Annual Stockholder Meeting

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board &
Chief Executive Officer

JUNE 2019

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' majority owned affiliate. 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, 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, 2018 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.

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

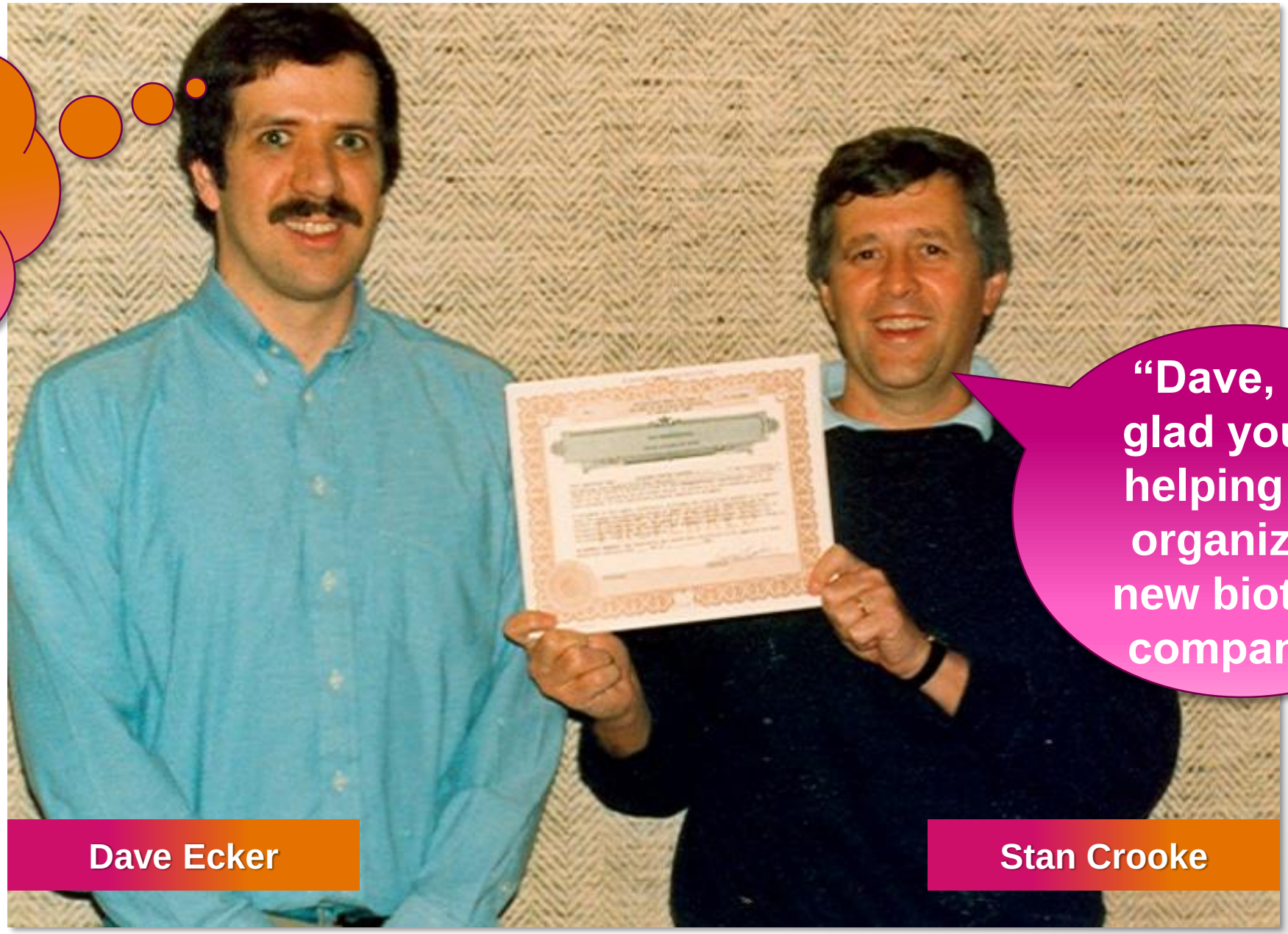
IONIS™

30 Years:

Our Extraordinary Journey

Prologue to an Exciting Future

Sure, it's not like I'm signing up for 20+ years.



"Dave, I'm glad you're helping me organize a new biotech company."

Dave Ecker

Stan Crooke

IONIS

Ionis: Delivering Hope to Patients

- Create and advance a new platform for drug discovery: Antisense
- Create a small, elite, focused R&D organization committed to innovation
- Create a culture with a prolonged cycle of innovation focused on delivering benefit to patients, covering a broad range of diseases

IONIS

Where is Ionis today?

Ionis: The Leader in RNA-Targeted Drug Discovery Technology, Focused on Innovation and Value Creation

Pioneer of **RNA** technology

Novel business model

Culture of **YES**

30 years advancing our technology

Ever-**better** performance

Greater commercial opportunities

3 commercial medicines

40+ in development

4+ in Phase 3 planned by YE **2019**

10+ in Phase 3 potentially by YE **2020**

IONIS

Ionis: The Leader in RNA-Targeted Drug Discovery Technology, Focused on Innovation and Value Creation

Pioneer of **RNA** technology

N

Culture of **YES**

30 years advancing our technology

Greater commercial opportunities

3 commercial medicines

40+ in development

10+ in Phase 3 potentially by YE **2020**

SUSTAINABLY PROFITABLE

IONIS

Key Recent Achievements
2018 and 2019 (1 of 4)

SPINRAZA	▪ The global foundation-of-care for the treatment of people of all ages with spinal muscular atrophy (SMA)
	▪ More than $3.1 billion in sales since launch[1]; Q1 2019 sales increased by 42% compared to Q1 2018
	▪ Over 7,500 patients on treatment[2]
	▪ Over 1,000 adult SMA patients on SPINRAZA in the U.S., accounted for 50% of new U.S. patient starts[1]
	▪ Approved in >40 countries, including across Asia and Latin America, with reimbursement in >30 countries[3]
TEGSEDI*	▪ Approved in the U.S., EU and Canada in 2018
	▪ Earned revenue of $9M since launch in late 2018
	▪ NICE authorized pricing and reimbursement in England
	▪ Filed and granted priority review in Brazil through PTC Therapeutics
WAYLIVRA*	▪ Approved in the EU
	▪ Earned $6M milestone from PTC Therapeutics for EU approval
	▪ EU launch preparations are underway, launching in Germany in Q3 2019

*Commercialized by Akcea

IONIS

[1]As of March 31, 2019
[2]Includes patients in commercial setting, EAP and clinical trials
[3]As of April 19, 2019

Key Recent Achievements
2018 and 2019 (1 of 4)

SPINRAZA is the first blockbuster RNA-targeted therapy; transforming the lives of SMA patients of all ages

TEGSEDI is approved in major markets; global launch successfully underway*

WAYLIVRA is the only approved medicine delivering benefit to patients with FCS; EU launch planned in Q3 2019*

*Commercialized by Akcea

IONIS

[1]*As of March 31, 2019*
[2]*Includes patients in commercial setting, EAP and clinical trials*
[3]*As of April 19, 2019*

Key Recent Achievements
2018 and 2019 (2 of 4)

Pipeline	▪ Advanced 2 medicines into Phase 3 studies; plus 2 medicines on track to enter Phase 3 studies this year
	▪ Tofersen (IONIS-SOD1$_{Rx}$) demonstrated trends towards clinical benefit in measures of disease in a Phase 1/2 study in SOD1-ALS patients
	▪ IONIS-HTT$_{Rx}$ (RG6042) demonstrated sustained mHTT lowering through 9 months of treatment in the OLE
	▪ Earned $150 million when Novartis licensed AKCEA-APO(a)-L$_{Rx}$ based on positive Phase 2 data; initiation of Phase 3 cardiovascular outcomes study ongoing
	▪ IONIS-DGAT2$_{Rx}$ demonstrated substantial liver fat reductions in patients with type 2 diabetes and NAFLD
	▪ Danvatirsen in combination with durvalumab demonstrated a response rate approximately double that of durvalumab alone in a Phase 2 study in patients with head and neck cancer
	▪ AKCEA-TTR-L$_{Rx}$ continued to progress towards pivotal program, which is on track to start in 2H 2019
	▪ Initiated clinical studies with IONIS-GHR-L$_{Rx}$, IONIS-C9$_{Rx}$, IONIS-FXI-L$_{Rx,}$ IONIS-ENAC-2.5$_{Rx}$ and IONIS-AZ4-2.5-L$_{Rx}$

IONIS

**Biogen is collaborating with regulators to further define the scope of the clinical data package required to support the registration of tofersen*

Key Recent Achievements
2018 and 2019 (2 of 4)

VALOR Phase 3 study of tofersen for SOD1 ALS underway*

Phase 3 study of IONIS-HTT$_{Rx}$ for Huntington's disease underway

AKCEA-APO(a)-L$_{Rx}$ advancing to a Phase 3 cardiovascular outcome study by YE 2019

AKCEA-TTR-L$_{Rx}$ advancing to a Phase 3 program in ATTR in 2H 2019

**Biogen is collaborating with regulators to further define the scope of the clinical data package required to support the registration of tofersen*

Key Recent Achievements
2018 and 2019 (3 of 4)

Technology	▪ Advanced 3 new chemical classes: Generation 2.5, Generation 2+ LICA, and Generation 2.5 LICA
	▪ Enabled respiratory delivery
	▪ Discovered new ASO mechanisms
	▪ Created new LICAs, e.g. pancreas LICA
	▪ Created new chemical approaches that increased therapeutic margins and further improved efficiency of ASO drug discovery

IONIS

Key Recent Achievements

2018 and 2019 (3 of 4)

Advances in the technology enabled new routes of administration…

… and significantly enhanced therapeutic margins and further improved efficiency of antisense drug discovery

Key Recent Achievements
2018 and 2019 (4 of 4)

Financial	▪ Achieved 7th consecutive year of revenue growth in 2018
	▪ Achieved 3rd consecutive year of non-GAAP operating profitability in 2018
	▪ Cash accretive seven of the last eight years
	▪ On track to meet or exceed 2019 guidance of >$725M revenue, >$100M operating income* and net income*

*Non-GAAP, which excludes stock-based compensation – please see reconciliation to GAAP in 1Q19 press release

Key Recent Achievements
2018 and 2019 (4 of 4)

On track to meet or exceed guidance of > $100 million in operating income*

and to be profitable at the bottom line*

*Non-GAAP, which excludes stock-based compensation – please see reconciliation to GAAP in 1Q19 press release

Strong Financial Performance

Resulting from Prolific Innovation and Intelligent Business Strategy

In Q1 2019…

$297 million in revenue

more than doubled over Q1 2018

$167 million

of operating income*

$126 million

of net income*

SPINRAZA® (nusinersen) injection 12 mg/5 mL

$60 million

royalty revenues increased by 46% over Q1 2018

$2.3 billion of cash

Enabling investment in commercial products and pipeline

On Track to Meet or Exceed 2019 Financial Guidance

IONIS

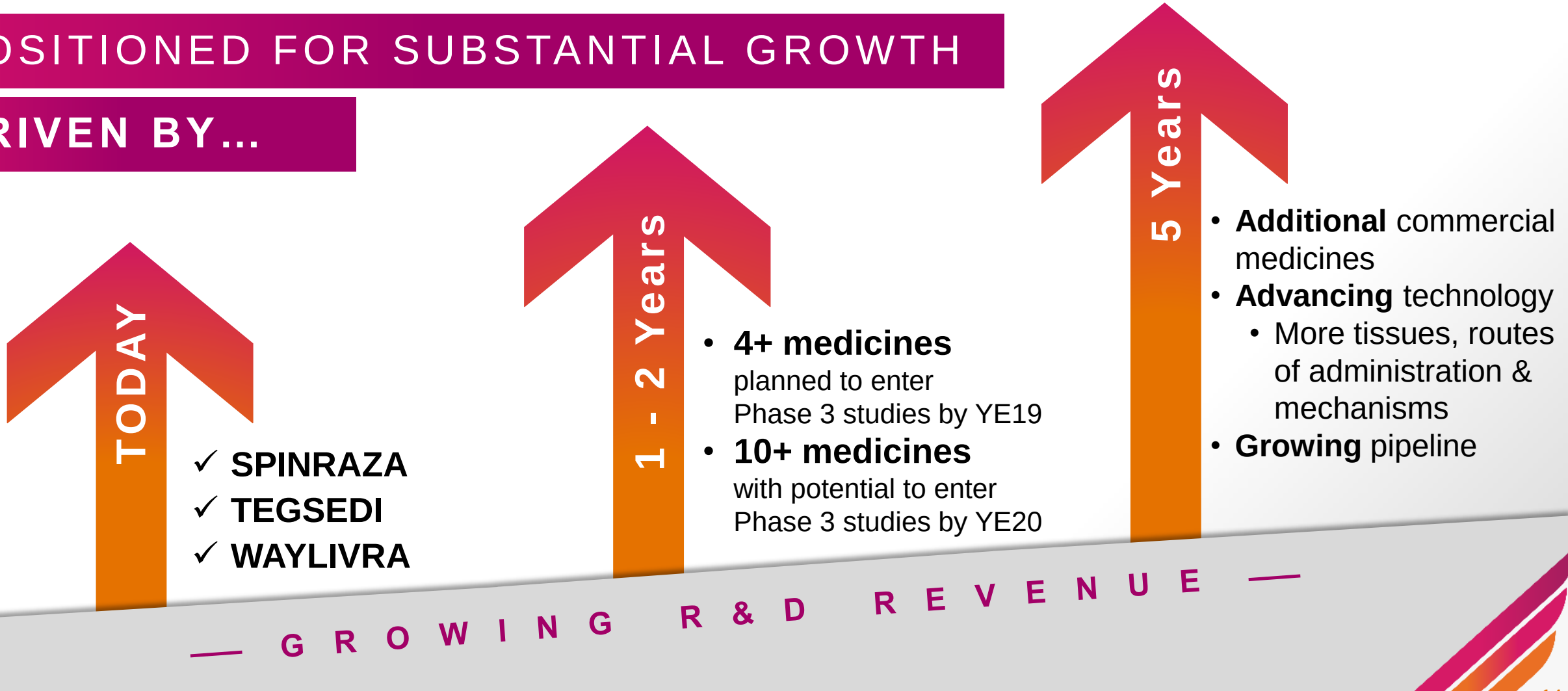
*Non-GAAP, which excludes stock-based compensation – please see reconciliation to GAAP in 1Q19 press release

