franchise

PRNP, hATTR-PN, GFAP, and FUS are the Foundation for our Neurology Franchise



PRNP, hATTR-PN, GFAP, and FUS are the Foundation for our Neurology Franchise



IONIS™

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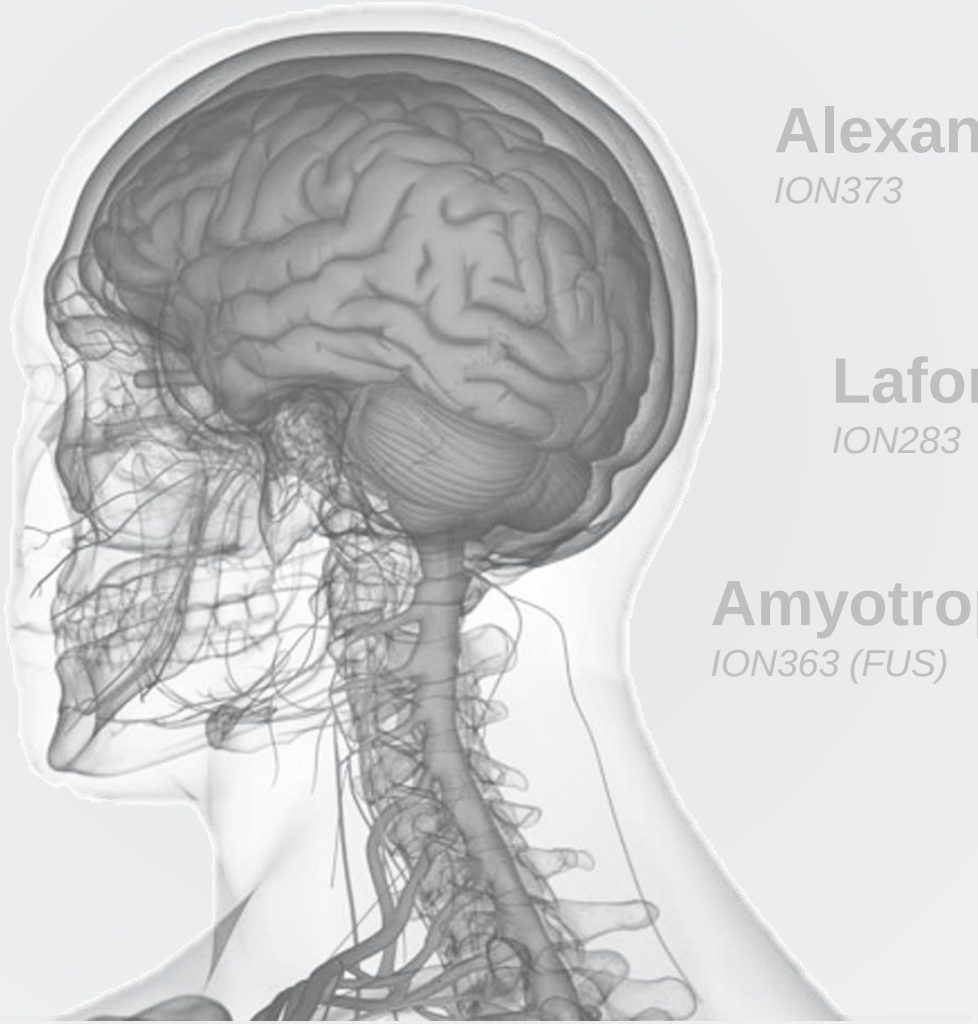


Alexander disease

ION373

Lafora disease

ION283

Amyotrophic Lateral Sclerosis

ION363 (FUS)

Prion diseases

ION716

And many more in research stage

ION716 Targeting All Forms of Prion Disease

First and best in class product profile potential

- Targets root cause of disease – prion protein
- Inhibits the production and accumulation of prion
- Potential to provide benefit to patient by:
  - Preventing or delaying disease progression in symptomatic patients
  - Improving survival
  - Preventing or delaying onset in genetic carriers

IONIS™

Building the Prion Disease Market to Drive a Successful Launch

KEY BUSINESS DRIVERS

- Timely diagnosis and treatment
- Awareness of effective new treatment option
- Consistent genetic testing in carrier families
- Active engagement of advocacy groups to support genetic registry and reimbursement efforts

CRITICAL ACTIVITIES

- Medical Affairs Scientific Exchange / Engagement
- Advocacy Engagement
- Payer and Scientific Exchange / Engagement

IONIS™

ION716 Has the Potential to Be First Approved Treatment in Prion Diseases

High Unmet Need	Prevalence per Registries and Expected to Grow	1st to Market Potential
100% fatal after symptom onset **No** approved treatment options	**~2K** Symptomatic **patients*** **~1K** Pre-symptomatic (genetic) **patients***	**>$500M** globally

IONIS™ * Ionis data on file

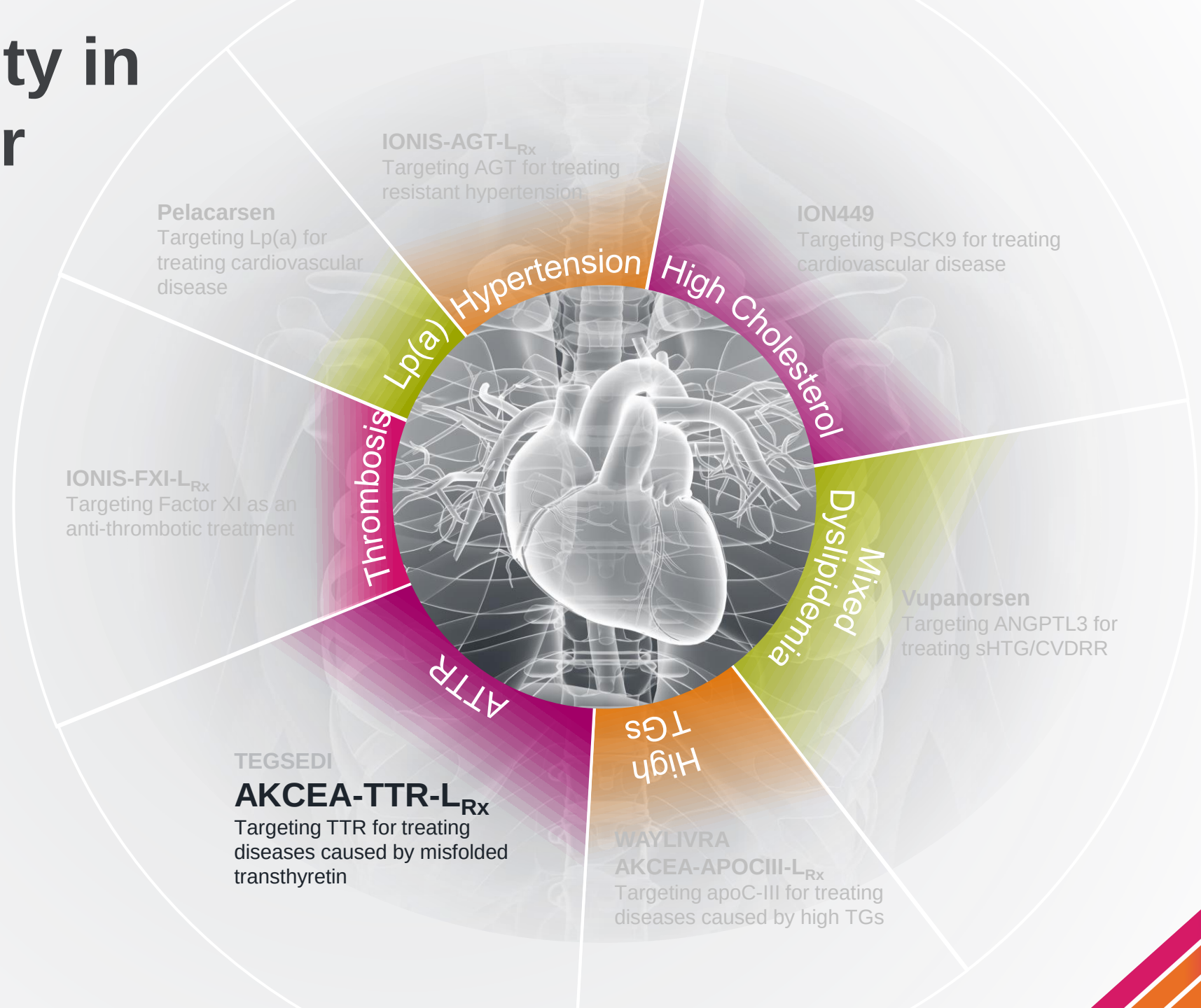
Changing the Standard of Care ….Driving Market Growth

Meaningfully impacting patients, their families and HCPs while reducing the burden on the healthcare system

- Elevated triglyceride diseases
- Amyloidosis
- Acromegaly
- Hereditary angioedema
- β-thalassemia

IONIS™

Our Opportunity in Cardiovascular Diseases



AKCEA-TTR-L_{Rx}: Multiple Indications

Expanding ATTR franchise in two sizable indications

Product profile

- Robust target reductions >90% demonstrated in Phase 1 study
- Potential to demonstrate efficacy in cardiomyopathy and polyneuropathy with and without standard of care
- Favorable safety and tolerability profile
- Flexibility of at home monthly self-administration

IONIS™

AKCEA-TTR-L_{Rx}: Significant Market Opportunity to Expand our ATTR Franchise

Fatal disease

affecting over 250,000 **patients** worldwide[1,2]

ATTR-PN (polyneuropathy)	ATTR-CM (cardiomyopathy)	Product Opportunity
~50K **patients** globally[1,2]	**~200K** **patients** globally[1,2]	**Multi-Billion $**

IONIS™

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.

AKCEA-TTR-L_{Rx}: Commercial Strategy

Sustainable competitive advantage in an evolving treatment paradigm

As the ATTR market expands, we expect AKCEA-TTR-L_{Rx} will become a foundational therapy in the treatment of hATTR-PN and ATTR-CM

- Planning to seek U.S. and EU approval for both hATTR-PN and ATTR-CM
- CARDIO-TTRansform Phase 3 study
  - Largest CM outcomes trial in ATTR patients (vs. 'Real World' standard of care)
  - CV death and events data has the potential to change the treatment paradigm
  - Generating data to demonstrate value separately and in combination with stabilizers
- Patient-friendly subcutaneous monthly administration

IONIS™

AKCEA-TTR-L_{Rx}: Executional Excellence Enabled by ATTR Market Experience

- Ability to **identify ATTR patients** via the Compass genetic testing program and enhanced data analytics
- **Experienced Medical Affairs** team to support KOL relationships and RWE
- Demonstrated **ability to gain strong formulary positioning** and reimbursement in U.S. and EU
- Ability to **support patients** with Akcea Connect
- Strong patient **advocacy relationships** with foundations and patients

IONIS™

KOL, key opinion leader. RWE, real-world evidence.

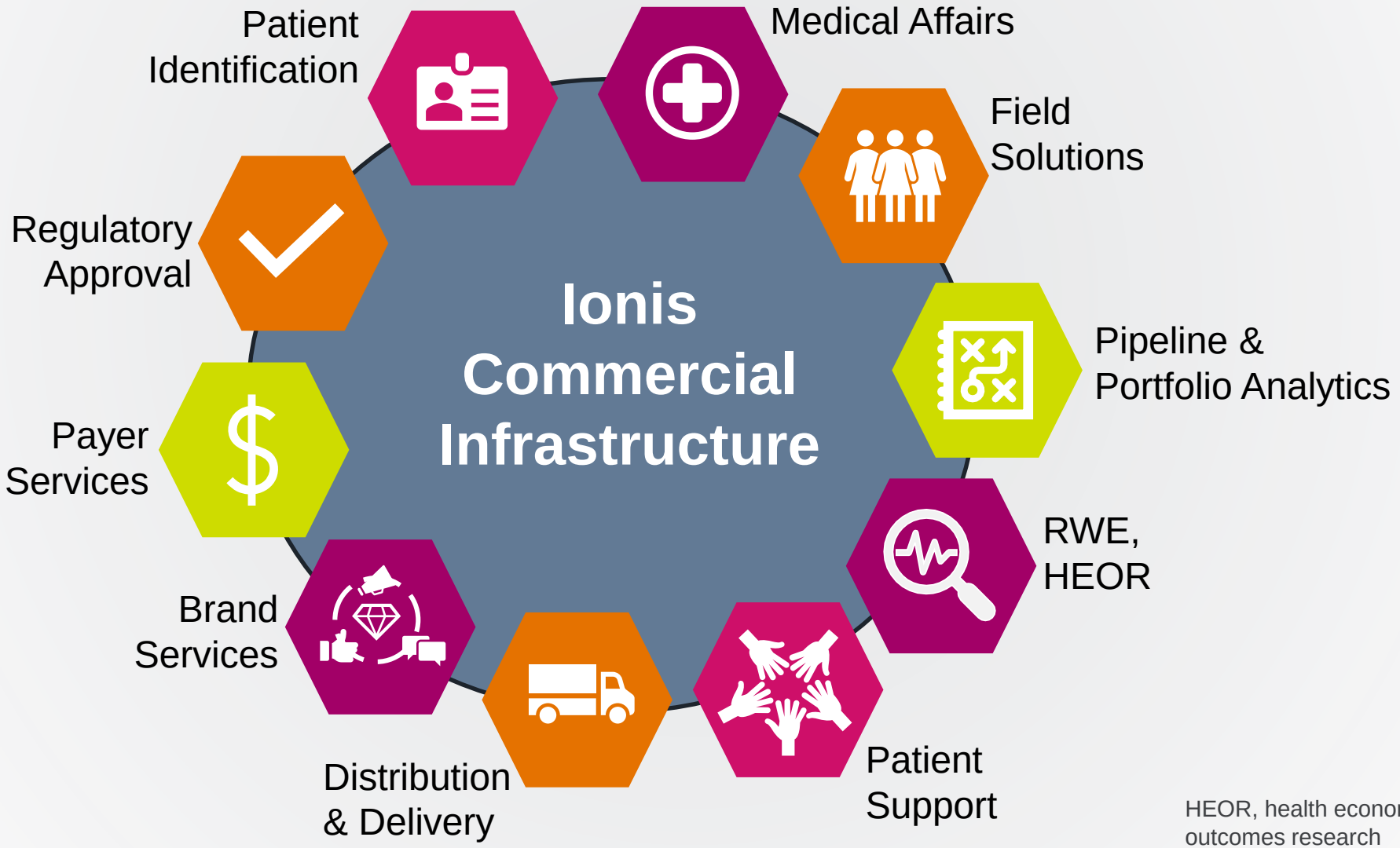
Akcea Acquisition

Advancing Ionis' commercial strategy

- Integration has gone smoothly and is ahead of schedule
- Leveraging and adapting Akcea's capabilities and experience
- Upon evaluating Akcea business operations, we entered into a distributorship arrangement with Sobi for Tegsedi and Waylivra in Europe
  - Akcea will continue to hold the marketing authorization for Tegsedi and Waylivra and maintain a commercial presence in Europe – building on the core KOL relationships we have established for our future products
  - Our regulatory and supply chain remain with Akcea to ensure we deliver these important medicines to the region
- This transaction allows us to reinvest resources to support our commercial plans

IONIS™

Leverage and Adapt Akcea's Capabilities



HEOR, health economics and outcomes research

Innovating to Identify, Reach and Support Patients Suffering from Serious and Rare diseases

Relentless Advocacy
Strong relationships with patient advocacy organizations

Big Data
Use of AI and predictive analytical tools to help find patients and maintain patients on treatment

Thought leadership
Experienced Medical Affairs organization to engage HCPs in dialogue and establish relationships

Virtual outreach
Utilization of non-personal promotion to reach larger prescribing population for higher prevalence indications

Compass
Expanded use of genetic testing to identify patients for earlier diagnosis and treatment

Akcea Connect
Patient support platform to support patients along their treatment journey

Investments in our Go-To-Market platform

IONIS™

Broadening our Commercial Reach

Additional rare disease product opportunities

Acromegaly
GHR-L_{Rx}

- Potential to more effectively control symptoms - including alleviating breakthrough symptoms – with monthly self-administered dosing

HAE
PKK-L_{Rx}

- >98% inhibition of proenzyme activation (Cohn et al., NEJM, Sep 2020)
- Potential for highly effective prevention of attacks, durability of response and high responder rates
- Potential for excellent tolerability & flexible at home administration

β-thal
TMPRSS6-L_{Rx}

- Potential to provide dual benefits of anemia and iron overload management in a single treatment
- Potential to address multiple indications and be a ‘pipeline in a product’

IONIS™

Advancing aerosol delivery of antisense medicines

- **Pulmonary diseases** are a common **cause** of **illness** and **morbidity**
- **High unmet** medical **need** and many diseases with genetically validated targets uniquely addressable by Antisense
- **IONIS-ENAC-2.5$_{Rx}$** demonstrates potential as a novel treatment for **cystic fibrosis** and **COPD**

Expanding Aerosol Delivery for Pulmonary Diseases

Opens the opportunity to treat multiple diseases of the lung

Cystic Fibrosis	Idiopathic Pulmonary Fibrosis
Phase 1/2	Discovery
~30K patients in U.S.[1]	~200K patients in U.S.[2]

1. American Lung Association (https://www.lung.org/lung-health-diseases/lung-disease-lookup/cystic-fibrosis/learn-about-cystic-fibrosis). 2. American Thorasic Society (https://www.thoracic.org/patients/lung-disease-week/2015/pulmonary-fibrosis-week/general-info.php)

Expanding Aerosol Delivery for Pulmonary Diseases

Opens the opportunity to treat multiple diseases of the lung

Cystic Fibrosis	Idiopathic Pulmonary Fibrosis	Chronic Obstructive Pulmonary Disease
Phase 1/2	Discovery	Phase 2
~30K patients in U.S.[1]	~200K patients in U.S.[2]	~16M patients in U.S.[3]

1. American Lung Association (https://www.lung.org/lung-health-diseases/lung-disease-lookup/cystic-fibrosis/learn-about-cystic-fibrosis). 2. American Thorasic Society (https://www.thoracic.org/patients/lung-disease-week/2015/pulmonary-fibrosis-week/general-info.php). 3. CDC (https://www.cdc.gov/copd/basics-about.html)

Delivering Growth by Delivering Transformational Medicines to Patients

Today **2** Ionis-owned commercial drugs

2026 **6+** Ionis-owned commercial drugs

CREATING DURABLE FRANCHISES IN NEUROLOGY AND CARDIOVASCULAR

EMERGING PRODUCTS IN HEMATOLOGY, ENDOCRINOLOGY & PULMONOLOGY

IONIS™

Beth Hougen
Chief Financial Officer

Ionis' Commercial Opportunities: Driving Substantial, Sustained Growth

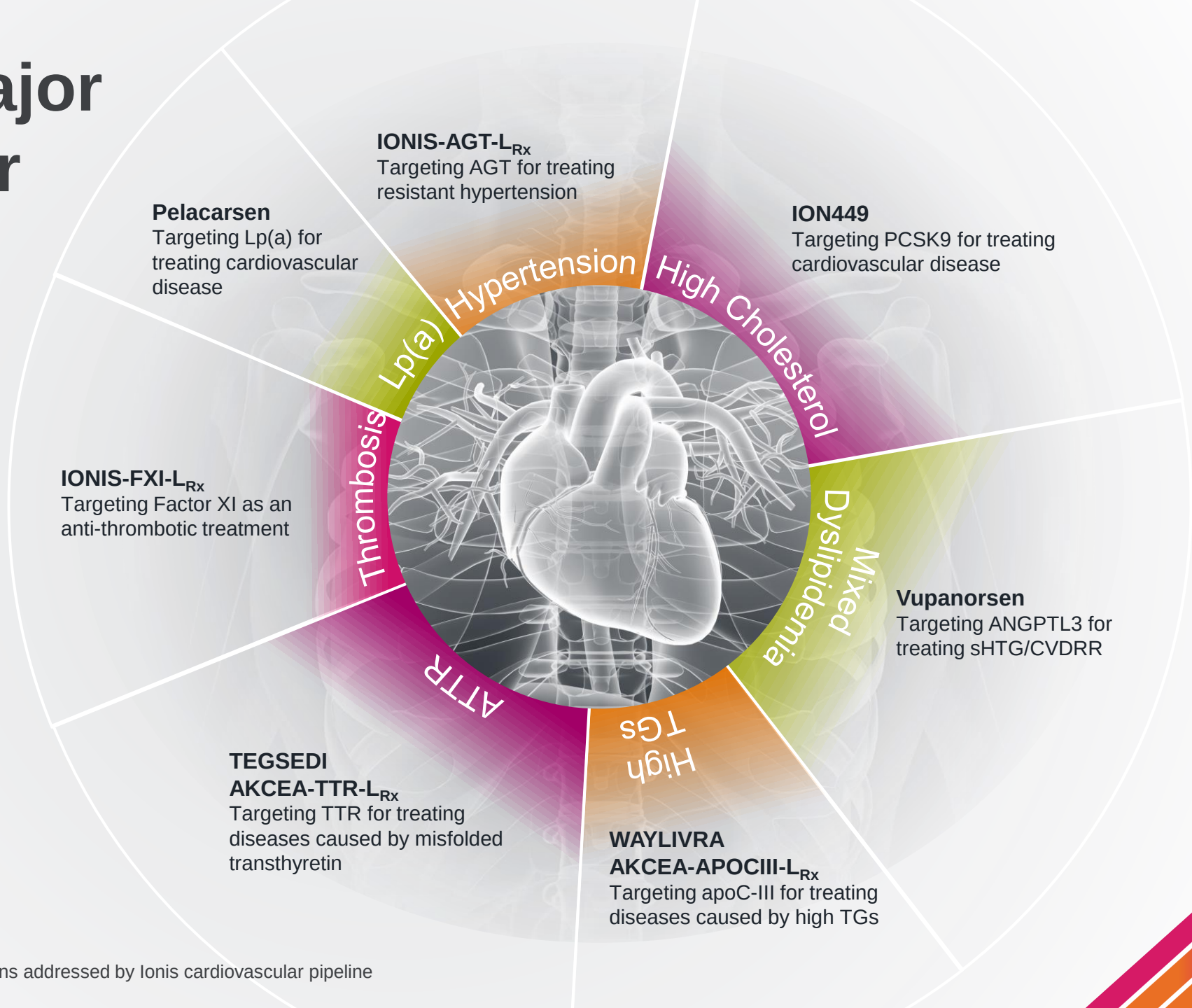
Investing in our strategic priorities

Substantial Financial Strength

- **Well capitalized**, with cash balance of nearly $2B*
- **Progress** our late- and mid-stage **programs**, positioning us for our next **wave** of **marketed products**
- **Advance** our **technology** platform to **enhance** our **leadership** position
- **Optimize commercial** capabilities to **maximize** the **value** of the **Ionis-owned** pipeline

*$2.3B as of September 30, 2020; $1.8B of pro forma cash following Akcea acquisition

Addressing Major Cardiovascular Disease Indications



IONIS-AGT-L_{Rx}
Targeting AGT for treating resistant hypertension

Pelacarsen
Targeting Lp(a) for treating cardiovascular disease

ION449
Targeting PCSK9 for treating cardiovascular disease

IONIS-FXI-L_{Rx}
Targeting Factor XI as an anti-thrombotic treatment

Vupanorsen
Targeting ANGPTL3 for treating sHTG/CVDRR

TEGSEDI
AKCEA-TTR-L_{Rx}
Targeting TTR for treating diseases caused by misfolded transthyretin

WAYLIVRA
AKCEA-APOCIII-L_{Rx}
Targeting apoC-III for treating diseases caused by high TGs

The cardiovascular disease market is

>$75B*

today

IONIS™

* Ionis data on file for indications addressed by Ionis cardiovascular pipeline

Addressing Neurological Diseases in All Major Brain Regions and CNS Cell Types

Tominersen
Huntington's Disease

ION373
Alexander Disease

ION716
Prion Diseases

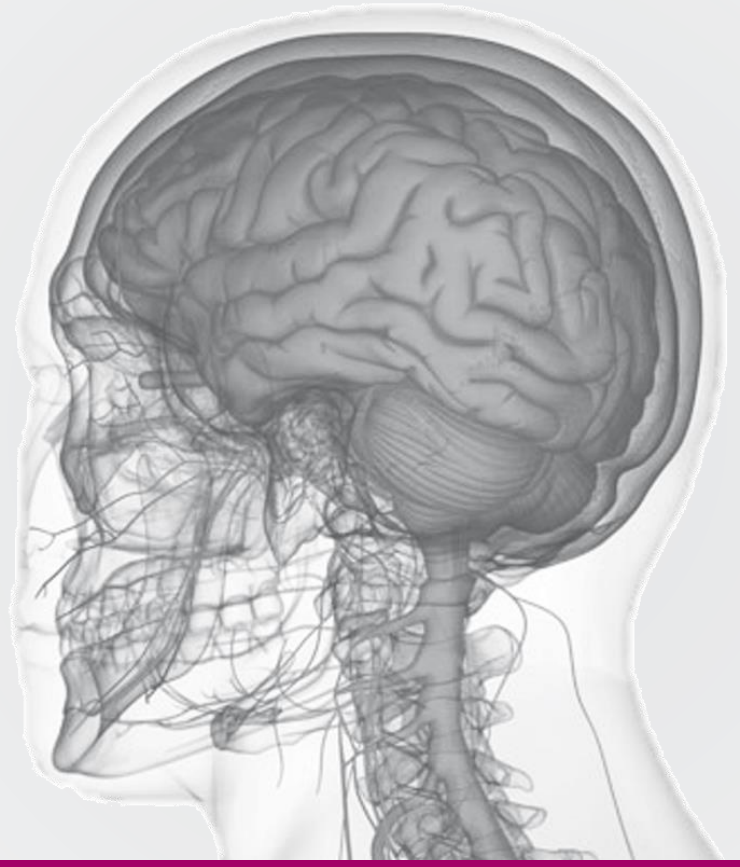
ION283
Lafora Disease

Tofersen
SOD1-ALS

IONIS-C9$_{Rx}$
C9-ALS

ION541
Sporadic-ALS

ION363
FUS-ALS



SPINRAZA® (nusinersen) injection 12 mg/5 mL
Spinal muscular atrophy

IONIS-MAPT$_{Rx}$
Alzheimer's Disease and Tauopathies

ION859
Parkinson's Disease

ION260
Undisclosed

ION464
Parkinson's Disease and synucleinopathies

ION582
Angelman syndrome

The neurological disease market is

>$15B*

today

Phase 3
Phase 1/2†
Preclinical

IONIS™

* Ionis data on file for indications addressed by Ionis neurological pipeline

† 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.