Delivering Value Today and in the Future

Growing Profits While Investing in Value-Focused Innovation

POSITIONED FOR SUBSTANTIAL GROWTH

DRIVEN BY…



Delivering Value Today and in the Future

Growing Profits While Investing in Value-Focused Innovation

POSITIONED FOR SUBSTANTIAL GROWTH

DRIVEN BY…

SPINRAZA® (nusinersen) injection 12 mg/5 mL ✓

Tegsedi™ (inotersen) injection 284 mg/1.5 mL ✓

waylivra® (volanesorsen) injection 285 mg/1.5 mL ✓

— GROWING R&D REVENUE —

SPINRAZA®
(nusinersen) injection
12 mg/5 mL

The Foundation-of-Care for SMA Patients of All Ages

> 7,500 patients now on therapy worldwide, some for up to 6 years*

Earlier and/or longer treatment = greater benefit

>$3.1 billion in sales since launch and growing**

Blockbuster medicine, commercialized by Biogen

Logan, living with SMA

**Includes commercial, EAP and clinical trial patients **As of March 31, 2019*

For important prescribing and safety information, please refer to: www.spinraza.com

SPINRAZA® (nusinersen) injection 12 mg/5 mL

The Foundation-of-Care and Trusted Leader in SMA Therapy

SMA BEFORE **SPINRAZA**

SMA AFTER **SPINRAZA**

IONIS

SPINRAZA® (nusinersen) injection 12 mg/5 mL

The Foundation-of-Care and Trusted Leader in SMA Therapy

SMA BEFORE SPINRAZA	SMA AFTER SPINRAZA
Most common genetic cause of infant death	Most babies achieving normal milestones with pre-symptomatic treatment
Progressive degeneration and dependence	Patients gaining strength and improved quality of life
Delayed diagnosis	Newborn screening beginning to provide earlier diagnosis and treatment

We are working with Biogen on SMA follow-on medicines with less frequent dosing

IONIS

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

Only Subcutaneous Medicine for hATTR Polyneuropathy

Provides the freedom to treat anytime, anywhere

Launched in major markets

$9 million* in sales since launch and growing

First approved medicine in TTR Franchise

Commercialized by Akcea

Chuck, living with hATTR

**As of Q1 2019*

For safety information about serious side effects, including thrombocytopenia and glomerulonephritis, please see full prescribing information at www.TEGSEDI.com

TEGSEDI: Multi-Country Launch Underway*

- Reimbursement progressing well
- Prescriptions coming from cardiologists, neurologists and hematologists
- Expanding into new markets

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

IONIS

For safety information about serious side effects, including thrombocytopenia and glomerulonephritis, please see full prescribing information at www.TEGSEDI.com

*Commercialized by Akcea

waylivra®
(volanesorsen) injection 285 mg/1.5 mL

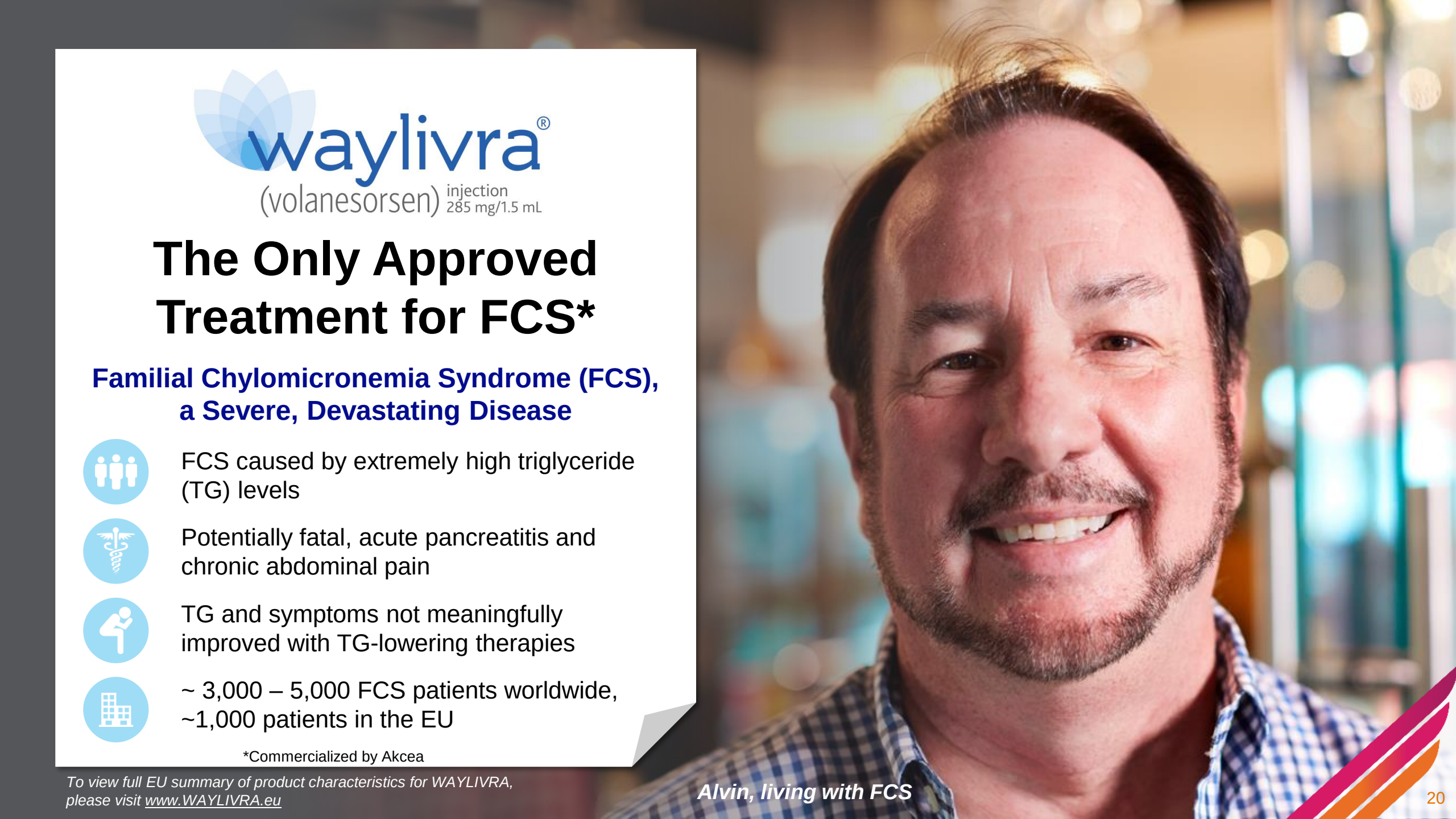
The Only Approved Treatment for FCS*

Familial Chylomicronemia Syndrome (FCS), a Severe, Devastating Disease

- FCS caused by extremely high triglyceride (TG) levels
- Potentially fatal, acute pancreatitis and chronic abdominal pain
- TG and symptoms not meaningfully improved with TG-lowering therapies
- ~ 3,000 – 5,000 FCS patients worldwide, ~1,000 patients in the EU

*Commercialized by Akcea

To view full EU summary of product characteristics for WAYLIVRA, please visit www.WAYLIVRA.eu



Alvin, living with FCS

waylivra®
(volanesorsen) injection 285 mg/1.5 mL

Only Approved Medicine for People with FCS

Only medicine to show substantial TG reduction in people with FCS*

EU launch planned for Q3 2019 in Germany

Launch in additional EU countries planned for 2020

Discussions continue with the FDA

Commercialized by Akcea

IONIS

To view full EU summary of product characteristics for WAYLIVRA, please visit www.WAYLIVRA.eu

**Based on results from Phase 3 study*

WAYLIVRA

Next Steps

EU launch in Q3 2019 starting in Germany, additional EU countries planned for 2020*

Confirm regulatory path forward with FDA

Complete BROADEN study in FPL in mid-2019

IONIS

*Commercialized by Akcea

Delivering Value Today and in the Future

Multiple Value Inflection Points in 2019

3 **Commercial Medicines with Growing Revenue**

✔ SPINRAZA ✔ TEGSEDI ✔ WAYLIVRA

4+ **Phase 3 Study Starts Planned**

✔ IONIS-HTT$_{Rx}$, ✔ Tofersen

AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$

6+ **Phase 2 Study Readouts Planned**

✔ Tofersen ✔ IONIS-DGAT2$_{Rx}$

Danvatirsen, IONIS-FXI$_{Rx}$, AKCEA-TTR-L$_{Rx}$, IONIS-HBV$_{Rx}$, and more

IONIS

Delivering Value Today and in the Future

Growing Profits While Investing in Value-Focused Innovation

POSITIONED FOR SUBSTANTIAL GROWTH

DRIVEN BY…

TODAY

- ✓ SPINRAZA
- ✓ TEGSEDI
- ✓ WAYLIVRA

1 – 2 Years

- **4+ medicines** planned to enter Phase 3 studies by YE19
- **10+ medicines** with potential to enter Phase 3 studies by YE20

5 Years

- **Additional** commercial medicines
- **Advancing** technology
  - More tissues, routes of administration & mechanisms
- **Growing** pipeline

— GROWING R&D REVENUE —

Poised to Deliver the Next Wave of Commercial Opportunities

At Least 4 Medicines Planned To Enter Phase 3 This Year

MEDICINE	INDICATION	PARTNER
✓ IONIS-HTT$_{Rx}$ (RG6042)	Huntington's disease	Roche
✓ Tofersen (IONIS-SOD1$_{Rx}$/BIIB067)	Amyotrophic lateral sclerosis	Biogen
✓ AKCEA-APO(a)-L$_{Rx}$	Cardiovascular disease	Akcea / Novartis
✓ AKCEA-TTR-L$_{Rx}$	Transthyretin amyloidosis	Akcea
IONIS-HBV$_{Rx}$ / IONIS-HBV-L$_{Rx}$	Hepatitis B virus infection	GSK
Danvatirsen (IONIS-STAT3-2.5$_{Rx}$)	Cancer	AstraZeneca
AKCEA-APOCIII-L$_{Rx}$	Cardiovascular disease	Akcea / Novartis
IONIS-MAPT$_{Rx}$ (BIIB080)	Alzheimer's disease/ Frontotemporal dementia	Biogen
IONIS-FXI$_{Rx}$ / IONIS-FXI-L$_{Rx}$	Clotting disorders	Bayer
AKCEA-ANGPTL3-L$_{Rx}$	Cardiometabolic disorders	Akcea / Ionis
IONIS-GHR-L$_{Rx}$	Acromegaly	Ionis

IONIS

✓ *= Phase 3 study ongoing or study initiation in progress*

Poised to Deliver the Next Wave of Commercial Opportunities

At Least 4 Medicines Planned To Enter Phase 3 This Year

MEDICINE	INDICATION	PARTNER
✓ **IONIS-HTT$_{Rx}$ (RG6042)**	**Huntington's disease**	**Roche**
✓ **Tofersen (IONIS-SOD1$_{Rx}$/BIIB067)**	**Amyotrophic lateral sclerosis**	**Biogen**
✓ **AKCEA-APO(a)-L$_{Rx}$**	**Cardiovascular disease**	**Akcea / Novartis**
✓ **AKCEA-TTR-L$_{Rx}$**	**Transthyretin amyloidosis**	**Akcea**
IONIS-HBV$_{Rx}$ / IONIS-HBV-L$_{Rx}$	Hepatitis B virus infection	GSK
Danvatirsen (IONIS-STAT3-2.5$_{Rx}$)	Cancer	AstraZeneca
AKCEA-APOCIII-L$_{Rx}$	Cardiovascular disease	Akcea / Novartis
IONIS-MAPT$_{Rx}$ (BIIB080)	Alzheimer's disease/ Frontotemporal dementia	Biogen
IONIS-FXI$_{Rx}$ / IONIS-FXI-L$_{Rx}$	Clotting disorders	Bayer
AKCEA-ANGPTL3-L$_{Rx}$	Cardiometabolic disorders	Akcea / Ionis
IONIS-GHR-L$_{Rx}$	Acromegaly	Ionis

IONIS

✓ *= Phase 3 study ongoing or study initiation in progress*

IONIS-HTT$_{Rx}$ (RG6042)

Potential Breakthrough Medicine for Huntington's Disease (HD)

Charles, living with Huntington's Disease

IONIS

IONIS-HTT$_{Rx}$ (RG6042)

Potential Breakthrough Medicine for Huntington's Disease (HD)

- Potentially the **first disease-modifying medicine for HD**
- **~30,000 symptomatic patients** in the U.S., similar number in EU
- **Robust reductions** in mutant huntingtin protein (mHTT)*
- mHTT reduction correlated with **improvement in clinical measures of HD****
- **Favorable safety and tolerability** profile*

IONIS

*Based on results from open-label extension (OLE) study; **Based on a post-hoc analysis of data from the Phase 1/2 study

IONIS-HTT$_{Rx}$ (RG6042)

Next Steps

- Complete **Phase 3 program**
- **Present** results from ongoing open label extension study
- Roche planning to engage with regulators regarding the potential for an **accelerated path to patients**

Tofersen (IONIS-SOD1$_{Rx}$)