Positioned for Substantial Revenue Growth

Delivering double digit revenue growth

12+
Marketed products

Ionis-owned Neuro
- ION283 (Lafora)
- TTR-L_{Rx} (hATTR-PN)
- ION716 (Prion)
- ION373 (Alexander)
- ION363 (FUS-ALS)

Partnered Neuro
- Tofersen (SOD1-ALS)
- Tominersen (HD)
- $C9_{Rx}$ (C9-ALS)
- ION541 (Broad ALS)

Ionis-owned Cardio
- TTR-L_{Rx} (ATTR-CM)
- APOCIII-L_{Rx} (TG diseases)
- AGT-L_{Rx} (RHTN)
- GHR-L_{Rx} (Acromegaly)

Partnered Cardio
- Pelacarsen (Lp(a) CVDRR)
- Vupanorsen (sHTG/CVDRR)
- FXI-L_{Rx} (ESRD)

Ionis-owned Other
- TMPRSS6-L_{Rx} (β-thal)
- PKK-L_{Rx} (HAE)

Partnered Other
- HBV_{Rx} (Hep B)

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Tegsedi® (inotersen) injection 284 mg/1.5 mL

waylivra® (volanesorsen) injection 285 mg/1.5 mL

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Tegsedi® (inotersen) injection 284 mg/1.5 mL

waylivra® (volanesorsen) injection 285 mg/1.5 mL

Increasing Our Leadership Position in RNA-targeted Therapeutics

New chemistries

Optimize designs

New routes of delivery

Human genomics investments

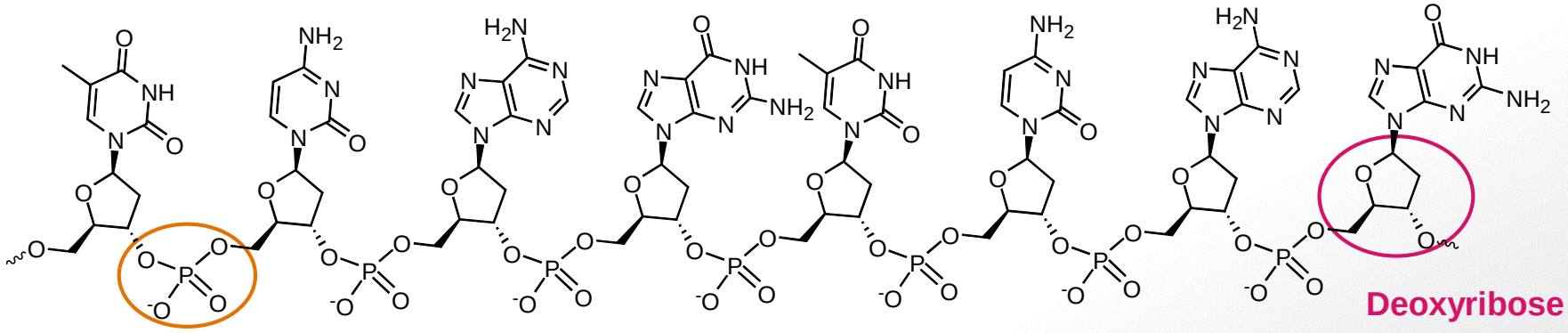
New technology platforms

Eric Swayze

Executive Vice President, Research

Oligonucleotide Drugs Require Chemical Technology

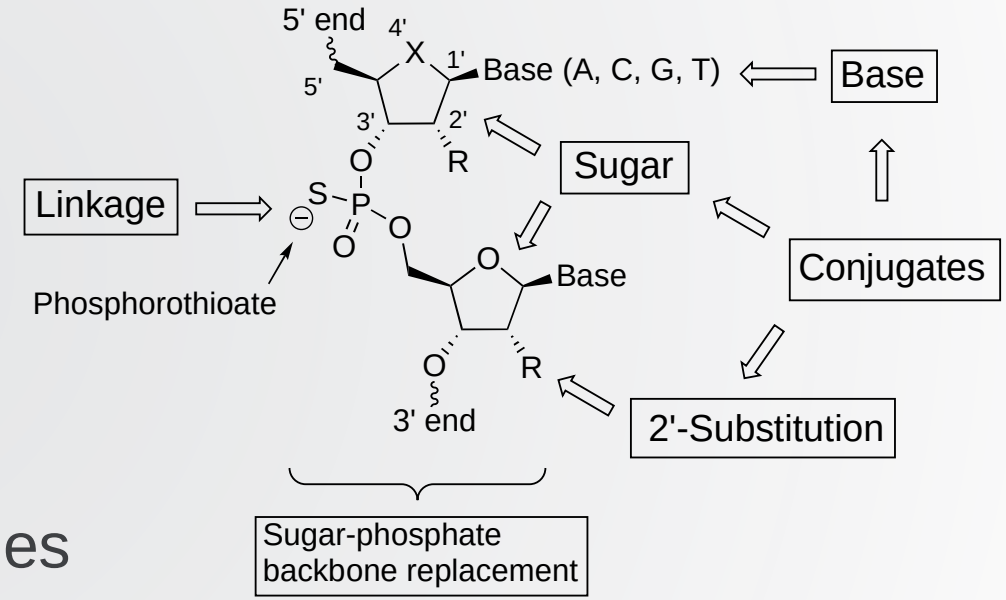
- Limitations of DNA and RNA as drug molecules
  - Insufficient affinity for target RNA: *Limits potency and target sites*
  - Have poor pharmacokinetics: *Requires frequent, high dosing*
    - Lack sufficient bio-stability
    - Rapidly excreted into urine
- The pharmaceutical industry has addressed these issues with other ‘natural products’ for over 100 years with medicinal chemistry



IONIS

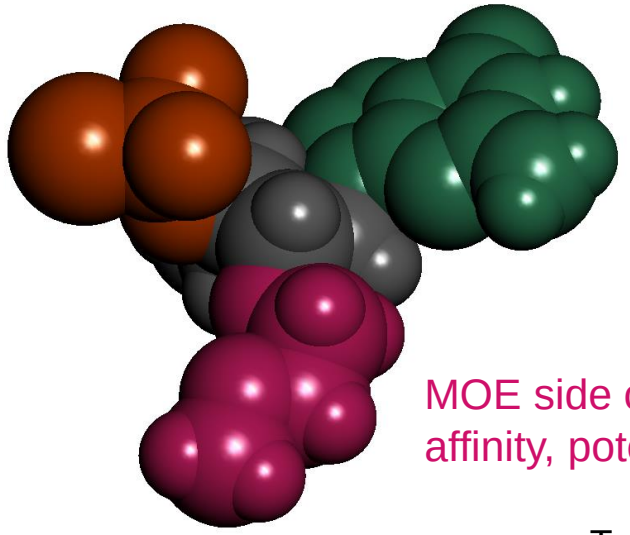
Ionis Antisense Oligonucleotide Technology is a Result of a Broad Medicinal Chemistry Program

- Created a set of novel chemicals by modifying every part of a nucleic acid that wasn't involved in target recognition
- Produced key technologies we use today
  - MOE
  - cEt BNA
  - LICA
- Continuing to produce new chemical technologies that will further improve performance



Benefits of MOE Chemistry

Stability of MOE allows use of ***either*** phosphorothioate ***or*** phosphodiester backbone



Heterocyclic Base
Recognizes target RNA

MOE side chain improves binding affinity, potency and safety

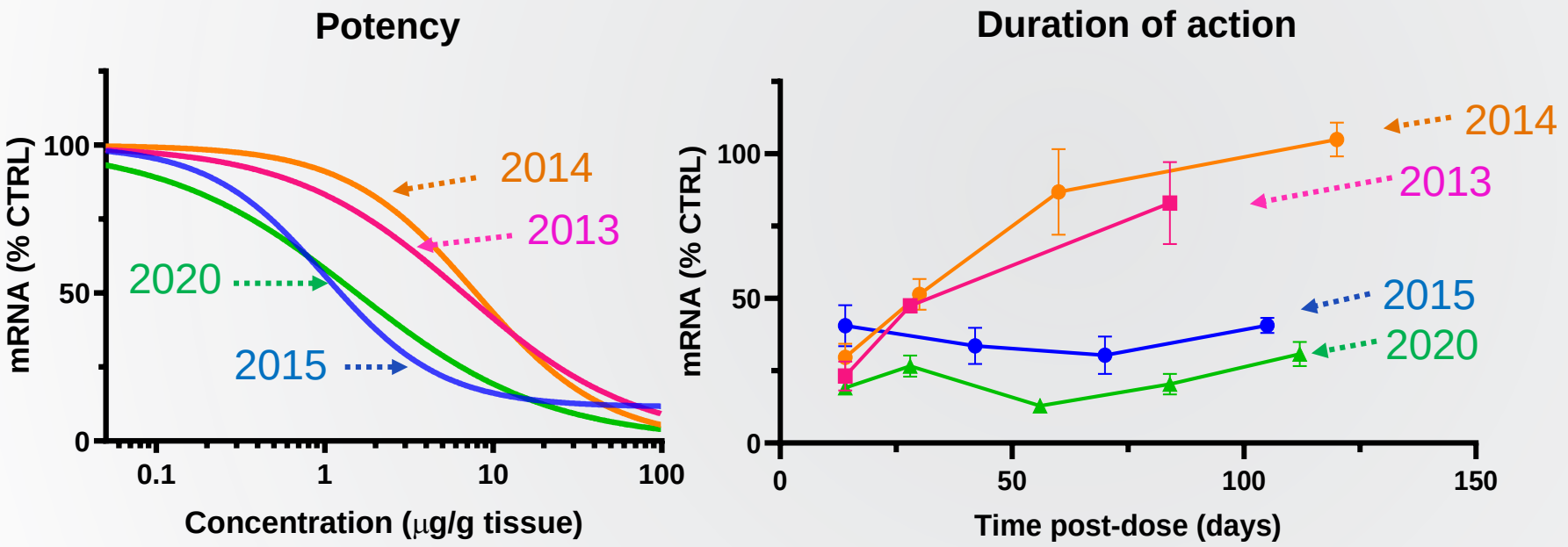
Teplova, et al. *Nat. Struct. Biol.* 1999, *6*, 535-539.

- Increases stability in biological systems
- Increases potency due to improved binding affinity and stability
- Improves safety profile by decreasing proinflammatory effects and class toxicities
- Improved duration and potency achieved via optimized ASO designs

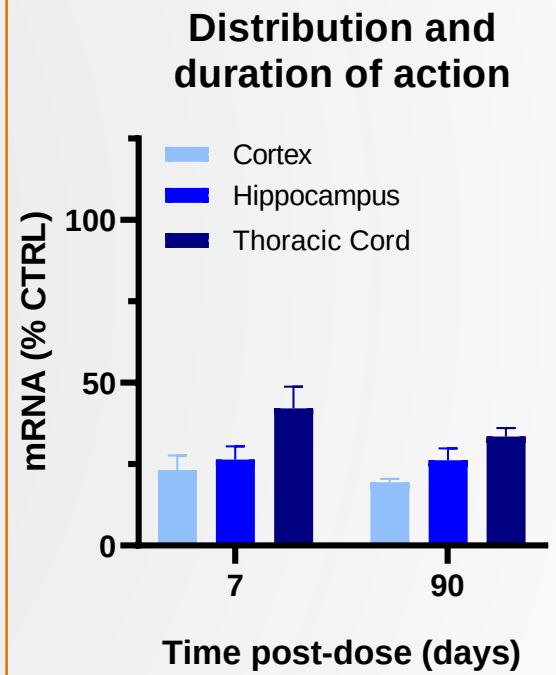
IONIS™

Optimized Designs Have Improved Duration and Potency of Antisense Medicines Addressing Neurological Diseases

Human transgenic mice

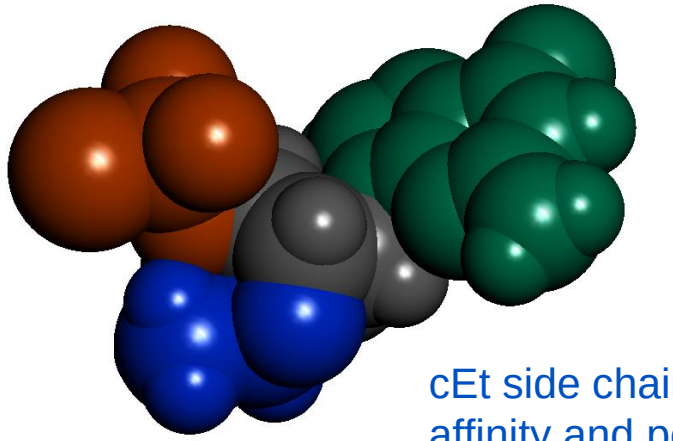


Non-human primate



cEt BNA Chemistry (Generation 2.5) has Improved Performance in Multiple Therapeutic Areas

Stability of cEt allows use of ***either*** phosphorothioate ***or*** phosphodiester backbone



Heterocyclic Base
Recognizes target RNA

cEt side chain improves binding affinity and potency

Pallan, et al. *Chem Commun (Camb)* **2012**, *48*, 8195-8197.

- Further increases potency by greatly increasing affinity to target RNA
- Maintains the extended dosing interval and safety profile
- Improves therapeutic index, and facilitates activity in new tissues

IONIS™

Advancing Aerosol Delivery of Antisense Medicines

- Pulmonary diseases are a common cause of illness and morbidity with high unmet medical need
- In preclinical studies, we have shown cEt BNA ASOs distribute and are effective throughout the lung with aerosol administration
- IONIS-ENAC-2.5$_{Rx}$ is our first pulmonary medicine using this technology
  - Preclinical data supports ENAC ASO as a novel treatment for cystic fibrosis and COPD
  - Phase 1 data demonstrates good target engagement in humans

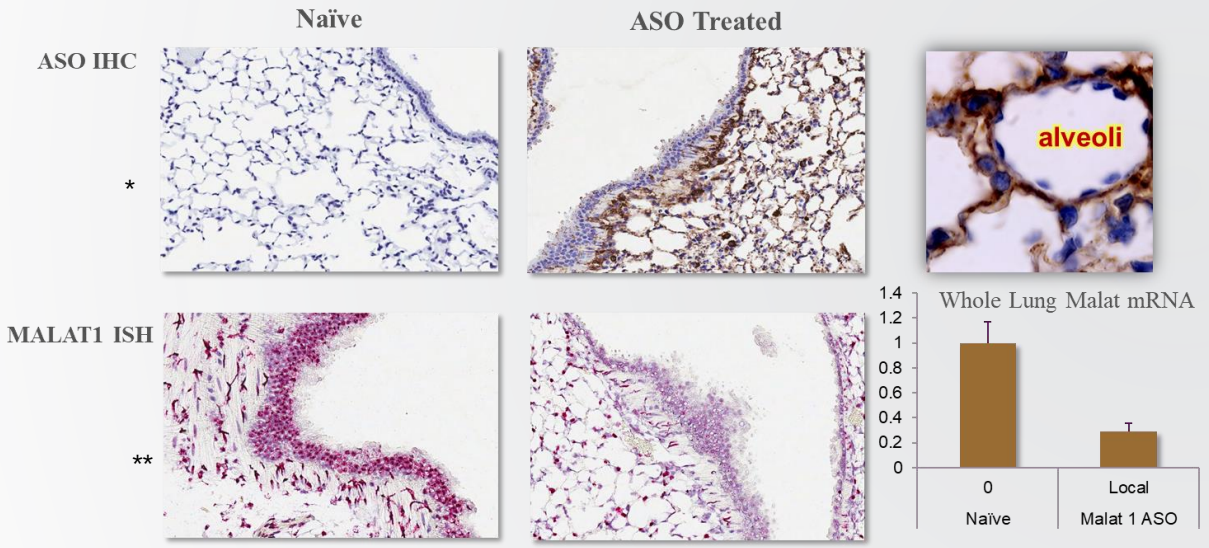
IONIS™

Aerosol Delivery

Broad distribution and potent activity in the lung with cET BNA chemistry

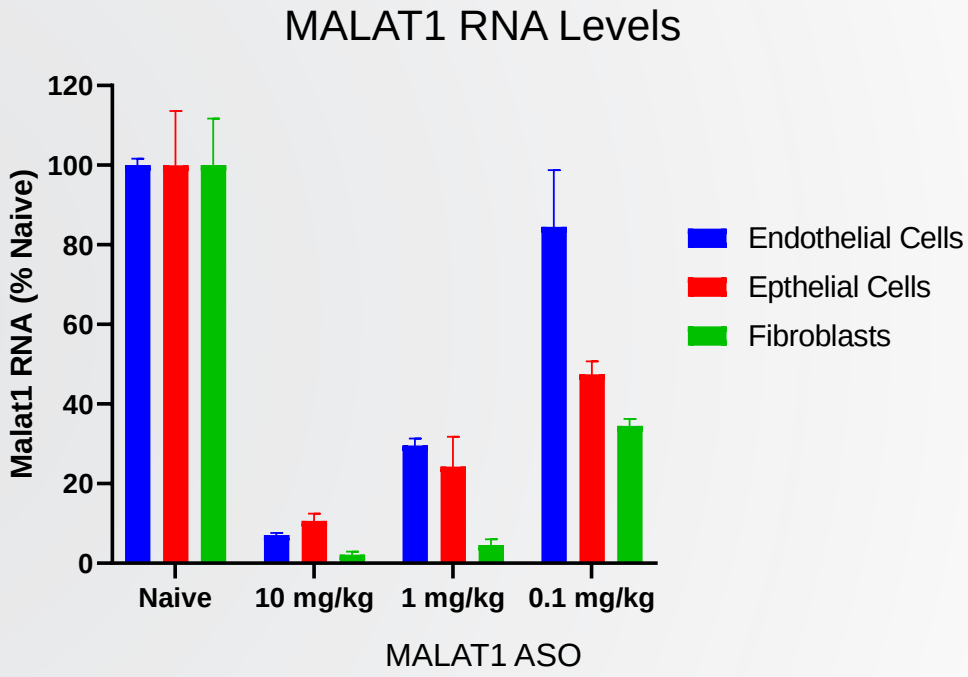
Aerosolized ASO Distributes Broadly in Mouse Lung

Aerosol delivery of ASO targeting MALAT1, an abundant nuclear ubiquitously expressed noncoding RNA



*IHC: Immunohistochemistry (Brown = ASO)
**ISH: In Situ Hybridization (Pink = target RNA)

Potent Activity in Different Cell Types

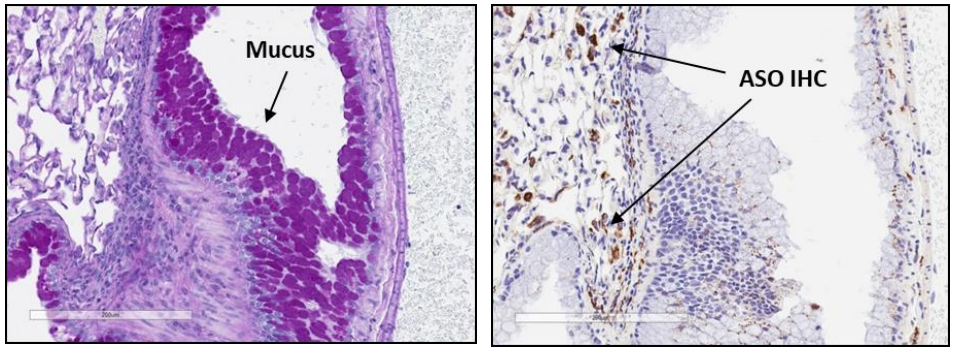


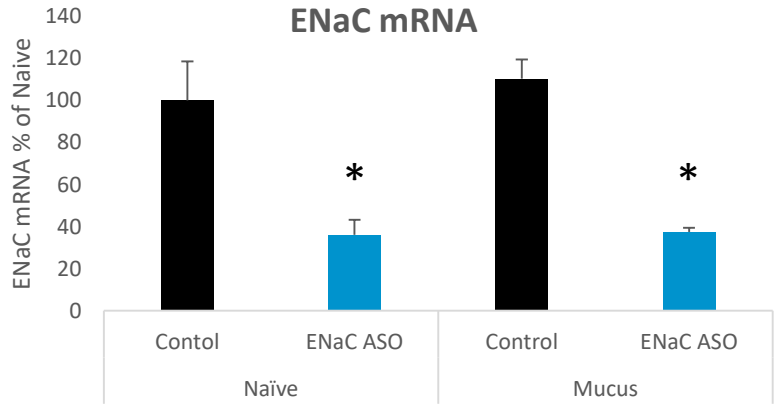
- **Long tissue half-life (~2 weeks) in the lung enables infrequent dosing**
- **Minimal systemic exposure after aerosol delivery**

ENaC mRNA Reductions of ~40% Resulted in Significant Improvement in Mouse Models of CF Lung Disease

Aerosol delivery of ASO reduces expression in diseased models where the lung is full of mucus

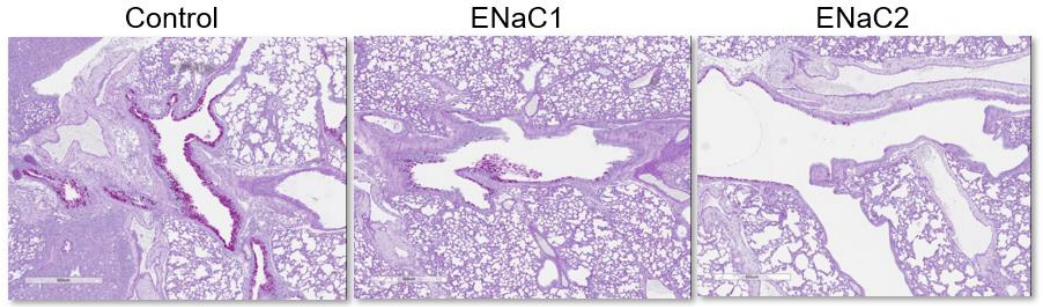
- ENaC ASO delivered after mucus was established with house dust mite
- Achieved similar ASO distribution and activity

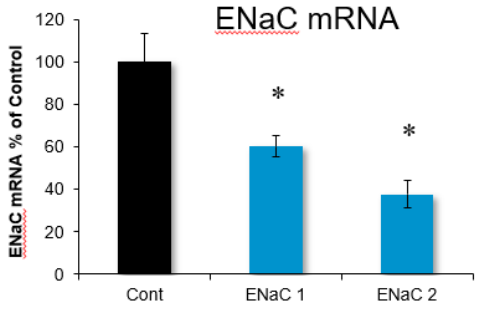


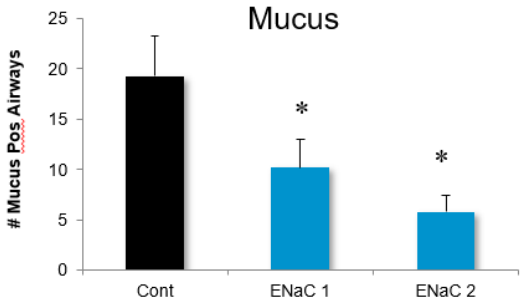


40% ENaC reduction resulted in significant **improvement of CF lung phenotype**

- Nedd4L knockout mice (CF lung disease model) was dosed with ENaC ASOs 1 or 2
- Resulted in reduction of mucus and inflammation







* p<0.05

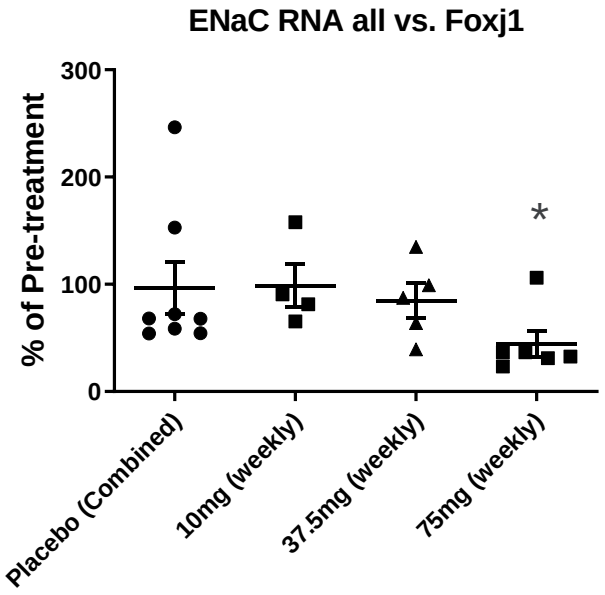
Crosby et al. JCF, 2017

IONIS-ENAC-2.5$_{Rx}$ Demonstrated Robust Target Reductions in the Lung

Phase 1 study of IONIS-ENAC-2.5$_{Rx}$

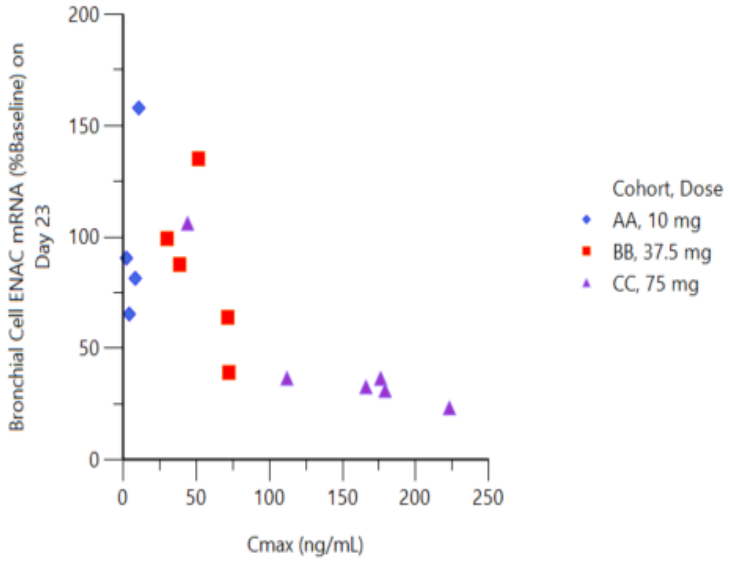
- **Favorable safety** and **tolerability** profile
- Mean **56% decrease** in ENaC mRNA expression at the 75mg dose
- The first time an **antisense medicine delivered directly to the lung** via a nebulizer has shown a significant reduction in ENaC mRNA levels