Potential Breakthrough Medicine for SOD1 Familial ALS

Sonny, living with ALS

IONIS

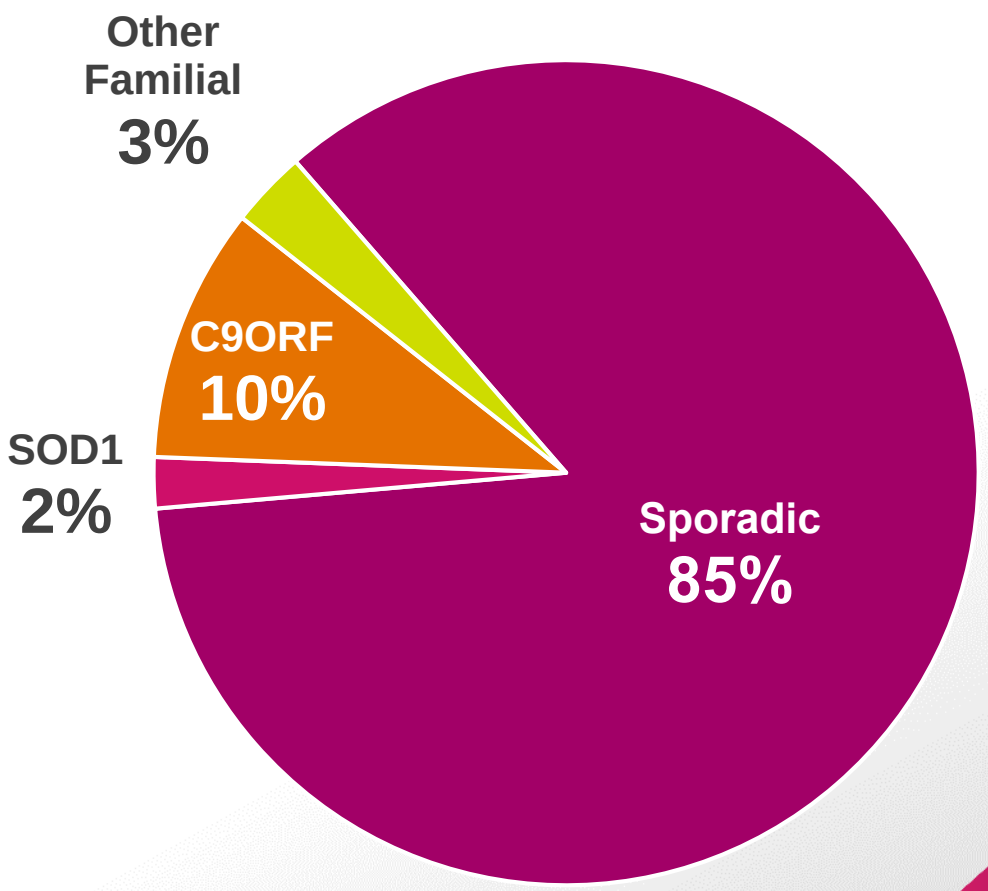
Amyotrophic Lateral Sclerosis (ALS)

A Fatal Disease with a Tremendous Unmet Medical Need

Genetic forms (familial) and **non-genetic** forms (sporadic) of **ALS** exist

- Approximately 15% of ALS cases have genetic causes
  - More than 1,000 ALS patients diagnosed with SOD1 mutations
- Devastating and rapidly progressing disease
- Patients become paralyzed, yet still have normal cognitive abilities
- Patients usually die of their disease within 2 to 5 years from symptom onset

Breakdown of ALS



IONIS

Taylor, J., et. al., (2016) Nature; 539: 197-206

Tofersen (IONIS-SOD1$_{Rx}$)

First Genetically Targeted Therapy Demonstrating Trends Towards Benefit in ALS

- Treatment with tofersen demonstrated **statistically significant SOD1 reductions** in the cerebrospinal fluid*
- Tofersen (100 mg) demonstrated numerical trends towards **slowing decline in clinical function, respiratory function and measures of strength after only 3 months** of treatment and was well tolerated*
- **VALOR Phase 3 study initiated** by Biogen in adult ALS patients with SOD1 mutations**

Innovative Phase 3 study with potential to support rapid path to patients**

IONIS

*Based on results from the Phase 1/2 study

**Biogen is collaborating with regulators to further define the scope of the clinical data package required to support the registration of tofersen

Tofersen (IONIS-SOD1$_{Rx}$)

Next Steps

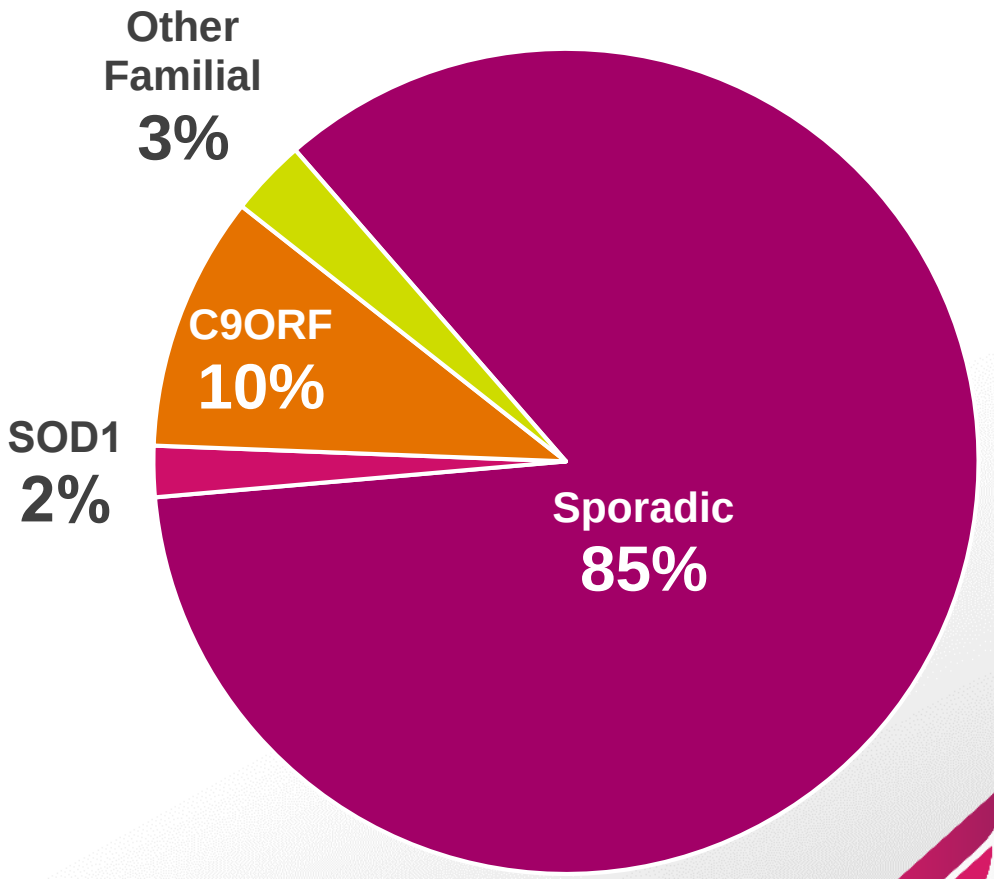
- Complete ongoing **VALOR Phase 3 study** supporting a potential **fast path to patients**
- Biogen collaborating with regulators to further define the scope of the clinical package required to support **registration for marketing approval**

Ionis and Biogen

Committed to Treating Patients with All Forms of ALS

- Tofersen: The **first** to demonstrate significant reductions in SOD1 and trends in **slowing of disease progression**
- IONIS-$C9_{Rx}$: **Clinical study ongoing in C9-familial ALS** (initiated Q4 2018)
- Programs advancing focused on **treating all forms of ALS** (e.g., sporadic)

Breakdown of ALS



IONIS

Taylor, J., et. al., (2016) Nature; 539: 197-206

Michael, living with Lp(a) driven Cardiovascular Disease

AKCEA-APO(a)-L_{Rx}

Addressing a Remaining Major Lipid Risk Factor in Cardiovascular Disease (CVD)

IONIS

Lipoprotein(a)

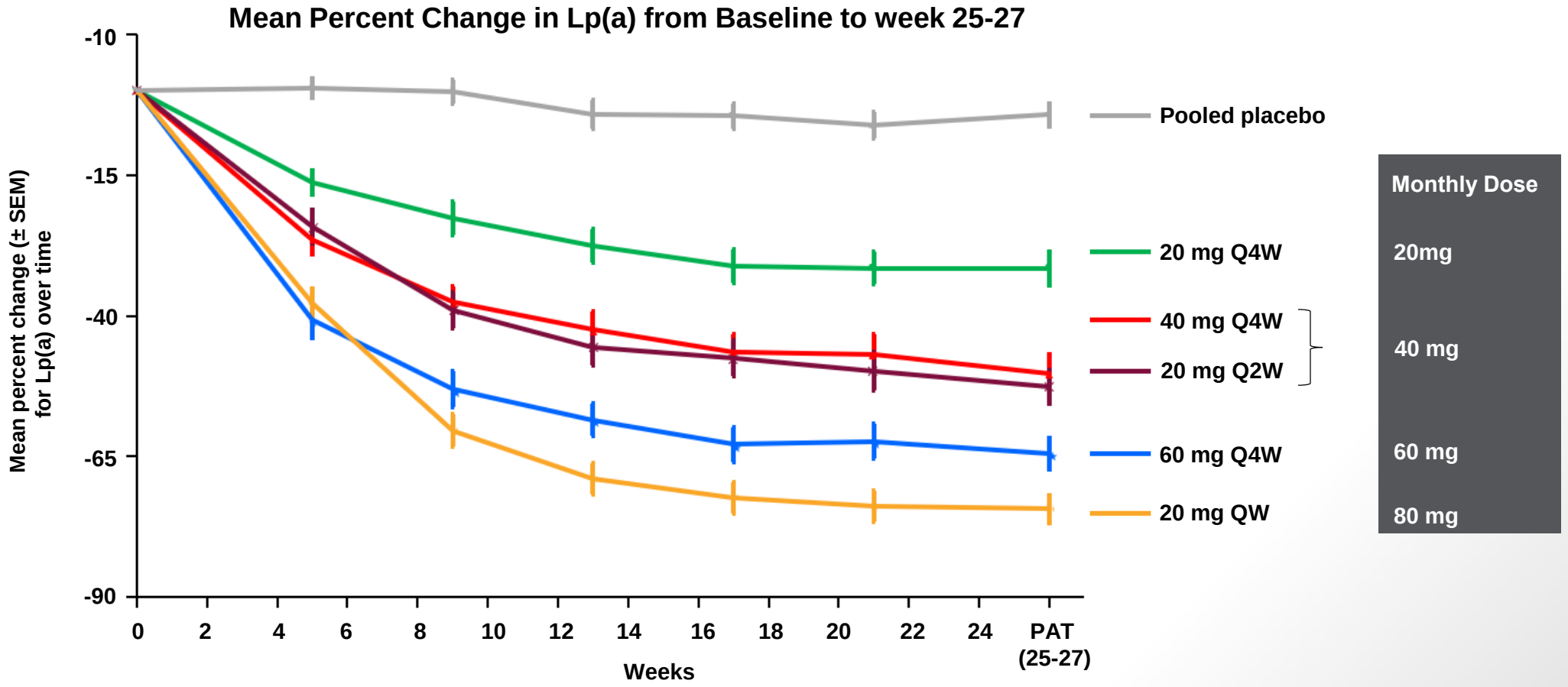
A Major Untreated Risk Factor for Cardiovascular Disease (CVD)

- Lp(a) level **genetically determined** at birth
- **No approved** pharmacological therapies
- **> 8 million people worldwide** that have Lp(a) driven CVD

IONIS

AKCEA-APO(a)-L_{Rx} (TQJ230) Phase 2 Study

Significant Dose-Dependent Lp(a) Reductions Achieved at All Doses and Frequencies



98% of patients receiving dose planned for Phase 3 achieved Lp(a) levels below cardiovascular disease risk threshold

PAT, primary analysis timepoint; QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks; Error bars = standard error of the mean

AKCEA-APO(a)-L_{Rx} (TQJ230) Phase 2 Study*

The Largest and Longest Study Conducted in Patients with Lp(a)-Driven CVD

- **Robust, dose-dependent and durable reductions in Lp(a)** levels in patients treated for 6 months, with some patients treated for up to 1 year
  - Same study population to be evaluated in planned Phase 3 cardiovascular outcomes study
- Reduced Lp(a) levels **below threshold levels associated with CVD** in nearly all patients at high dose
  - 80 mg monthly dose chosen for planned Phase 3 cardiovascular outcomes study
- Favorable **safety and tolerability** profile and **excellent compliance**
  - Approximately 90% of patients completed treatment
  - Comparable discontinuation between the active and placebo groups
- Convenient, **once monthly, low volume, subcutaneous** dose

IONIS

**Co-developing with Akcea*

AKCEA-APO(a)-L_{Rx} (TQJ230)

Next Steps

- Novartis' activities are underway to **initiate a Phase 3 cardiovascular outcomes study this year**
  - First patients expected to initiate treatment early 2020
- Novartis is also investing in a study to **identify patients** and characterize the **course of their disease**

AKCEA-TTR-L$_{Rx}$

For Patients with Hereditary and Wildtype ATTR

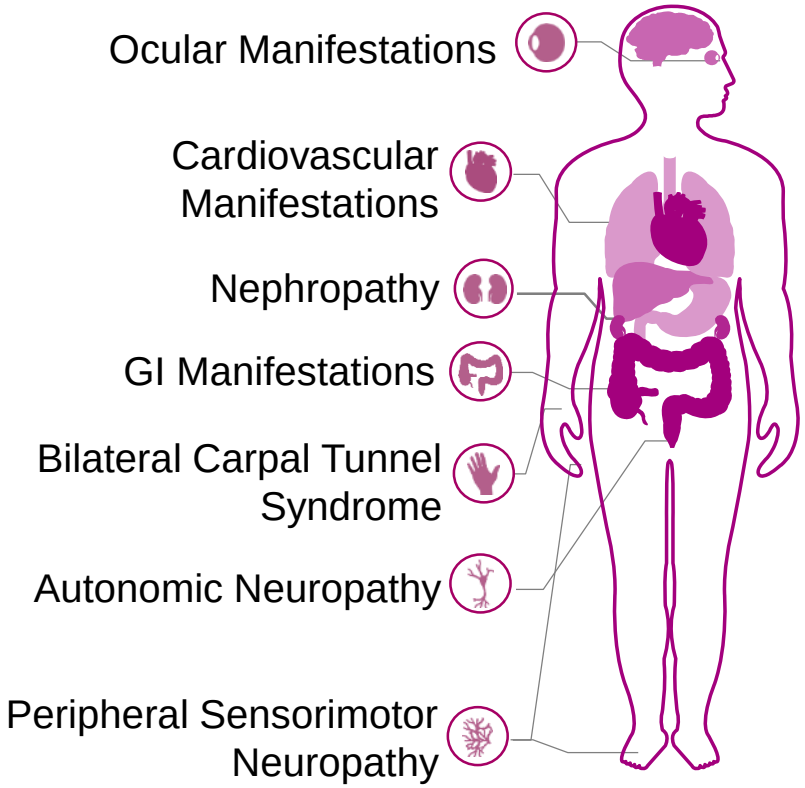
Clay, living with ATTR

IONIS

TTR Amyloidosis (ATTR)

A Devastating and Fatal Disease

ATTR affects many organ systems[1,5]



ATTR is a fatal disease affecting over 200,000 patients worldwide[1,2]

ATTR is a disease marked by the formation of TTR amyloid deposits leading to multi-organ failure[1,2]

ATTR patients suffer from progressive neuropathy, cardiac disease, nephropathy and gastrointestinal symptoms

ATTR is a progressive disease resulting in a rapid decline in quality of life and a 3 – 15 year[3] life expectancy and 2 – 5 years[4] with cardiac involvement

IONIS

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. 5. Sperry B et al. *J Am Coll Cardiol*. 2018;72:2040-2050.