Reduction in ENaC mRNA from Bronchial Brushings



* p<0.05

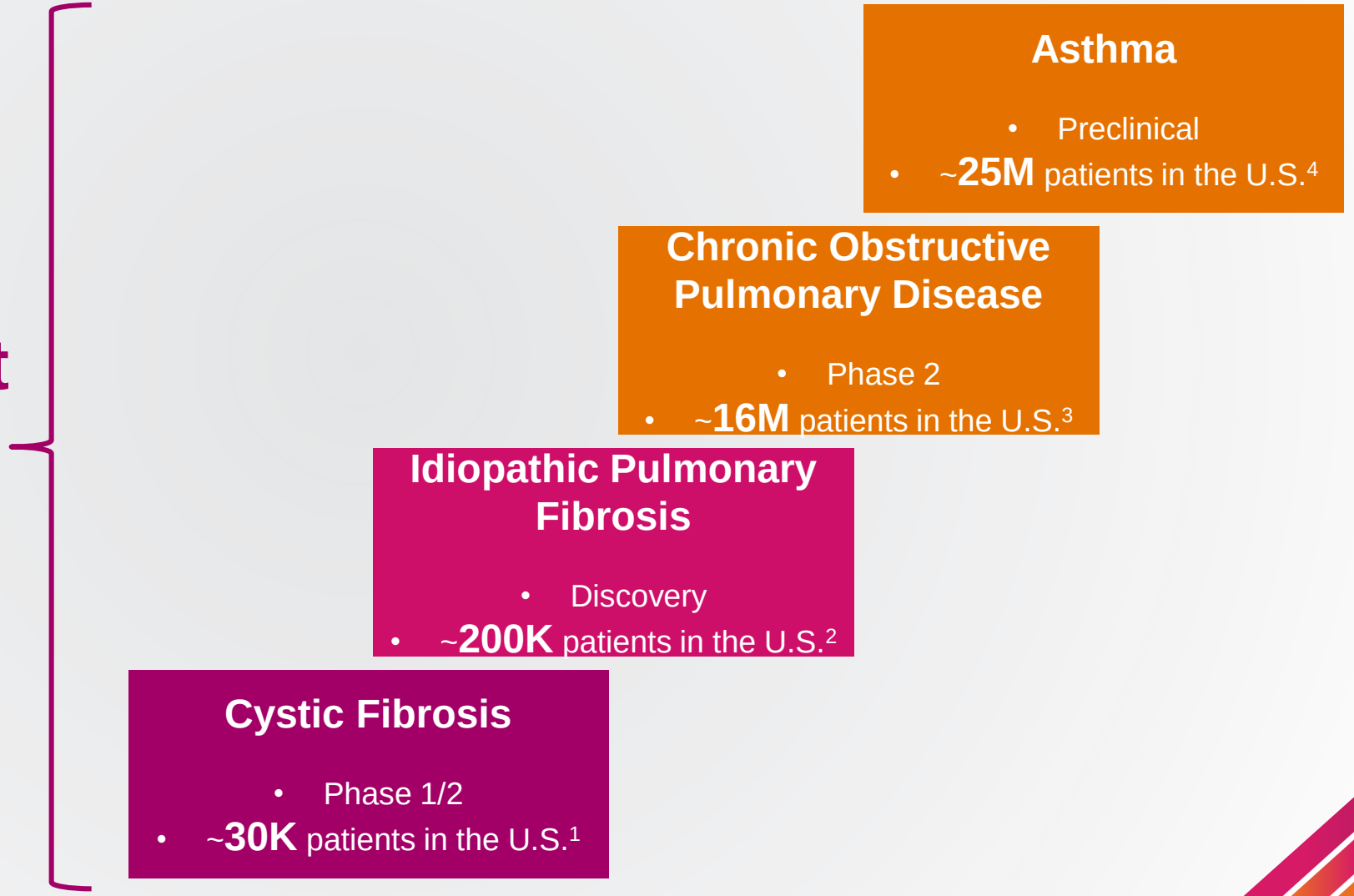
High Correlation between PK & PD



Aerosol delivery broadens the application of Antisense medicines for pulmonary diseases

Expanding Aerosol Delivery of Ionis-owned Medicines

Opens the opportunity to treat multiple diseases of the lung



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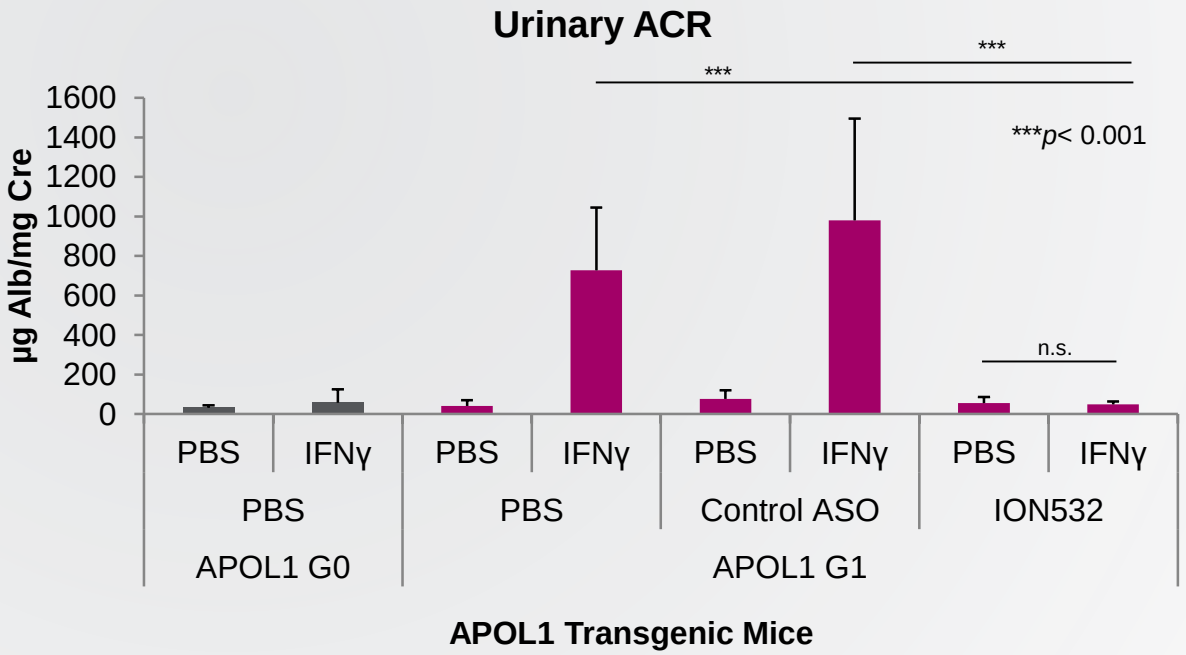
1. American Lung Association (https://www.lung.org/lung-health-diseases/lung-disease-lookup/cystic-fibrosis/learn-about-cystic-fibrosis). 2. American Thorasic Society (https://www.thoracic.org/patients/lung-disease-week/2015/pulmonary-fibrosis-week/general-info.php). 3. CDC (https://www.cdc.gov/copd/basics-about.html) 4. AAFA (https://www.aafa.org/asthma-facts/)

cEt BNA Chemistry Enables a Potential Precision Medicine for the Treatment of CKD in African Americans

- ApoL1 risk alleles (G1 and G2) are strongly associated with end-stage renal disease in African Americans (AA) (Freedman et al. JASN, 2010)
  - These risk alleles are largely responsible for the increased risk of ESRD in AAs
  - ~50% AA possess at least one risk allele, ~13% possess two risk alleles (~6M AA at-risk)

- Mice expressing human APOL1 G1 risk allele, but not G0 (WT) allele, showed albuminuria upon IFNγ challenge
- ION532 (APOL1 ASO) treatment prevented IFNγ-induced albuminuria