Inotersen in Patients with ATTR Cardiomyopathy (ATTR-CM)

Benson Investigator Initiated Study (Indiana University School of Medicine)

Single center, investigator trial in 33 patients* with **ATTR-CM**

Objective is to evaluate **long-term safety & clinical efficacy**** in patients with ATTR-CM

Inotersen 300 mg subcutaneous weekly (no loading dose)

IONIS

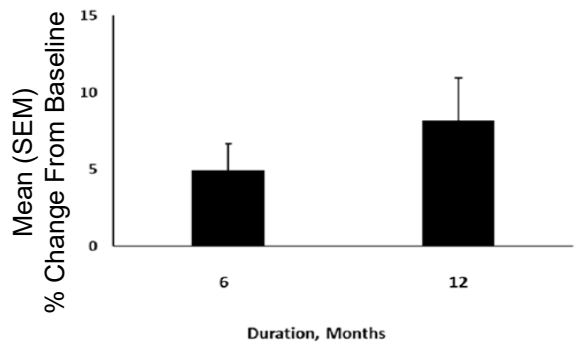
*As of October 2018; **Compared to natural history data

Inotersen in Patients with ATTR-CM

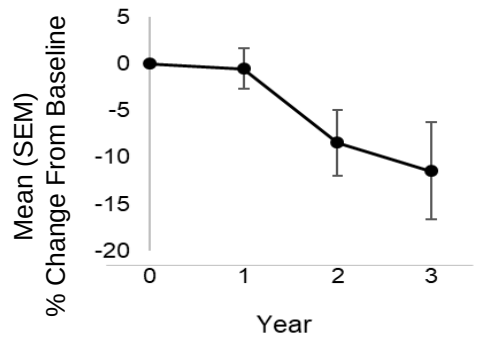
Improvements or Stabilization Observed in Dr. Benson's Investigator Initiated Study

Increasing Left Ventricular Mass (LVM)

Natural History Data[1]
(hereditary amyloidosis, n=9)



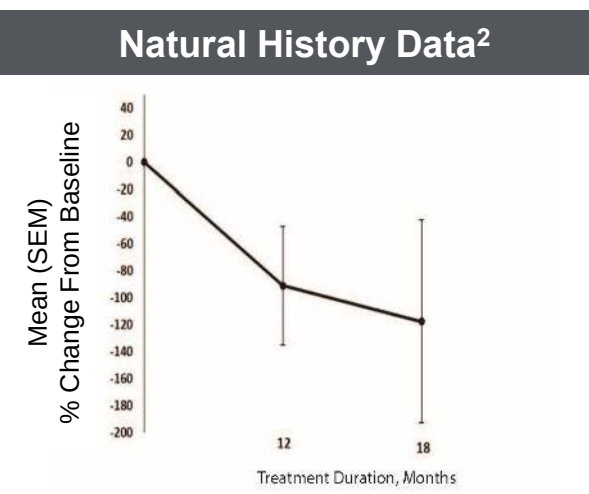
Inotersen
(WT and hereditary, n=10)



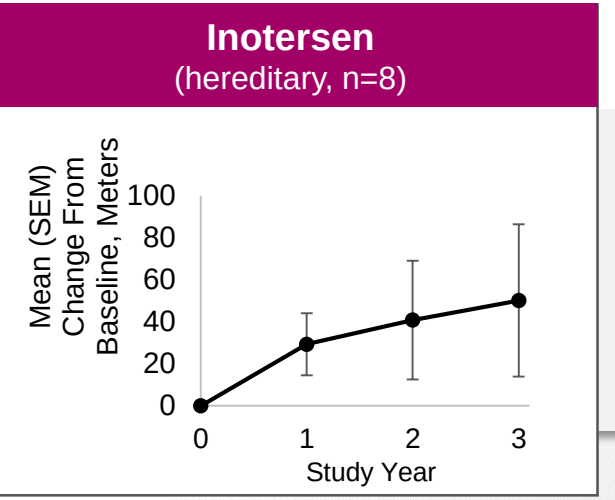
Decreasing Left Ventricular Mass (LVM)

Declining 6 minute walk distance (6MWT)

Natural History Data[2]



Inotersen
(hereditary, n=8)



Improving 6 minute walk distance (6MWT)

IONIS

1. Benson MD, et. al., (2011) *Am J Cardiol* 108(2) 285-9. Benson, M.D., AAN. 2. Ruberg et al. (2012) *Am Heart J*. 64:222-228.e1. Benson, M.D., AAN.

AKCEA-TTR-L_{Rx}*

In Development to Treat Patients with All Forms of TTR Amyloidosis

- Utilizes our most **advanced LICA chemistry**, providing high potency with greatly **improved convenience and tolerability**
- Phase 1/2 study underway in **all forms of TTR amyloidosis**
  - Robust **TTR reductions > 90%** observed and **well tolerated**
  - Phase 1 study expected to **complete in 2H 2019**

IONIS

**Co-developing with Akcea*

AKCEA-TTR-L_{Rx}

Initiating Pivotal Study in 2019

- Productive discussions with **regulatory authorities**
- Initiate rapid pivotal study in **hATTR polyneuropathy in 2H 2019**
- Initiate Phase 3 study in **ATTR cardiomyopathy in 2H 2019**

Delivering Value Today and in the Future

Growing Profits While Investing in Value-Focused Innovation

POSITIONED FOR SUBSTANTIAL GROWTH

DRIVEN BY…

TODAY

- ✓ SPINRAZA
- ✓ TEGSEDI
- ✓ WAYLIVRA

1 – 2 Years

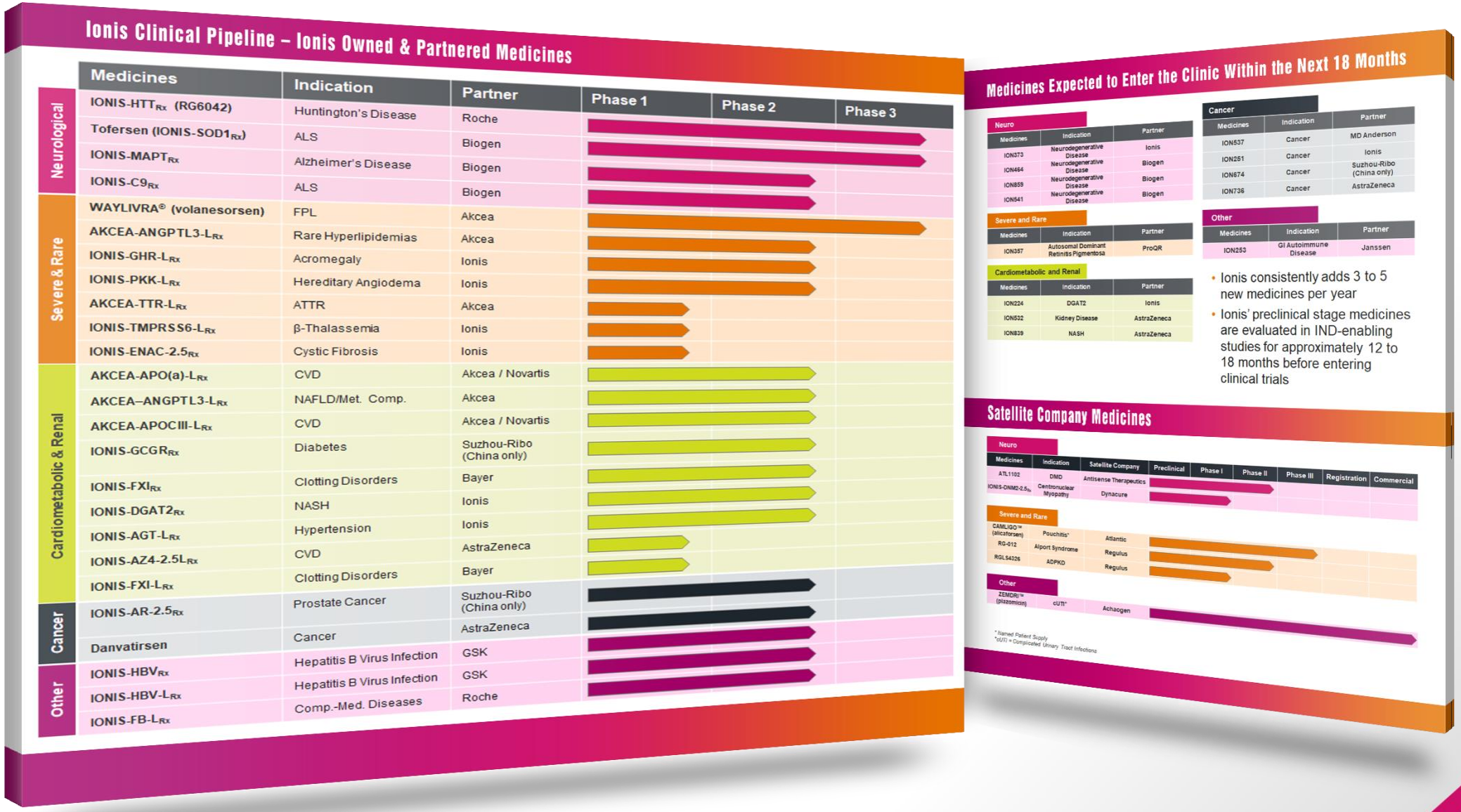
- **4+ medicines**
  planned to enter
  Phase 3 studies by YE19
- **10+ medicines**
  with potential to enter
  Phase 3 studies by YE20

5 Years

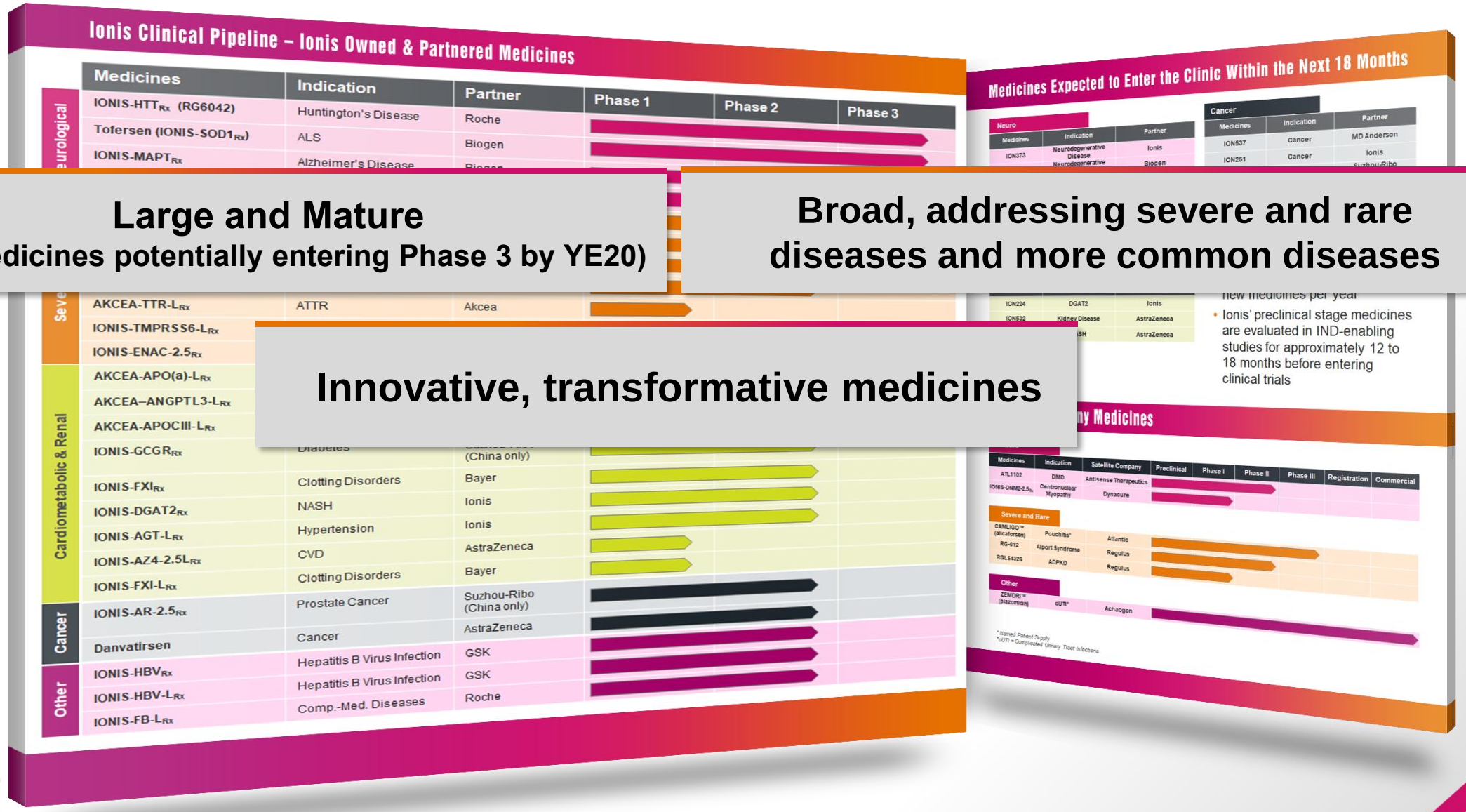
- **Additional** commercial medicines
- **Advancing** technology
  - More tissues, routes of administration & mechanisms
- **Growing** pipeline