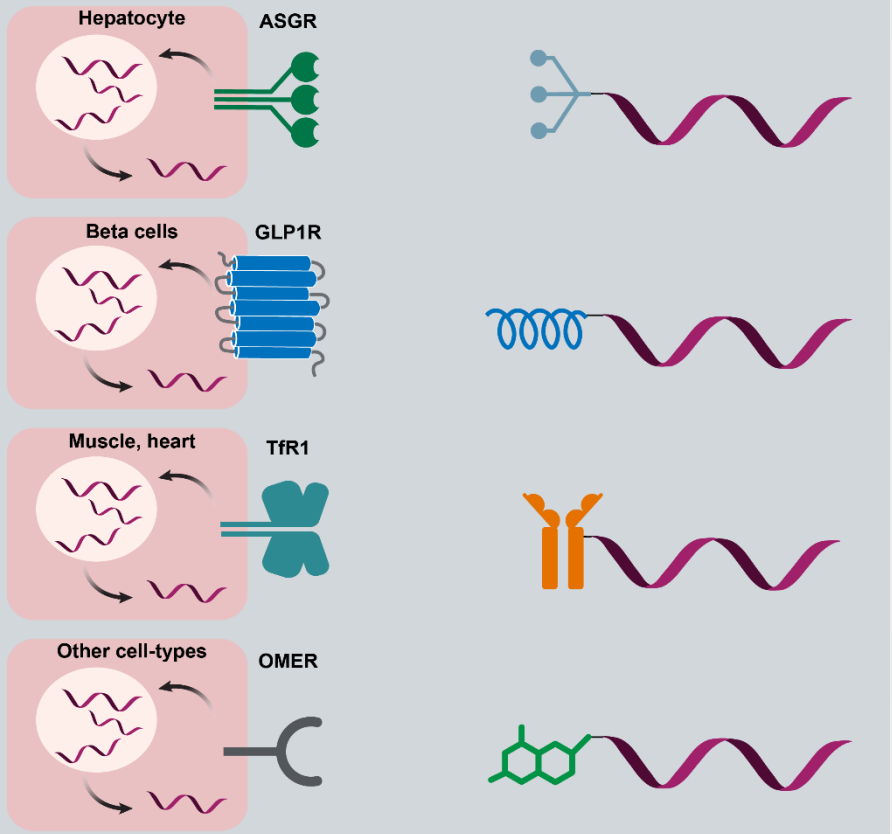
Aghajan et al. JCII, 2019

ION532 (APOL1) Phase 1 study underway

Ionis LICA Platform Continues to Expand

Multiple Tissues

- Liver
- Pancreas
- Muscle
- Many others in research stage

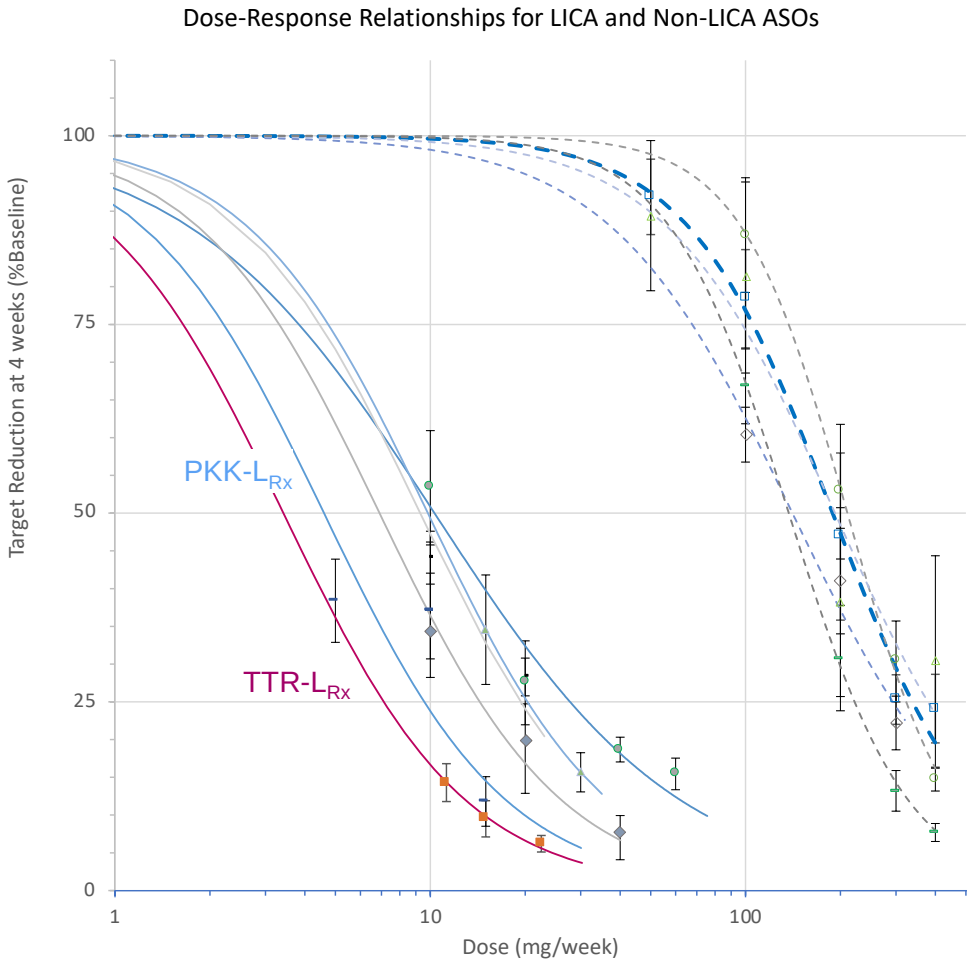


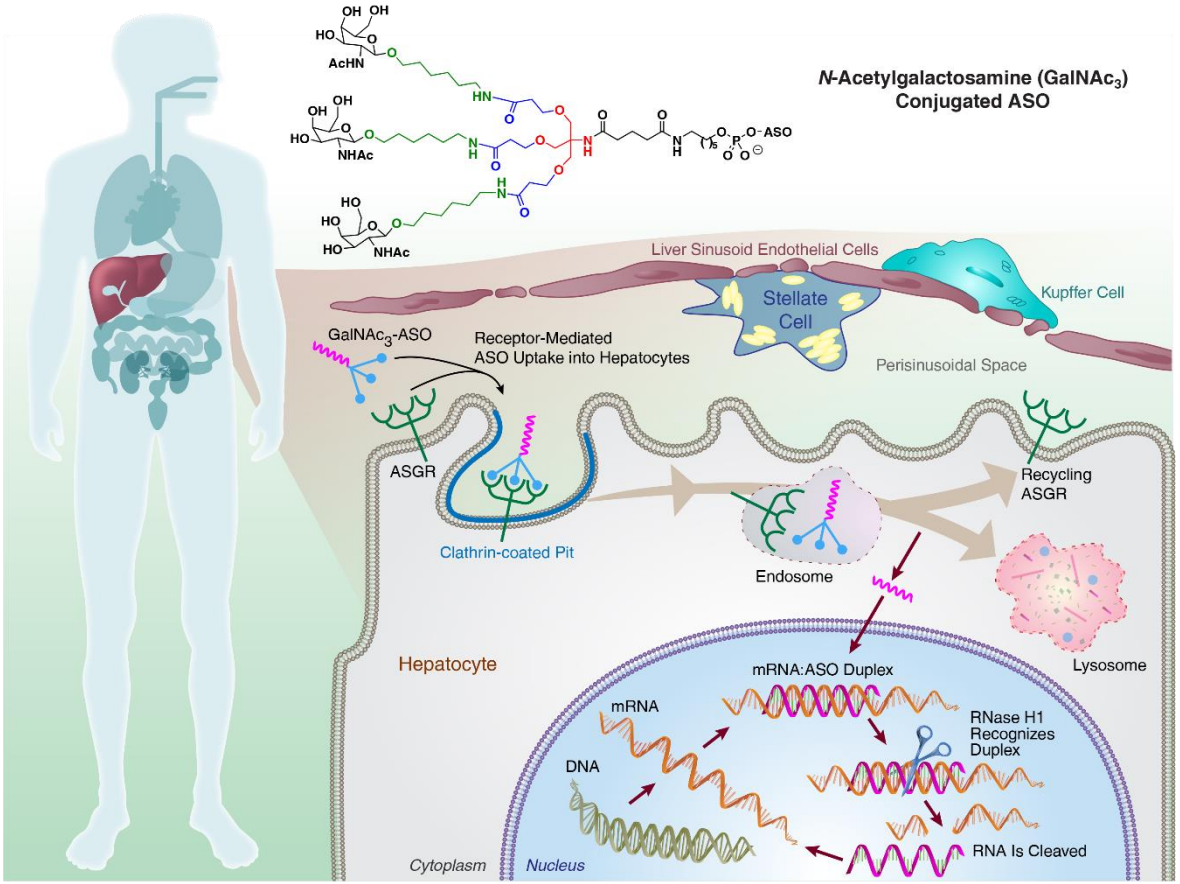
Multiple Ligands

- Carbohydrates
- Peptides
- Antibodies and FAB fragments
- Small molecules

LICA Technology – Liver

Liver LICA (GalNAc) increases potency of ASOs in humans by ~20-30 fold





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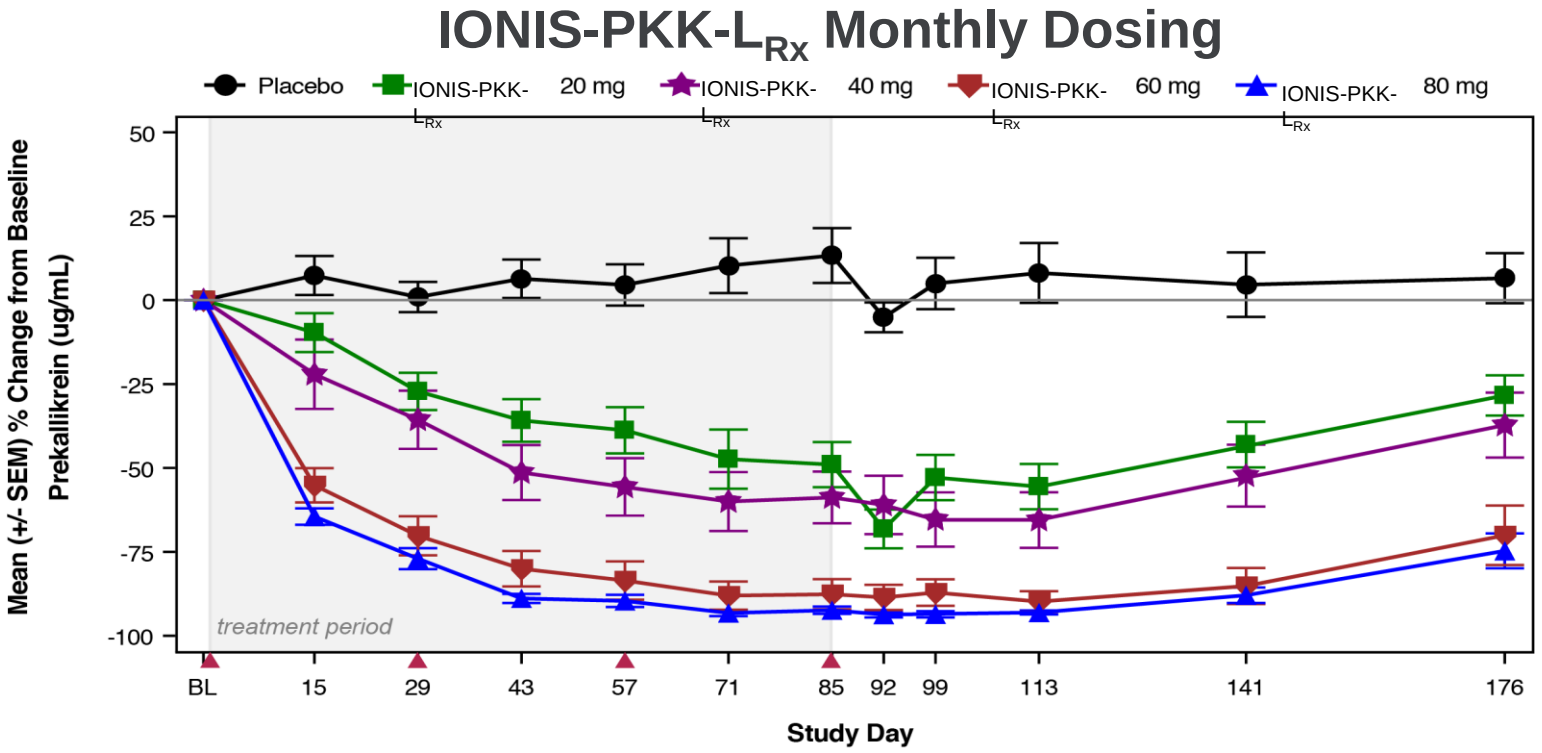
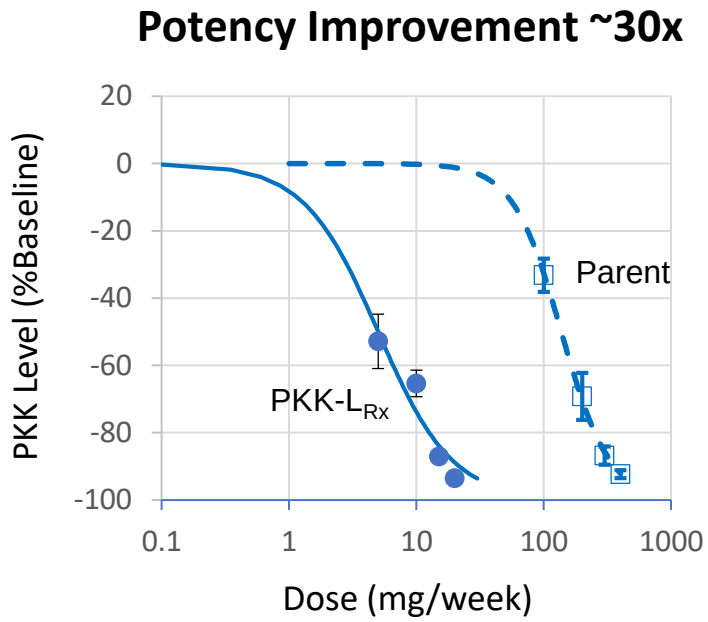
Crooke, S., et al. (2018), Nucleic Acid Therapeutics. http://doi.org/10.1089/nat.2018.0753; updated with more internal data

Ionis Antisense Technology – IONIS-PKK-L_{Rx}

Optimized designs improve duration and potency with liver-targeted antisense medicines





Cohn, et al. Antisense Inhibition of Prekallikrein to Control Hereditary Angioedema. *N Engl J Med* **2020**, *383*, 1242–1247.

Long duration of effect supports monthly to quarterly dosing interval

Low dose improves safety profile and therapeutic margins

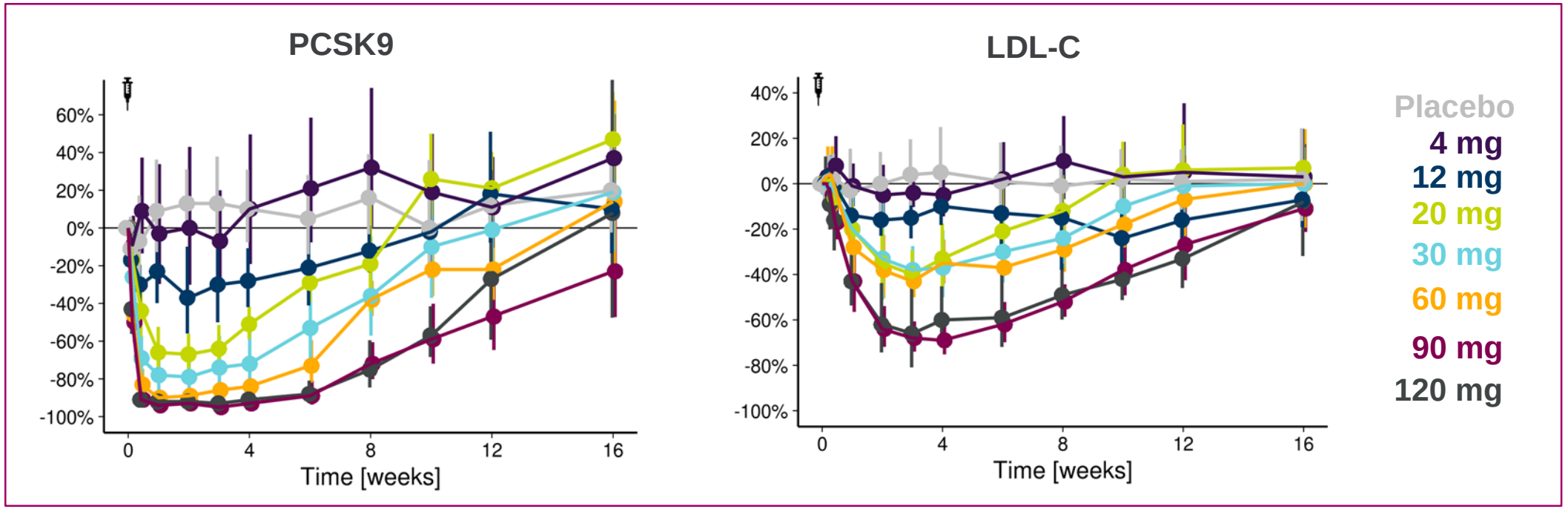
Currently 13 Liver LICA Medicines in Clinical Trials

- **Outstanding safety and efficacy profile**
  - More than 1,200 subjects treated and over 400 subjects on treatment for six months or longer
  - No safety concerns related to platelet, liver or kidney signals, no flu-like symptoms, very low incidence of injection site reactions

MEDICINE	INDICATION	TARGET	PHASE 1	PHASE 2	PHASE 3
Pelacarsen	Lp(a) CVDRR	Apo(a)			
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis	TTR			
AKCEA-APOCIII-L_{Rx}	FCS	ApoCIII			
Vupanorsen	sHTG/CVDRR	ANGPTL3			
IONIS-GHR-L_{Rx}	Acromegaly	GHr			
IONIS-FB-L_{Rx}	Complement-mediated diseases	FB			
IONIS-PKK-L_{Rx}	Hereditary angioedema/COVID-19	PKK			
IONIS-TMPRSS6-L_{Rx}	β-thalassemia	TMPRSS6			
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension	AGT			
IONIS-FXI-L_{Rx}	Clotting disorders	FXI			
ION449	Cardiovascular disease	PCSK9			
ION839	Nonalcoholic steatohepatitis	PNPLA3			
ION224	Nonalcoholic steatohepatitis	DGAT2			

ION449 – Our First cEt BNA LICA Has the Potential for Best-in-class Reductions in PCSK9 and LDL-C

- In a Phase 1 study, **single subcutaneous doses** of ION449 demonstrated **reductions** in **plasma PCSK9** protein and **LDL-C** levels up to **>90%** and up to **~70%** respectively
- **Favorable safety** and **tolerability** profile
- Currently in **Phase 2b** (Partnered with AstraZeneca)

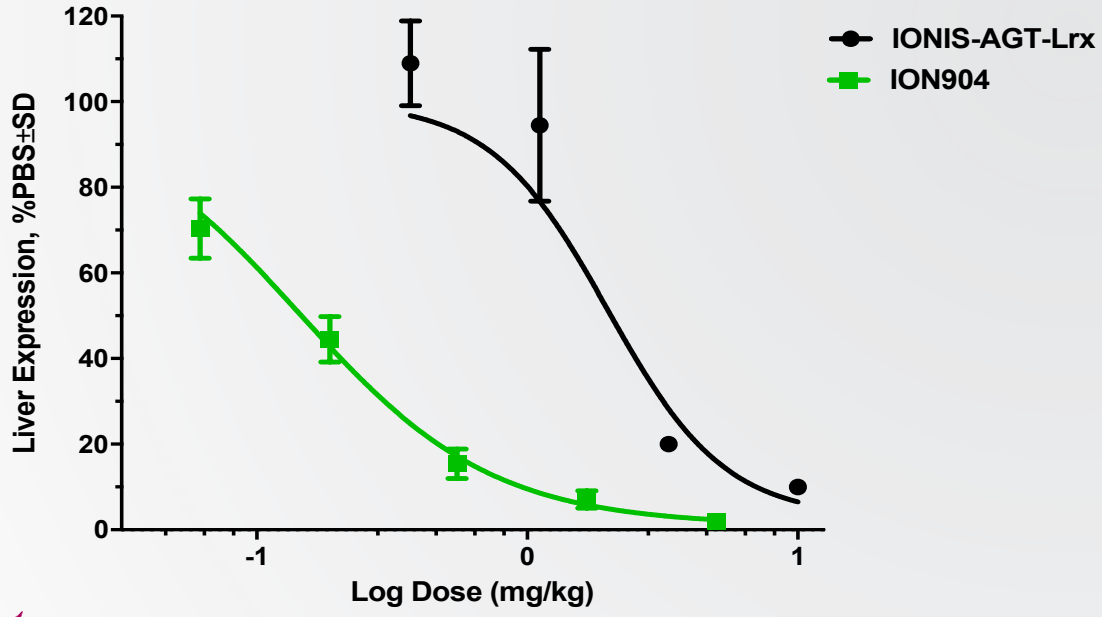


Plots show geometric mean and SD of % change from baseline. n = 6 per AZD8233 cohort and n = 14 in placebo arm, PCSK9 measured as protein in plasma

ION904 – AGT Follow-on Program
cEt BNA Demonstrates >10-Fold Improved Potency

- ION904 activity was similar to that observed with ION449 (PCSK9 ASO)
- Status: Plan to start clinical trials in 2021

AGT mRNA in Human Transgenic Mouse



ASO*	ED_{50} (mg/kg)
IONIS-AGT-L_{Rx}	2.0
ION904 (follow-on AGT ASO)	0.14
ION449 (PCSK9 ASO)	0.25

*AGT ASOs were given over 2 doses to human AGT transgenic mice; ION449 given over 5 doses to human PCSK9 transgenic mice

Oral Delivery of Antisense Medicines

- Oral bioavailability has previously been achieved in humans
  - 5-10% oral bioavailability (BAV) was demonstrated with an early ASO[1]
  - This was not commercially viable due to low potency
- The potency of current liver LICA medicines makes oral feasible
  - Most liver LICA drugs require < 100 mg total dose per month for desired efficacy
  - ASOs have long half lives (> 1 month) and therefore will accumulate in tissues over time even with the low doses achieved with oral delivery
  - Simple math: 40 mg/per day at 5% BAV = 2 mg/day x 30 days = 60 mg/month
- The ION449 PCSK9 program is the first example of a liver LICA ASO to advance to oral clinical development

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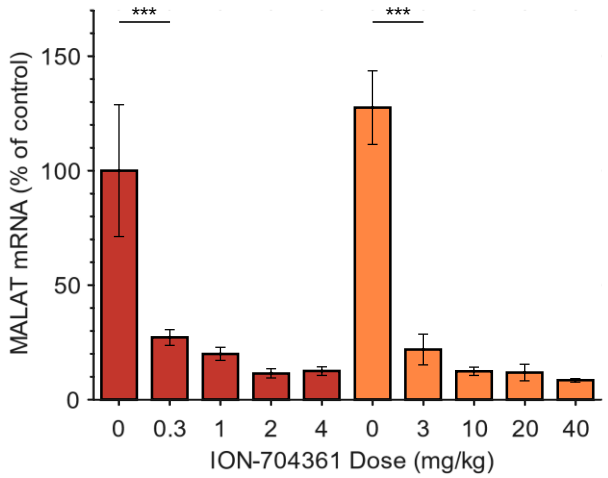
[1]Tillman, et al. J. Pharm. Sci. 2008, 97, 225

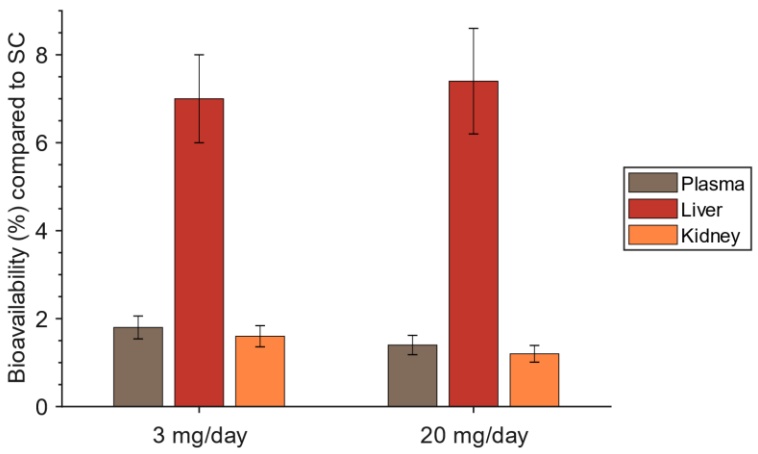
The Potential for Oral Delivery of ION449 Has Been Established in 3 *in vivo* Studies

5% liver bioavailability following intrajejunal administration in rodents



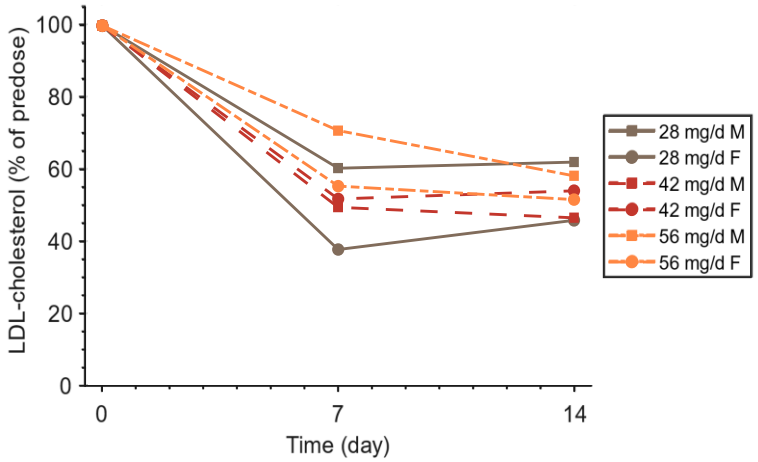
Horizontal bars indicate the significant difference between treatments (***p ≤ 0.005) for Tukey's honestly significant difference test. Error bars: SEM

7% liver bioavailability of ION449 tablets demonstrated in dog



Bioavailability of tablets compared to SC injection in dogs after 4 weeks once daily oral administration. Plasma exposure in form of AUC 0–24 h after last dose; Liver and kidney exposure 24 h after last dose. n = 4–5 per group; Error bars: SEM

LDL-cholesterol reduction demonstrated after repeated oral administration in healthy monkeys



Pre-dose-corrected LDL-C time profiles following repeated oral once daily dosing of AZD8233 with permeation enhancer for 14 days (n = 2 per group). Data are relative to the average of two pre-dose values sampled two and one weeks before the start of treatment. F, female; M, male

Gennemark, P., et al. (2020). An oral antisense oligonucleotide for PCSK9 inhibition in humans. AHA 2020, November 13–17.

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PCSK9 Program Status

- Ionis and AstraZeneca are committed to bringing the best possible PCSK9 ASO drugs to patients and have been collaborating on both SC and oral formulations
  - ION449 SC has a potential best-in-class profile and is advancing rapidly towards Phase 3 development
  - We have generated preclinical and early clinical data giving us confidence that we can achieve effective oral delivery of ION449 (and other ASOs) with the current formulation
- However, based on ongoing research and our experience to date, we believe we can improve upon the current oral formulation
  - We have therefore decided to stop the ongoing Phase 1 oral PCSK9 study
- Ionis and AstraZeneca will continue to broadly work together to further optimize the oral delivery of ASOs – including ION449

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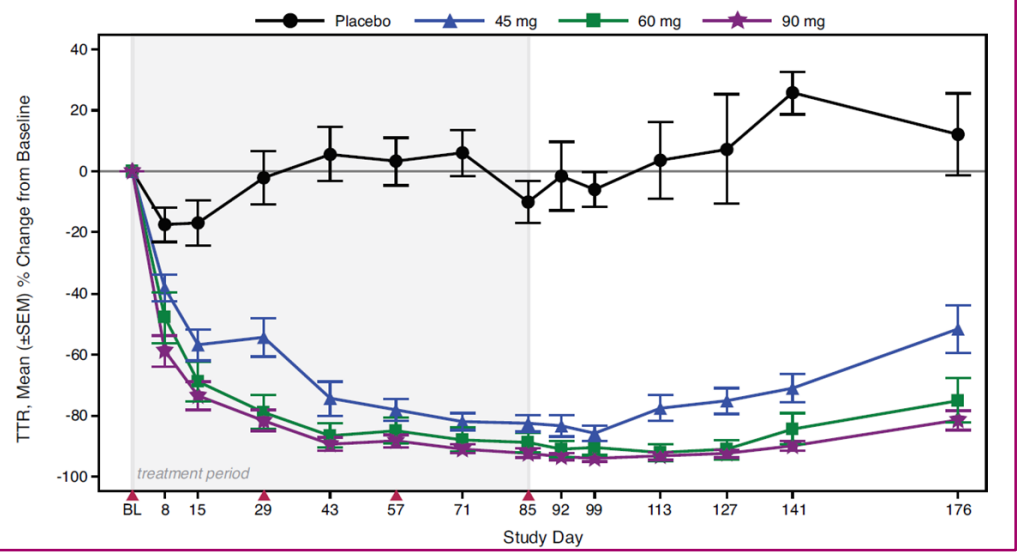
Existing Oral Bioavailability Could Deliver Efficacy Equal to a Monthly SubQ LICA ASO

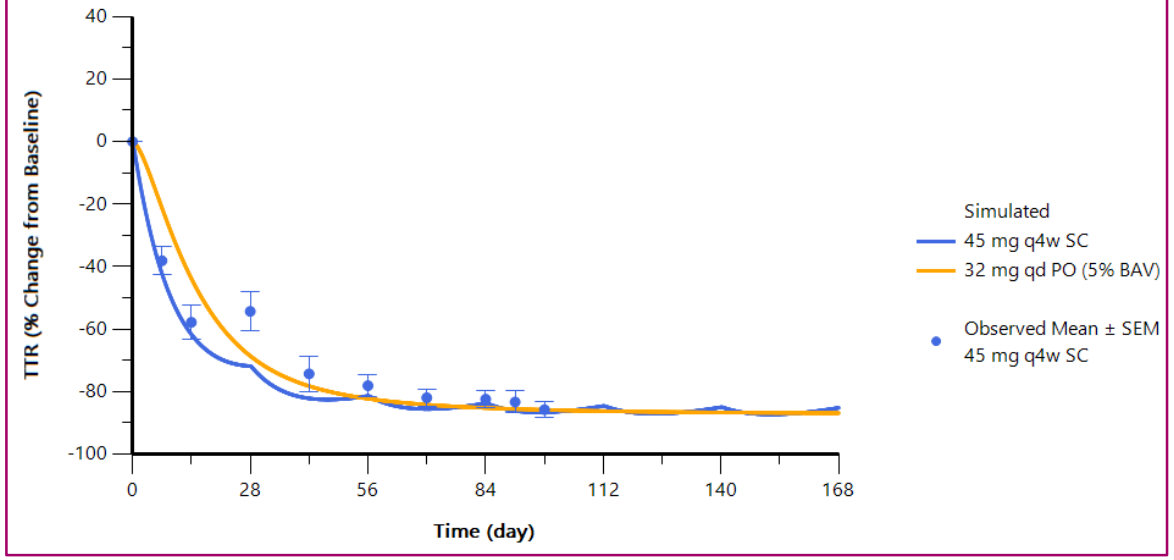
TTR-L_{RX} Monthly SubQ Data

SubQ 45 mg monthly gives > 80% reduction in humans



Simulation of SubQ and Oral TTR-L_{Rx}

Daily oral 32 mg with 5% bioavailability provides efficacy equal to monthly SC 45 mg



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We Plan to Expand Oral Delivery to Ionis-owned Medicines

- We plan to work with AstraZeneca to further optimize the oral delivery of ASOs in our partnership – including ION449 PCSK9 ASO
- We have increased our internal investment in oral research to optimize oral formulations to achieve our goal of >5% in humans
- We plan to initiate development for ≥ 1 Ionis-owned program in 2021
  - Candidates: TTR-L_{Rx}, PKK-L_{Rx}, ION904 (AGT), ION547
- Success would further enhance the commercial value of Ionis-owned programs

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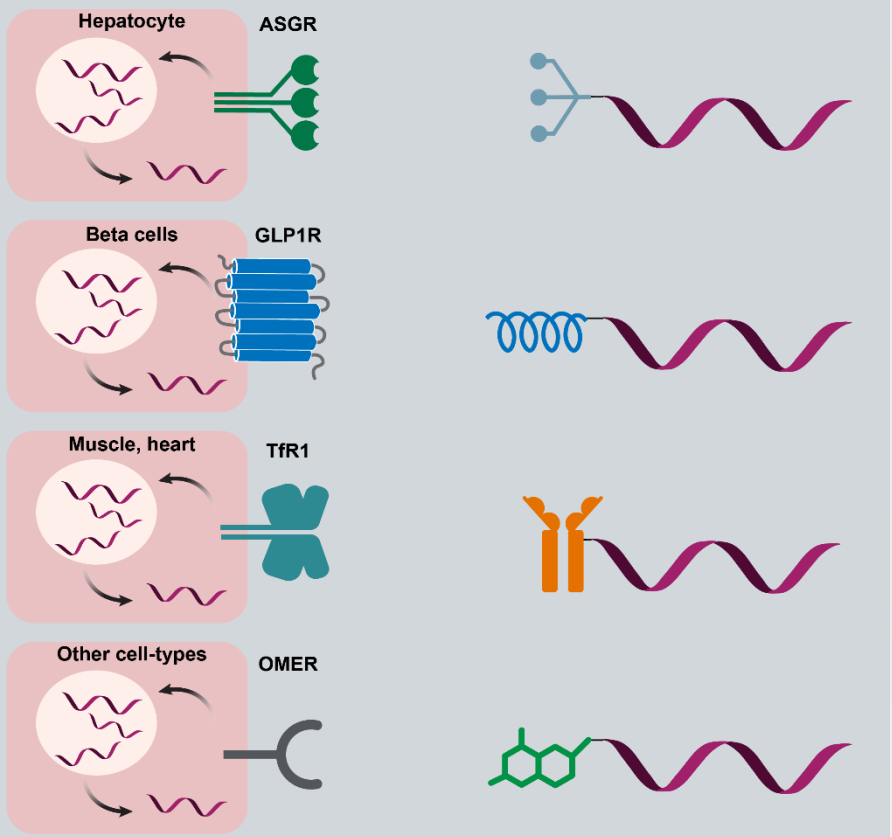
Ionis LICA Platform Continues to Expand