— GROWING R&D REVENUE —

Advancing and Growing Pipeline of Over 40 Medicines



Advancing and Growing Pipeline of Over 40 Medicines



Large and Mature
(10+ medicines potentially entering Phase 3 by YE20)

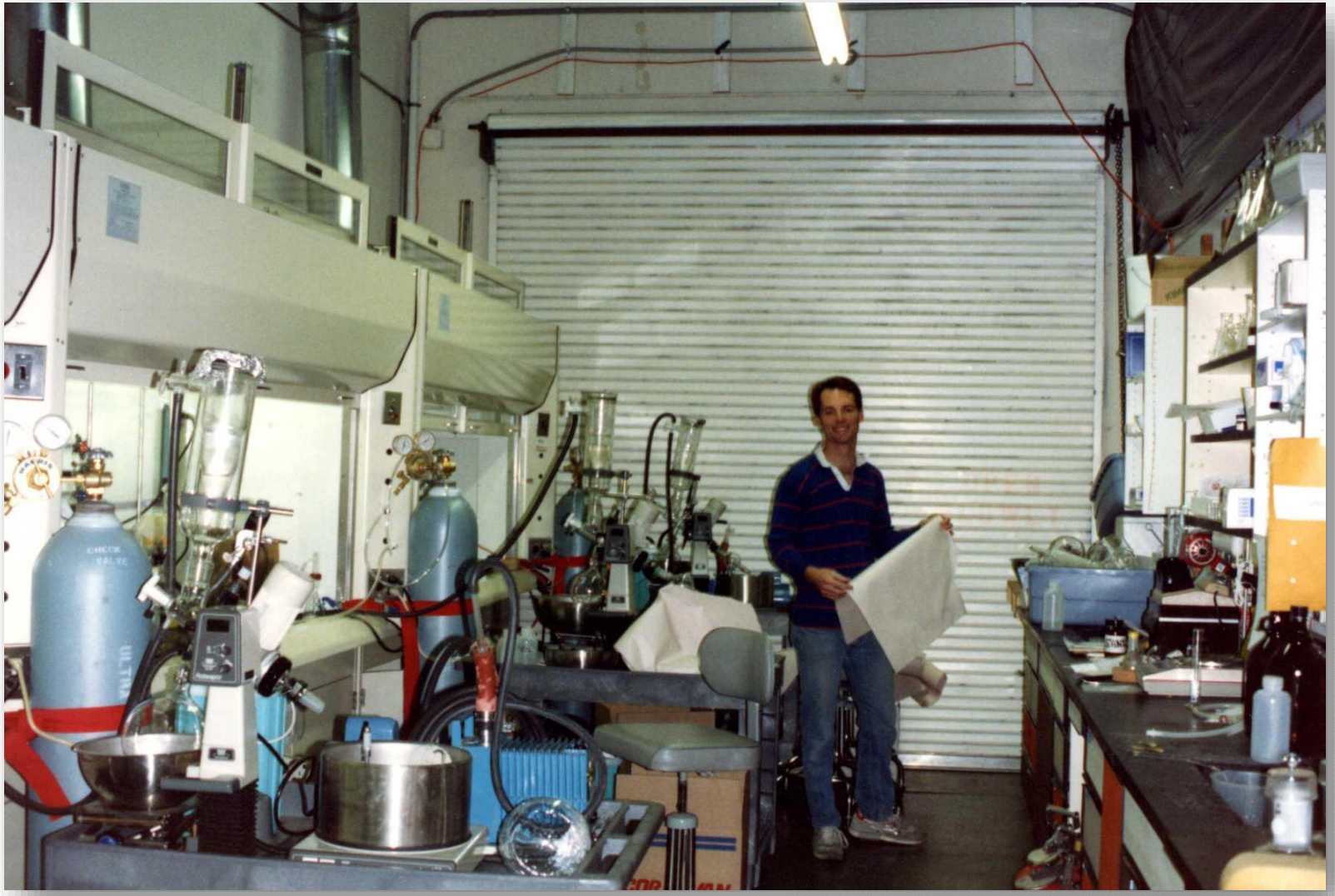
Broad, addressing severe and rare diseases and more common diseases

Innovative, transformative medicines

How We Got Here

In the Beginning

First Lab Space in Sorrento Valley



IONIS

Our Technology

Technology

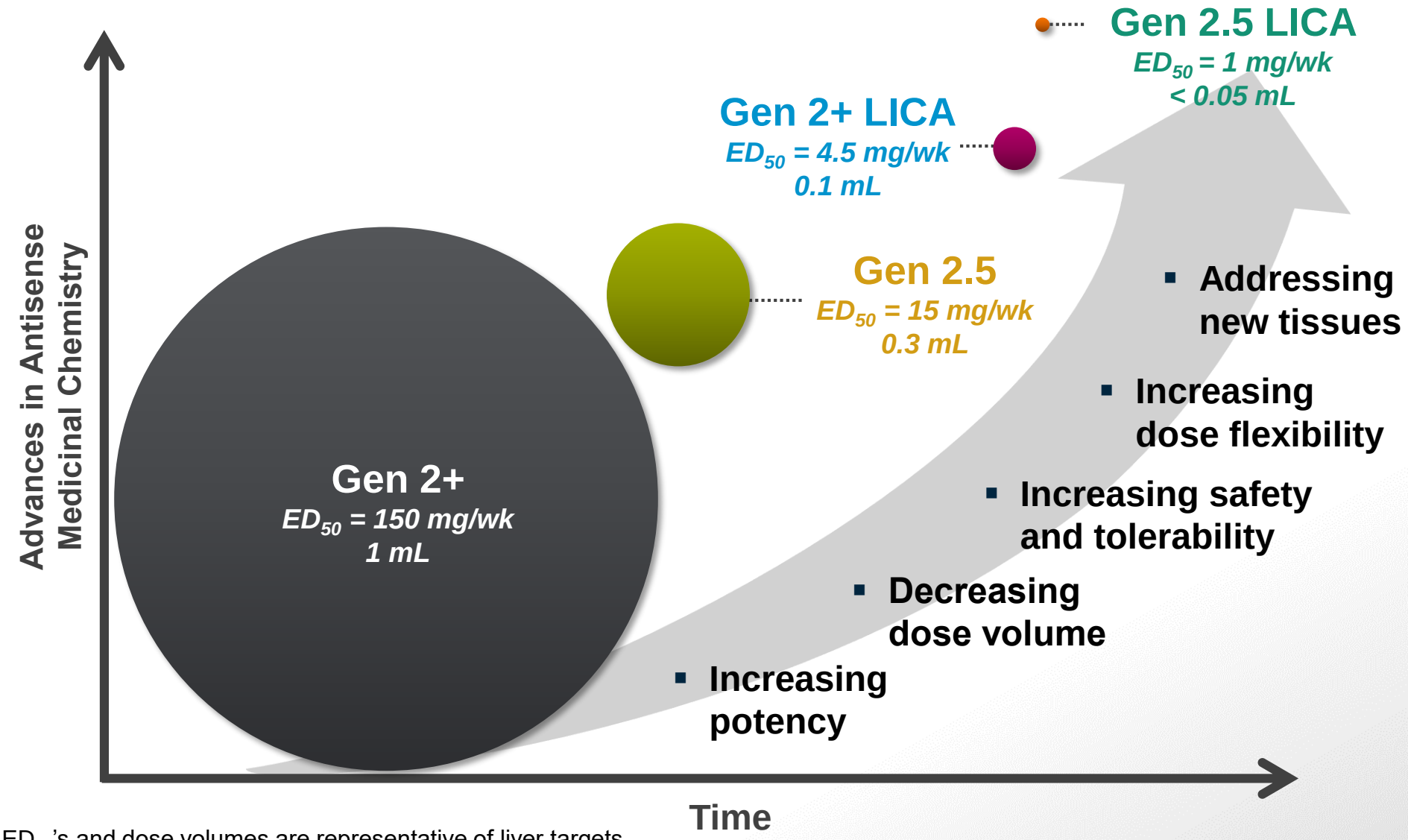
We Set Out to Create and Advance a New Platform for Drug Discovery

Antisense

- Invest broadly and deeply in every element necessary to create a new platform
- Identify potential problems and solve them
- Retain outstanding people to assure that we retain knowledge and experience

IONIS

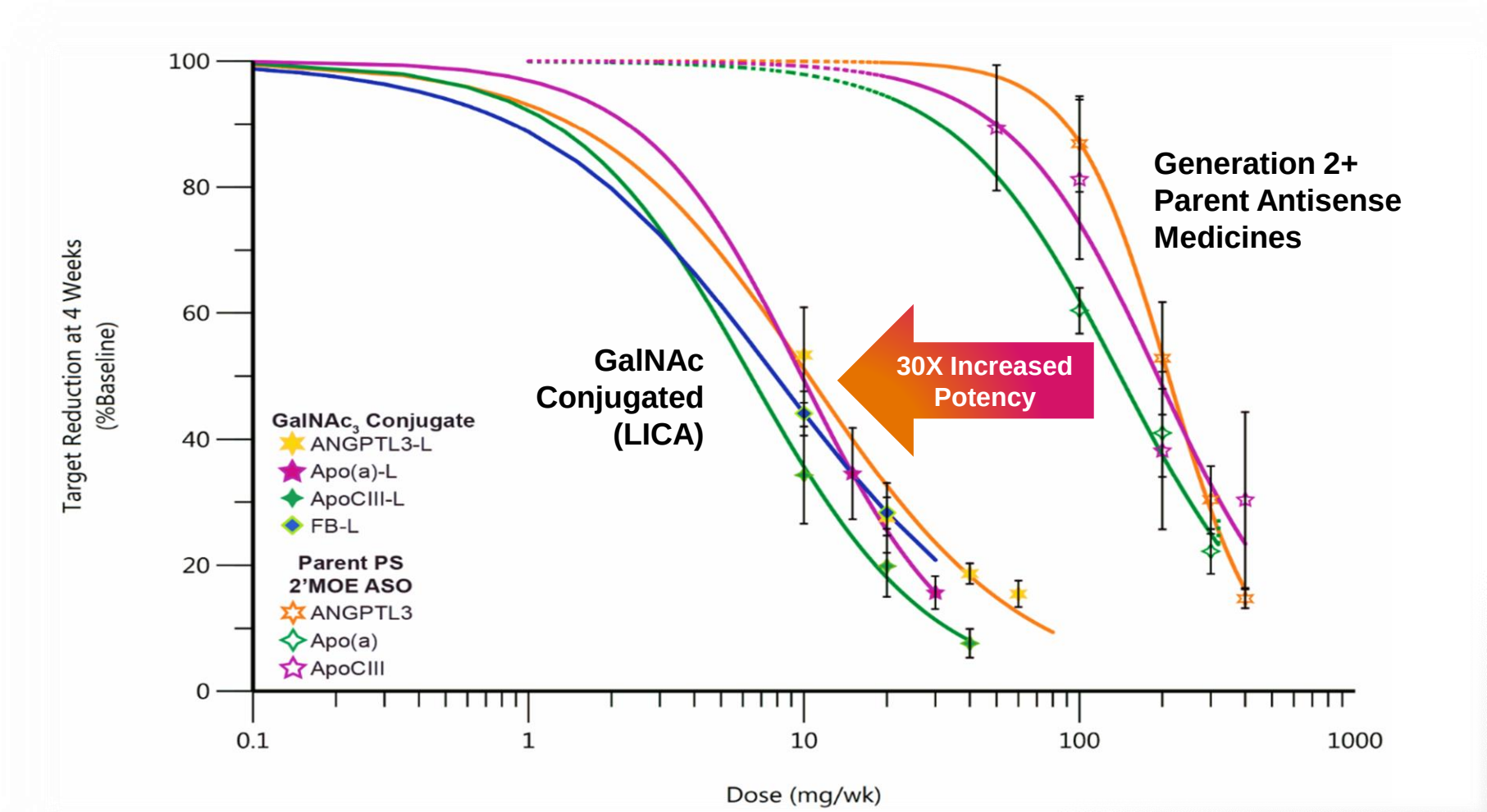
Advances in Our Technology Substantially Improve the Utility of Antisense Medicines



ED_{50}'s and dose volumes are representative of liver targets

New Directions for Medicinal Chemistry

Liver LICA: Targeting Specific Tissues and Cells with Ligands



Greater than 30-fold increase in potency of LICAs targeting the liver

Crooke, S., et al. (2018), Nucleic Acid Therapeutics. http://doi.org/10.1089/nat.2018.0753

Liver LICA

An Example of Advances in Technology Enhancing the Value of Our Pipeline

14 LIVER-TARGETED LICA MEDICINES IN PIPELINE

MEDICINE	INDICATION	PHASE I	PHASE II	PHASE III
AKCEA-APO(a)-L_{Rx}	Cardiovascular disease			
AKCEA-ANGPTL3-L_{Rx}	Cardiometabolic disorders			
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease			
IONIS-GHR-L_{Rx}	Acromegaly			
IONIS-HBV-L_{Rx}	Hepatitis B virus infection			
IONIS-FB-L_{Rx}	Complement-mediated diseases			
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension			
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia			
IONIS-PKK-L_{Rx}	Hereditary angioedema			
IONIS-FXI-L_{Rx}	Clotting disorders			
IONIS-AZ4-2.5-L_{Rx}	Cardiovascular disease			
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis			
ION224	Nonalcoholic steatohepatitis			
ION839	Nonalcoholic steatohepatitis			

SEVERE AND RARE

CARDIOMETABOLIC AND RENAL

OTHER

Liver LICA

An Example of Advances in Technology Enhancing the Value of Our Pipeline

14 LIVER-TARGETED LICA MEDICINES IN PIPELINE

MEDICINE	INDICATION	MARKET OPPORTUNITY
AKCEA-APO(a)-L_{Rx}	**Cardiovascular disease**	**Addressing large patient populations**
AKCEA-APOCIII-L_{Rx}	**Cardiovascular disease**	
IONIS-HBV-L_{Rx}	**Hepatitis B virus infection**	
IONIS-FB-L_{Rx}	**Complement-mediated diseases**	
IONIS-AGT-L_{Rx}	**Treatment-resistant hypertension**	
IONIS-FXI-L_{Rx}	**Clotting disorders**	
IONIS-AZ4-2.5-L_{Rx}	**Cardiovascular disease**	
ION224	**Nonalcoholic steatohepatitis**	
ION839	**Nonalcoholic steatohepatitis**	
AKCEA-ANGPTL3-L_{Rx}	Metabolic disorders	Medium
IONIS-TTR-L_{Rx}	Transthyretin amyloidosis	Medium
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia	Medium
IONIS-GHR-L_{Rx}	Acromegaly	Small (Rare)
IONIS-PKK-L_{Rx}	Hereditary angioedema	Small (Rare)

Gen 2.5 Liver LICA

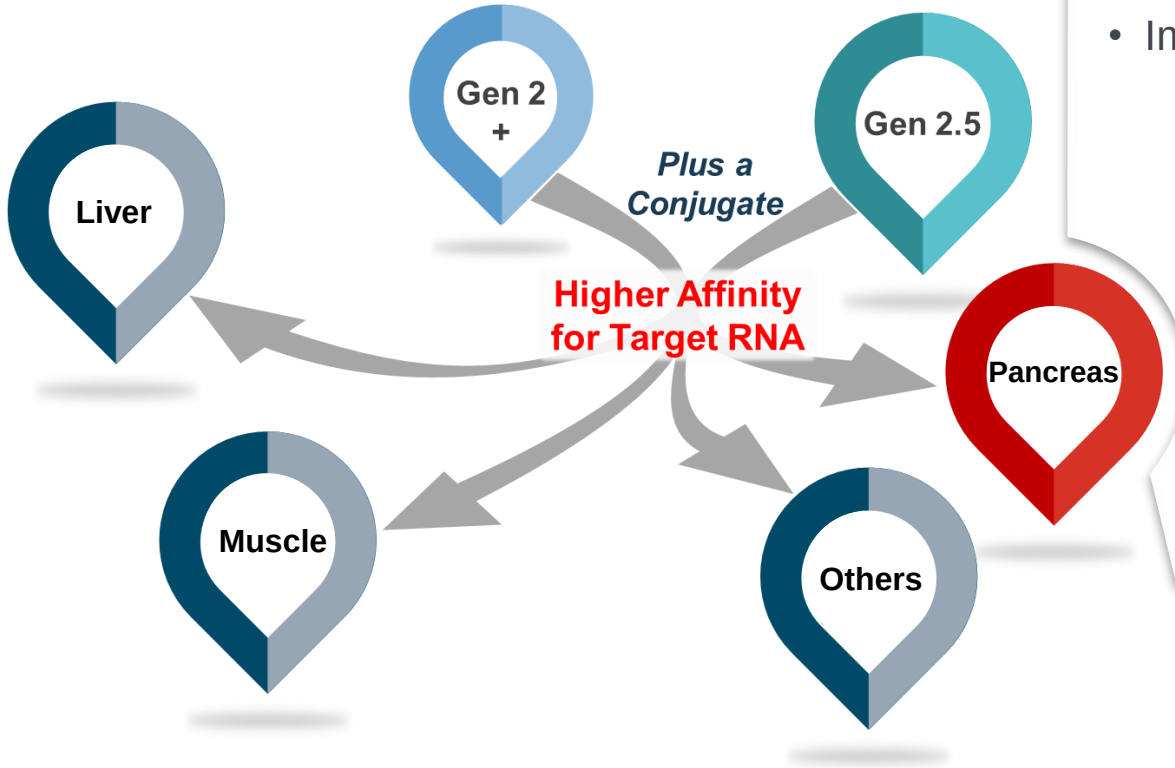
An Example of Advances in Technology Enhancing the Value of Our Pipeline

2 LIVER-TARGETED Gen 2.5 LICA MEDICINES IN PIPELINE

MEDICINE	INDICATION	MARKET OPPORTUNITY
AKCEA-APO(a)-L_{Rx}	Cardiovascular disease	Large
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease	Large
IONIS-HBV-L_{Rx}	Hepatitis B virus infection	Large
IONIS-FB-L_{Rx}	Complement-mediated diseases	Large
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension	Large
IONIS-FXI-L_{Rx}	Clotting disorders	Large
ION224	Nonalcoholic steatohepatitis	Large
IONIS-AZ4-2.5-L_{Rx}	**Cardiovascular disease**	**Potential for commercially attractive oral delivery**
ION839	**Nonalcoholic steatohepatitis**	
AKCEA-ANGPTL3-L_{Rx}	Metabolic disorders	Medium
IONIS-TTR-L_{Rx}	Transthyretin amyloidosis	Medium
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia	Medium
IONIS-GHR-L_{Rx}	Acromegaly	Small (Rare)
IONIS-PKK-L_{Rx}	Hereditary angioedema	Small (Rare)

Chemistry Evolution

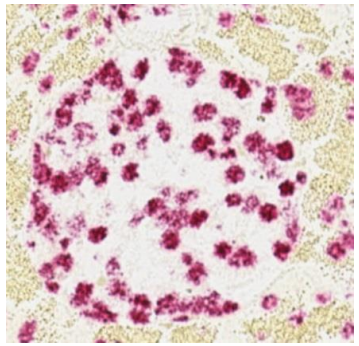
The Power of Conjugations



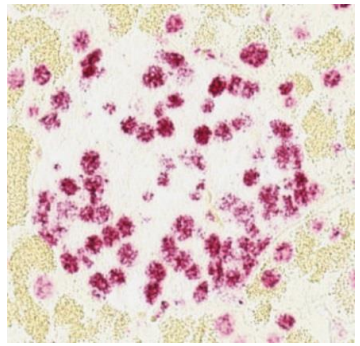
GLP 1 LICA Targeting Pancreas

Gen 2+ and Gen 2.5

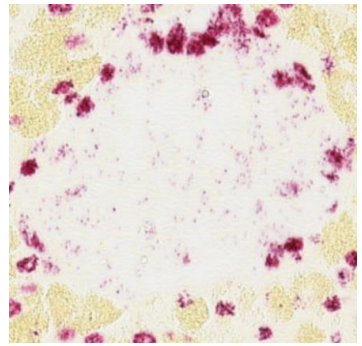
- Improves uptake in pancreas beta cells



Saline



Gen 2.5 ASO



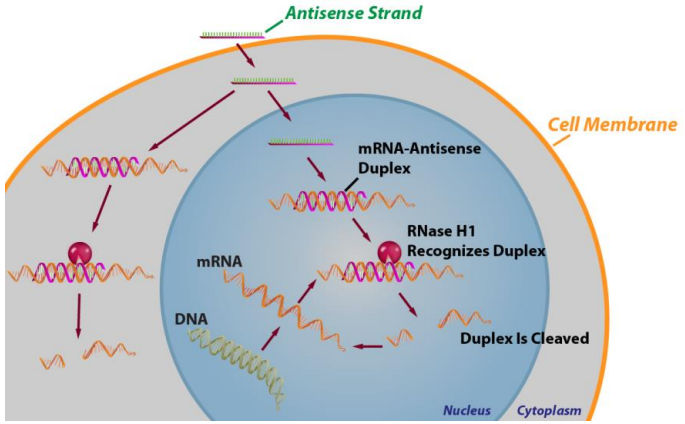
Gen 2.5 + LICA ASO

Antisense Mechanisms:

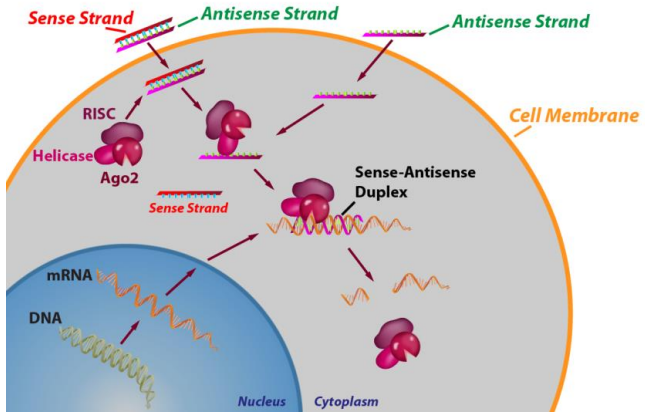
Simplified

Enzymatic RNA Degradation

RNase H1

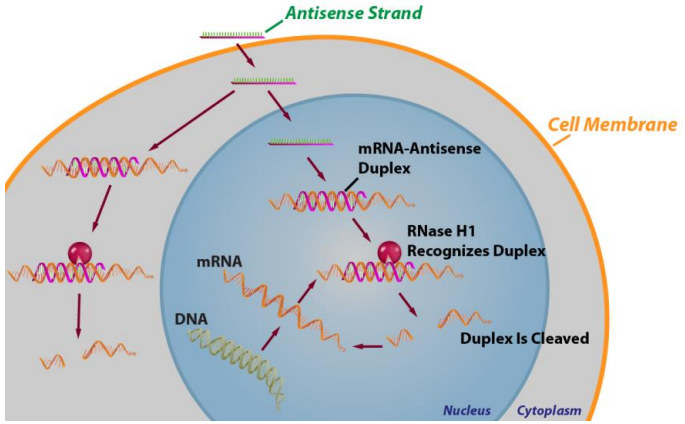


siRNA

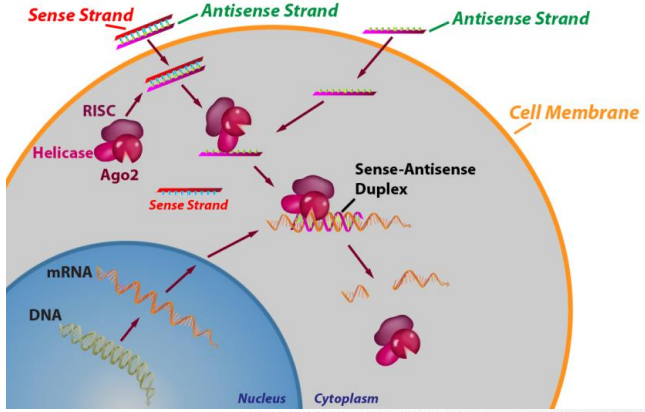


Occupancy Only Mechanisms

Splicing Modulation



Translation Arrest



IONIS

In Antisense Drug Technology: Principles, Strategies, and Applications, Second Edition, Crooke, ST. (ed), Baco Raton, FL, CRC Press, Chapter 1, 3-46, 2008.

Post RNA Hybridization Mechanisms for Antisense Validated by Ionis

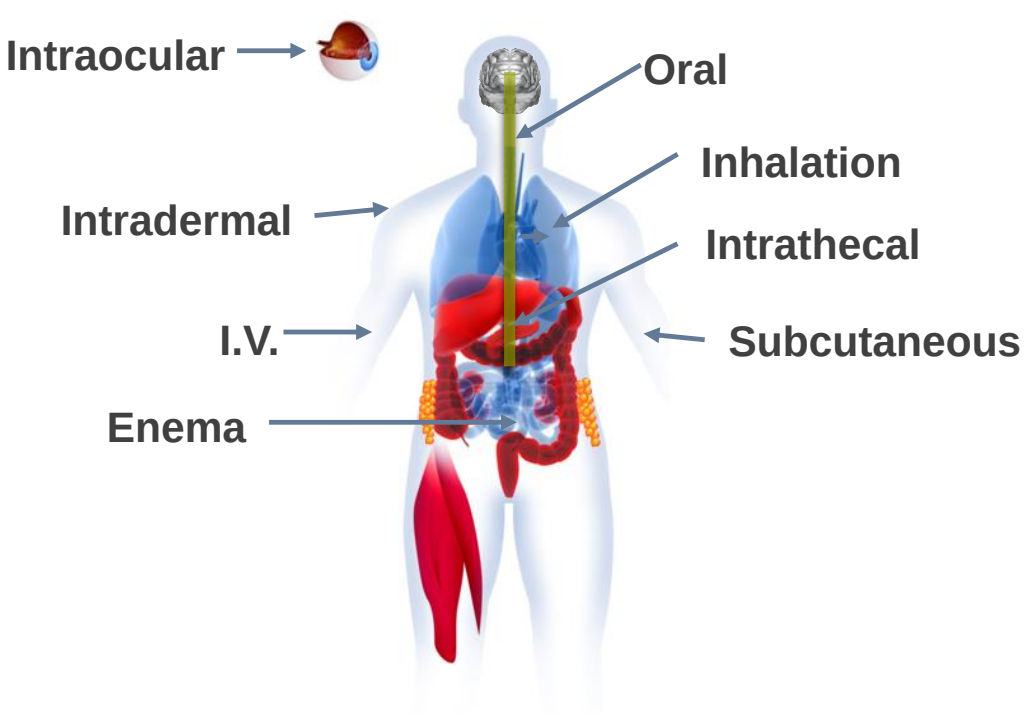
Occupancy Only		Occupancy Induced Degradation
Loss of Function	**Gain of Function**	
5’ cap inhibition	Altered processing	RNAse H1
Translational arrest	uORF utilization	AGO2
Alternate polyadenylation signal utilization	TIE utilization	NMD
	NMD inhibition	No Go decay
	PTC readthrough	

uORF, Upstream Open Reading Frame; TIE, Translation Inhibitor Element; NMD, Nonsense Mediated Decay; PTC, Premature Termination Codon; AGO2, Argonaute 2