Multiple Tissues

- Liver
- Pancreas
- Muscle
- Many others in research stage



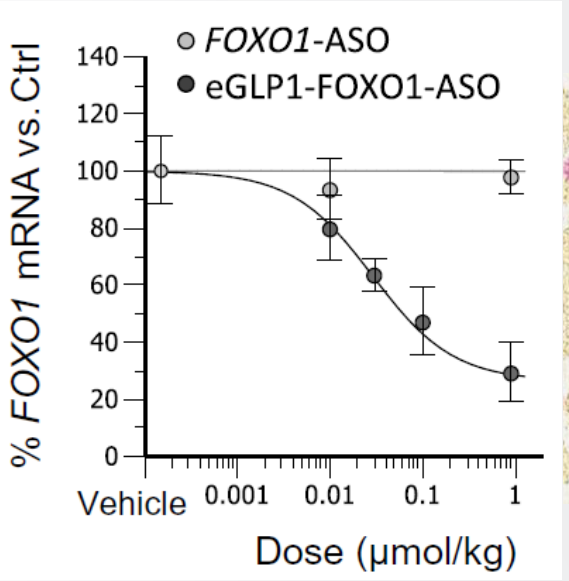
Multiple Ligands

- Carbohydrates
- Peptides
- Antibodies and FAB fragments
- Small molecules

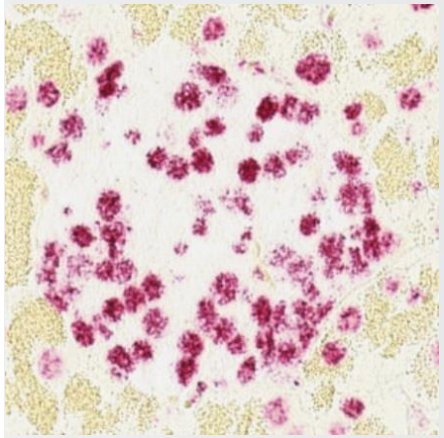
LICA Technology – Pancreas

Pancreatic beta-cell LICA (GLP1) substantially enhances potency in mice and pigs

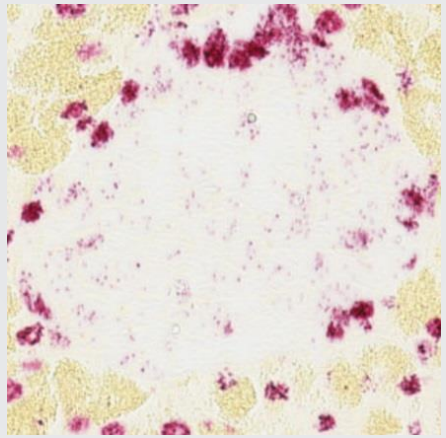
Mouse



***Malat1*-ASO**

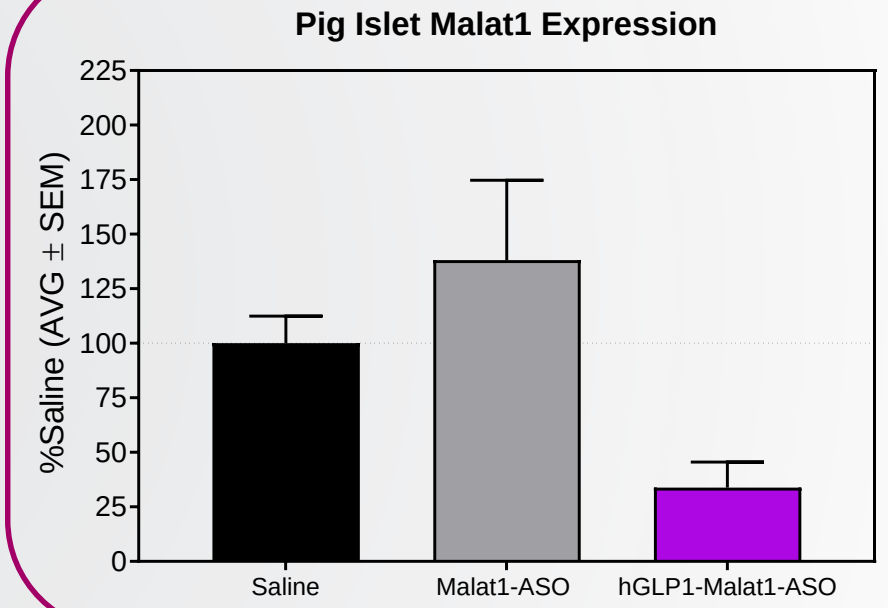


eGLP1-*Malat1*-ASO



Pink=Malat1 RNA Target

Pig



- GLP1 LICA status: optimal ligand identified
- Next steps: couple with specific β-cell target and identify human candidate

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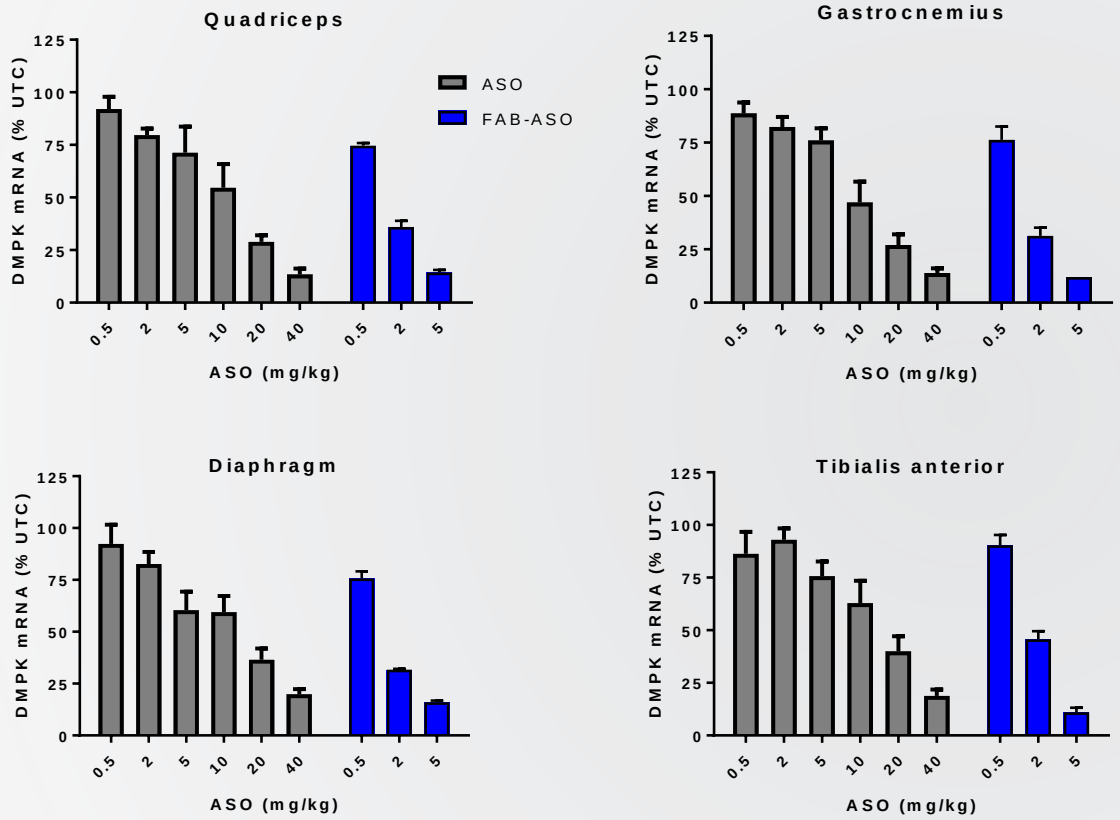
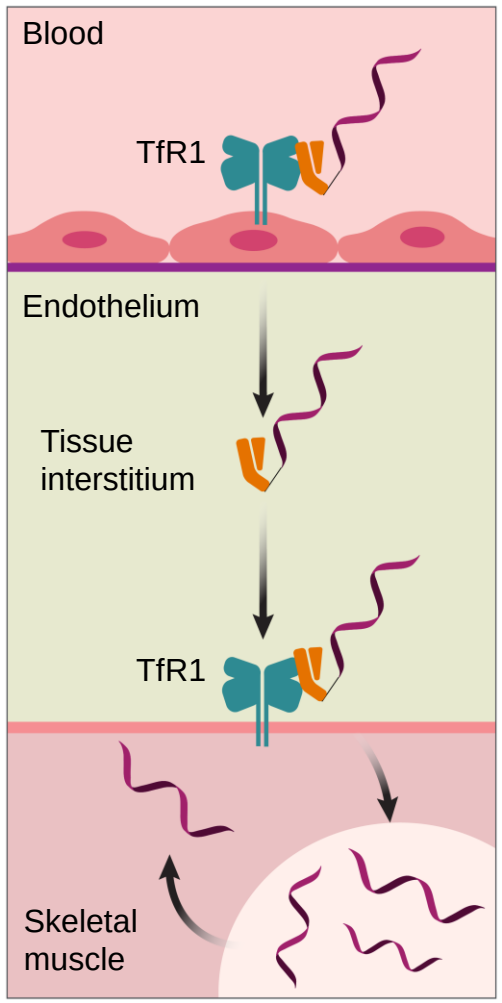
*Ammala et al, Sci Adv.,*v.4(10); 17 Oct 2018

LICA Technology – Muscle

TfR1 LICA enhances ASO potency 10-fold in skeletal muscle tissues



ASO	ED_{50} (mg/kg)			
	TA	Quadricep	Diaphragm	Gastroc.
ASO	14	10	11	10
FAB-ASO	1.8	1.2	1.2	1.1



Our Continuous Investment in our Technology Maintains Ionis' leadership Position in RNA-targeted Therapeutics

- **cEt BNA (Gen 2.5) is being deployed broadly in clinical programs**
  - Improves potency in established tissues providing potential best in class molecules (PCSK9)
  - Opens up new tissues for therapeutic opportunities such as pulmonary (ENAC) and kidney (APOL1)
- **Optimized designs improve potency and duration of effect**
  - Monthly to quarterly for liver LICA programs
  - >6 months for CNS programs
- **Liver LICA has and will continue to deliver value**
  - Infrequent, low volume injectables with great product profiles
  - Potential for oral administration, with Ionis oral programs moving toward development
- **LICA platform is expanding to more tissues**
  - Pancreas has progressed with next steps to bring a drug forward
  - Proof of principle in muscle achieved and we are moving aggressively forward

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2021 and Beyond

Brett Monia, Ph.D.
Chief Executive Officer

LOOKING AHEAD

Catalyst-rich 2021

PIVOTAL PROGRAMS

- Tofersen Phase 3 data in SOD1-ALS
- ≥ 2 new Phase 3 study starts
- Continued progress with ongoing six Phase 3 studies

MID-STAGE PROGRAMS

- ≥ 15 total mid-stage programs
- ≥ 5 clinical POC data readouts
- ≥ 4 new mid-stage study starts

COMMERCIAL

- Further advance commercial capabilities, accelerated with Akcea integration
- Prepare for initial rare disease product launches

TECHNOLOGY

- Advance more pulmonary programs
- Advance oral formulation for additional programs
- Extend duration
- New LICAs for enhanced delivery to new tissues

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2021: A Year of Value-driving Pipeline Catalysts

DATA READOUTS				H1	H2
GHR-L$_{Rx}$	Phase 2	•	Acromegaly	●	
ENAC-2.5$_{Rx}$	Phase 1/2	•	Cystic Fibrosis	●	
PKK-L$_{Rx}$	Phase 2	•	Hereditary Angioedema	●	
	Phase 2	•	Severe COVID-19	●	
Tominersen	OLE & NHS	•	Huntington's Disease	●	●
Tofersen	VALOR P3	•	SOD1-ALS		●
C9$_{Rx}$	Phase 1/2	•	C9-ALS		●
MAPT$_{Rx}$	Phase 1/2	•	Alzheimer's Disease		●
Vupanorsen	Phase 2b	•	Dyslipidemia		●

STUDY INITIATIONS				H1	H2
ION363	Phase 3	•	FUS-ALS	●	
ION373	Phase 1/2	•	Alexander disease	●	
ION716	Phase 1/2	•	Prion disease		●
Tofersen	ATLAS P3	•	Presymptomatic SOD1-ALS		●
APOCIII-L$_{Rx}$	Phase 3	•	Second indication		●

● Neurology
● Cardiometabolic
● Pulmonary, allergy and infectious

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Growing as a Premier Biotech

Today

3 drugs
commercialized

2	Ionis-owned commercial drugs
6	Phase 3 Programs
2	Core Therapeutic Areas
4	Tissues (liver, CNS, lung, kidney)

2026

12+ drugs
commercialized

6+	Ionis-owned commercial drugs
12+	Phase 3 Programs
3	Core Therapeutic Areas
6	Tissues (liver, CNS, lung, kidney, muscle, pancreas)

Delivering Value

Delivering transformational medicines to millions of patients

Advancing and diversifying our drug discovery platform capabilities

Culture of innovation and commitment to patients

IONIS™

Positioned for Substantial and Sustained Growth

Excellence in Science, Research & Drug Development

Commercial Strength and Flexibility

Sustained, Growing Patient & Shareholder Value

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Ionis: A Force for Life

Thank you

Q&A Session

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