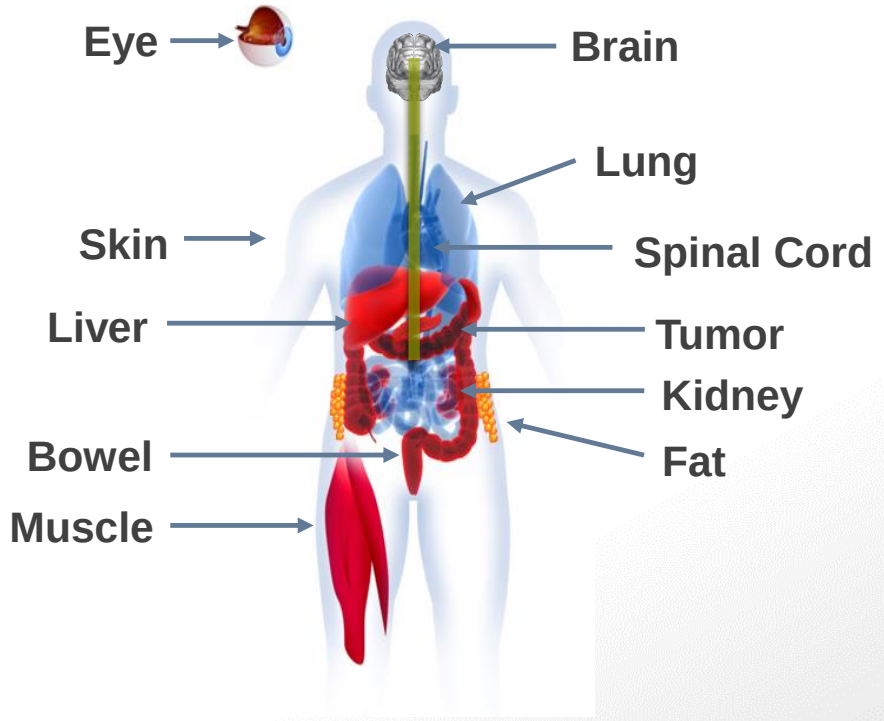
Crooke, S.T. (2017) NAT 27(2):70-77. Sigova, A. et. al. Second Edition, Crooke, ST. (ed), Baco Raton, FL, (2008) CRC Press, Chapter 2, 75-88. Fire, A. et.al. (1998) Nature, 391, 806. Hammond, S.M. et. al. (2001) Science, 293, 1146. Crooke, S.T., et. al. (2018) Cell Metabolism 27: 715-739. Liang, X.H., et. al. (2016) NBT 34:875-882. Liang, X.H., et. al. (2017) NAR, 45(16):9528-9546,. Liang, X.H., et. al. (2017) RNA Activation, Volume 983, of the series Adv Exp Med Biol, Springer Nature Singapore Pte Ltd., ed Li, Long-Cheng, 983(9):129-146. Vickers, T., Crooke, S.T. (2014) PLos One 9(10):e108625. Lima, W.F., et. al. Second Edition, Crooke, ST. (ed), Baco Raton, FL, (2008) CRC Press, Chapter 2, 47-74. Crooke, S.T., et. al. (2017) NBT 35:230-237. Crooke, S.T, Second Edition, (2007) CRC Press. Huang, L, and Monia, B., unpublished data. Laing, X.H., et al., (2019) NAR, in press

Methods of Administration and Technology Advances Create Breadth in Our Pipeline Today

ADMINISTERED THROUGH MULTIPLE ROUTES OF DELIVERY

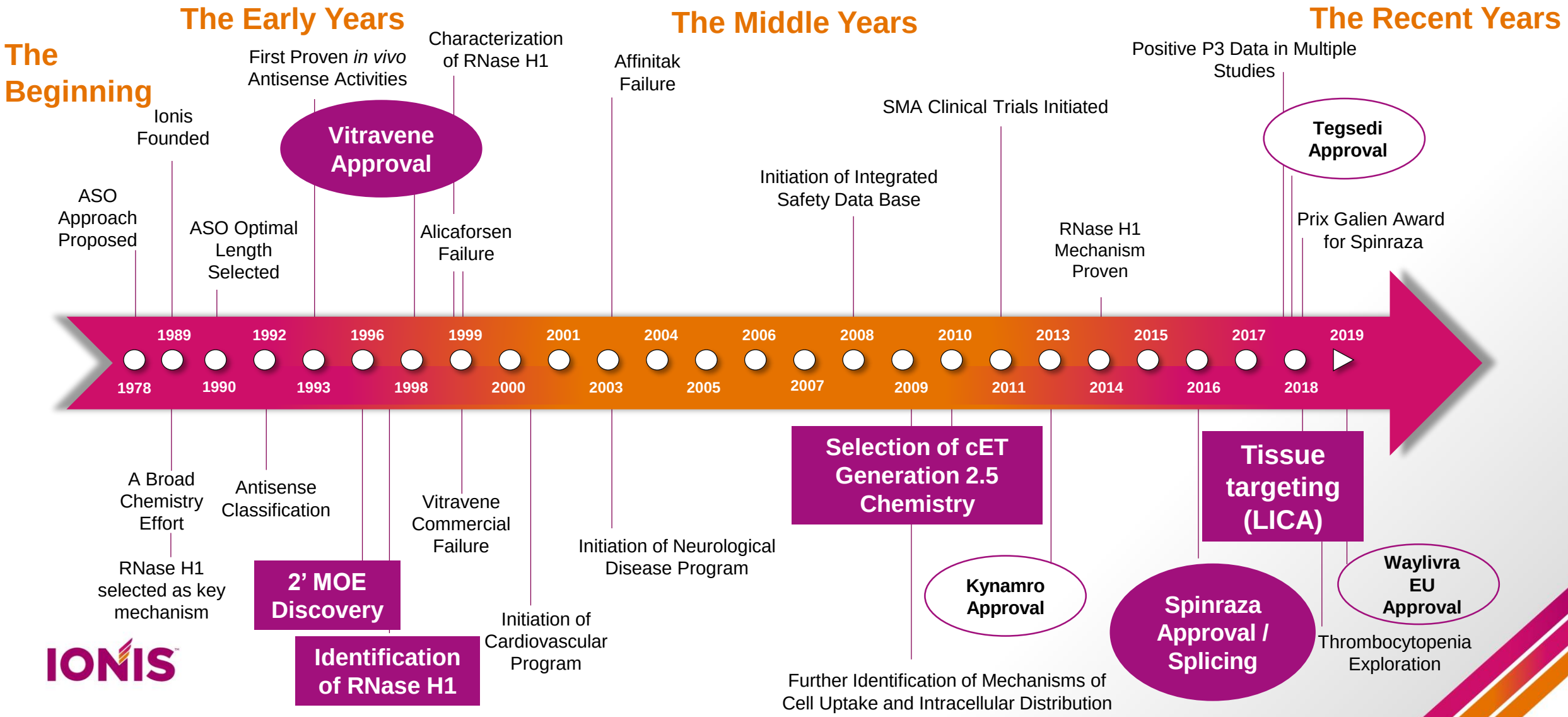


BROAD CLINICAL ACTIVITY IN MULTIPLE TISSUES

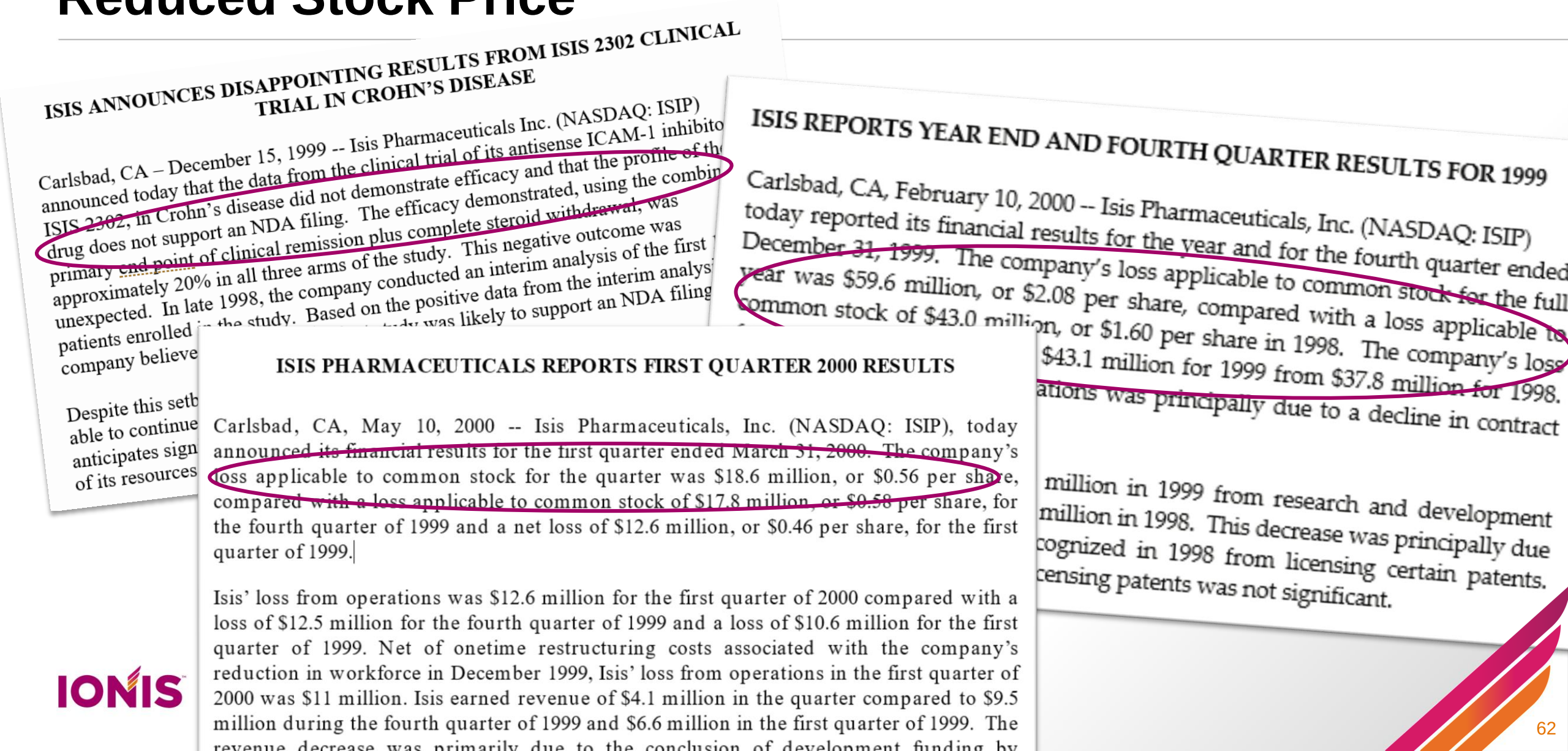


Multiple routes of delivery, multiple target tissues

Technology Timeline



In Late 1999, the Alicaforsen Phase 2 Failure Dramatically Reduced Stock Price



ISIS ANNOUNCES DISAPPOINTING RESULTS FROM ISIS 2302 CLINICAL TRIAL IN CROHN'S DISEASE

Carlsbad, CA – December 15, 1999 -- Isis Pharmaceuticals Inc. (NASDAQ: ISIP) announced today that the data from the clinical trial of its antisense ICAM-1 inhibito ISIS 2302, in Crohn's disease did not demonstrate efficacy and that the profile of th drug does not support an NDA filing. The efficacy demonstrated, using the combin primary end point of clinical remission plus complete steroid withdrawal, was approximately 20% in all three arms of the study. This negative outcome was unexpected. In late 1998, the company conducted an interim analysis of the first patients enrolled in the study. Based on the positive data from the interim analysi company believe study was likely to support an NDA filing

Despite this setb able to continue anticipates sign of its resources

ISIS PHARMACEUTICALS REPORTS FIRST QUARTER 2000 RESULTS

Carlsbad, CA, May 10, 2000 -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIP), today announced its financial results for the first quarter ended March 31, 2000. The company's loss applicable to common stock for the quarter was $18.6 million, or $0.56 per share, compared with a loss applicable to common stock of $17.8 million, or $0.58 per share, for the fourth quarter of 1999 and a net loss of $12.6 million, or $0.46 per share, for the first quarter of 1999.

Isis' loss from operations was $12.6 million for the first quarter of 2000 compared with a loss of $12.5 million for the fourth quarter of 1999 and a loss of $10.6 million for the first quarter of 1999. Net of onetime restructuring costs associated with the company's reduction in workforce in December 1999, Isis' loss from operations in the first quarter of 2000 was $11 million. Isis earned revenue of $4.1 million in the quarter compared to $9.5 million during the fourth quarter of 1999 and $6.6 million in the first quarter of 1999. The revenue decrease was primarily due to the conclusion of development funding by

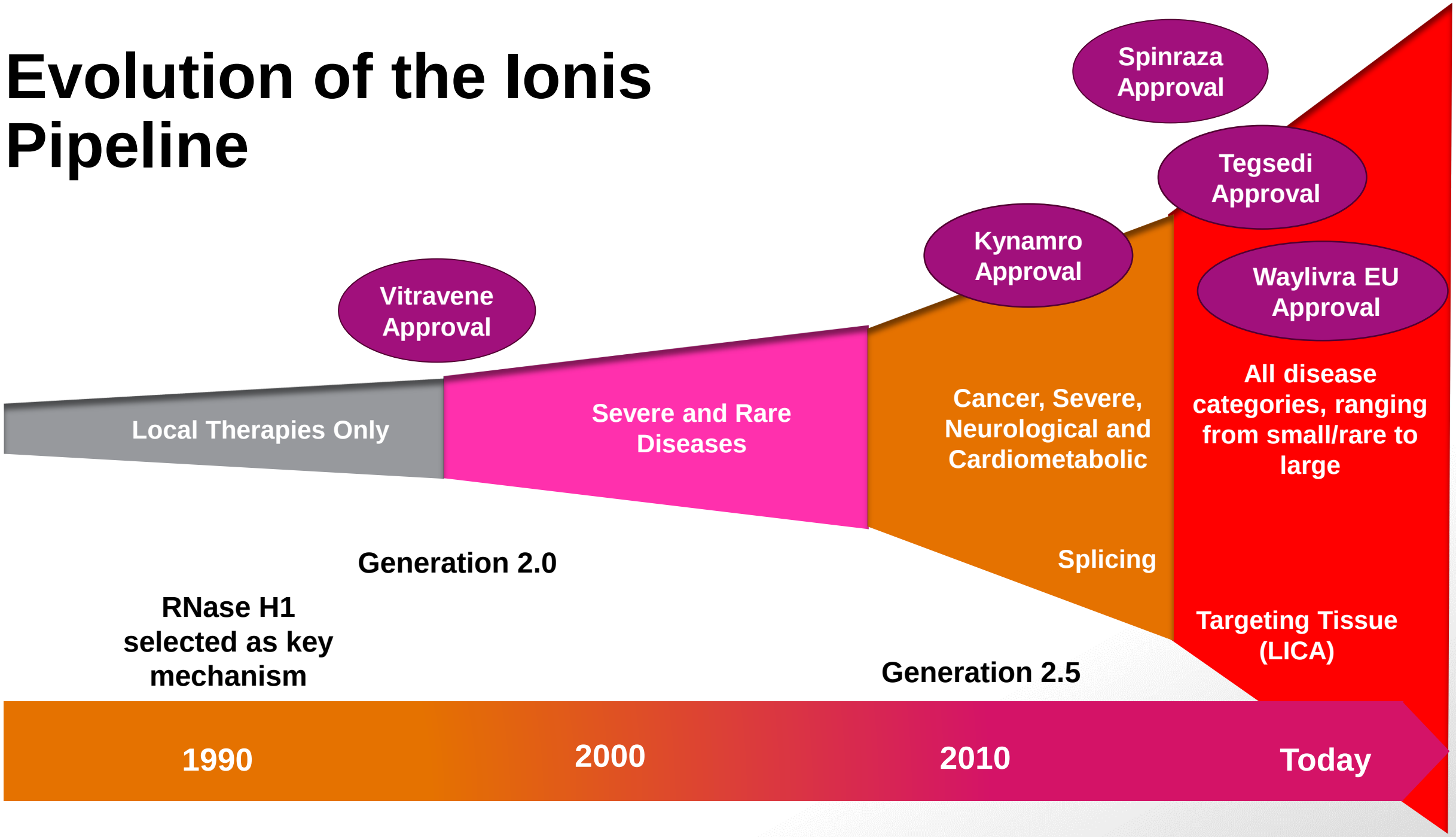
ISIS REPORTS YEAR END AND FOURTH QUARTER RESULTS FOR 1999

Carlsbad, CA, February 10, 2000 -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIP) today reported its financial results for the year and for the fourth quarter ended December 31, 1999. The company's loss applicable to common stock for the full year was $59.6 million, or $2.08 per share, compared with a loss applicable to common stock of $43.0 million, or $1.60 per share in 1998. The company's loss $43.1 million for 1999 from $37.8 million for 1998. ations was principally due to a decline in contract

million in 1999 from research and development million in 1998. This decrease was principally due cognized in 1998 from licensing certain patents. censing patents was not significant.

IONIS

Evolution of the Ionis Pipeline



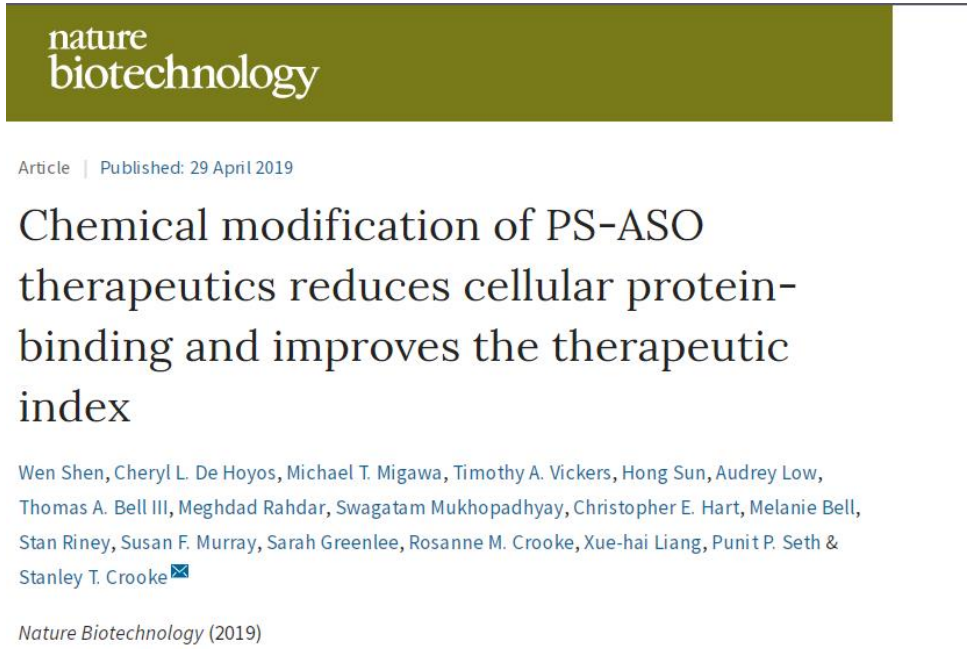
Ionis Created, Validated, and Continues to Advance an Efficient RNA-Targeting Platform

DELIVERING GREAT VALUE TODAY AND BEYOND

Most Direct Route from Gene to Medicine	**Uniquely specific and broadly applicable**
Efficient Discovery & Early Development	**Dramatically reduced cost and increased success through clinical proof of concept**
Consistent Performance Within Chemical Classes	**Higher success rate in discovery and development**
Advances Rapidly Incorporated Across the Entire Pipeline	**Chemistry, manufacturing, formulation, analytical methods**
Consistent Pipeline Growth	**Robust, mature, diversified pipeline, adding 3-5 new medicines per year**

New Directions for Medicinal Chemistry

Targeting Specific Sites in the Cell and Cellular Functions



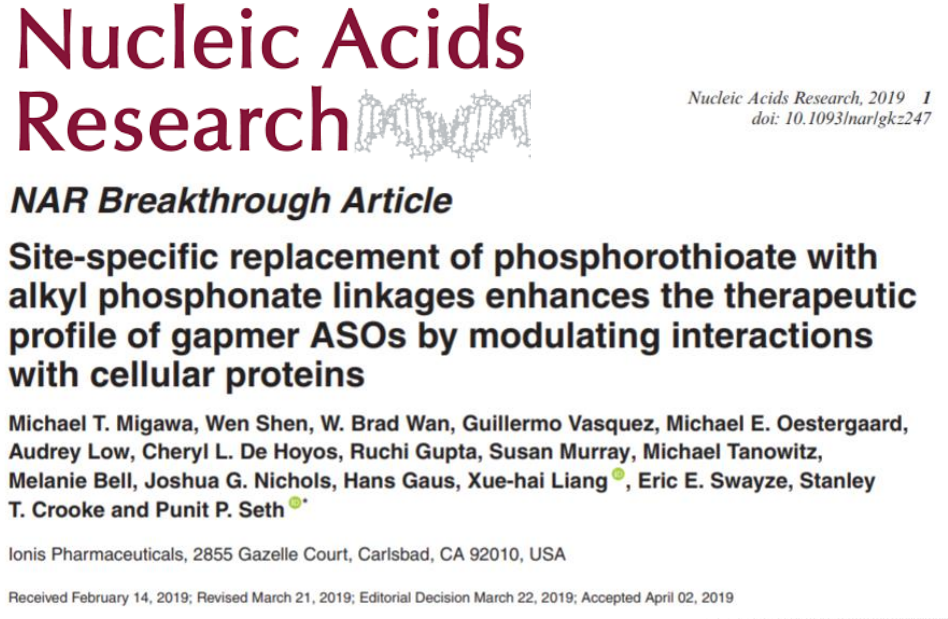
nature biotechnology

Article | Published: 29 April 2019

Chemical modification of PS-ASO therapeutics reduces cellular protein-binding and improves the therapeutic index

Wen Shen, Cheryl L. De Hoyos, Michael T. Migawa, Timothy A. Vickers, Hong Sun, Audrey Low, Thomas A. Bell III, Meghdad Rahdar, Swagatam Mukhopadhyay, Christopher E. Hart, Melanie Bell, Stan Riney, Susan F. Murray, Sarah Greenlee, Rosanne M. Crooke, Xue-hai Liang, Punit P. Seth & Stanley T. Crooke

Nature Biotechnology (2019)



Nucleic Acids Research

Nucleic Acids Research, 2019 1
doi: 10.1093/nar/gkz247

NAR Breakthrough Article

Site-specific replacement of phosphorothioate with alkyl phosphonate linkages enhances the therapeutic profile of gapmer ASOs by modulating interactions with cellular proteins

Michael T. Migawa, Wen Shen, W. Brad Wan, Guillermo Vasquez, Michael E. Oestergaard, Audrey Low, Cheryl L. De Hoyos, Ruchi Gupta, Susan Murray, Michael Tanowitz, Melanie Bell, Joshua G. Nichols, Hans Gaus, Xue-hai Liang, Eric E. Swayze, Stanley T. Crooke and Punit P. Seth*

Ionis Pharmaceuticals, 2855 Gazelle Court, Carlsbad, CA 92010, USA

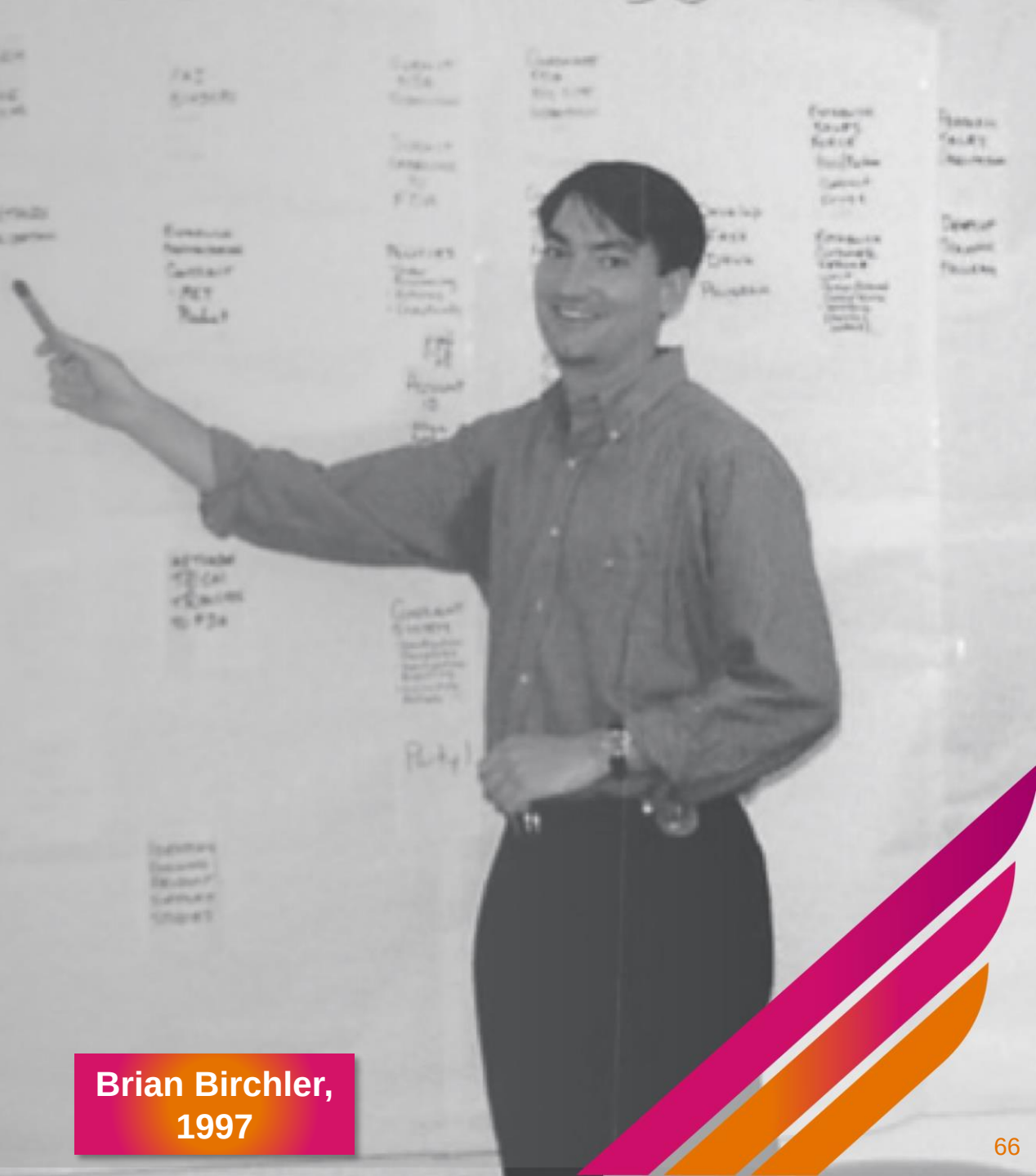
Received February 14, 2019; Revised March 21, 2019; Editorial Decision March 22, 2019; Accepted April 02, 2019

Ionis' work published in *Nature Biotechnology* and *Nucleic Acids Research* demonstrate new advances in ASO technology

IONIS

Shen, et al., (2019) NBT e-pub May 4; Migawa, M., et. al., (2019) NAR

Novel Business Model



Brian Birchler, 1997

Ionis' Novel Business Model

Committed to Innovation

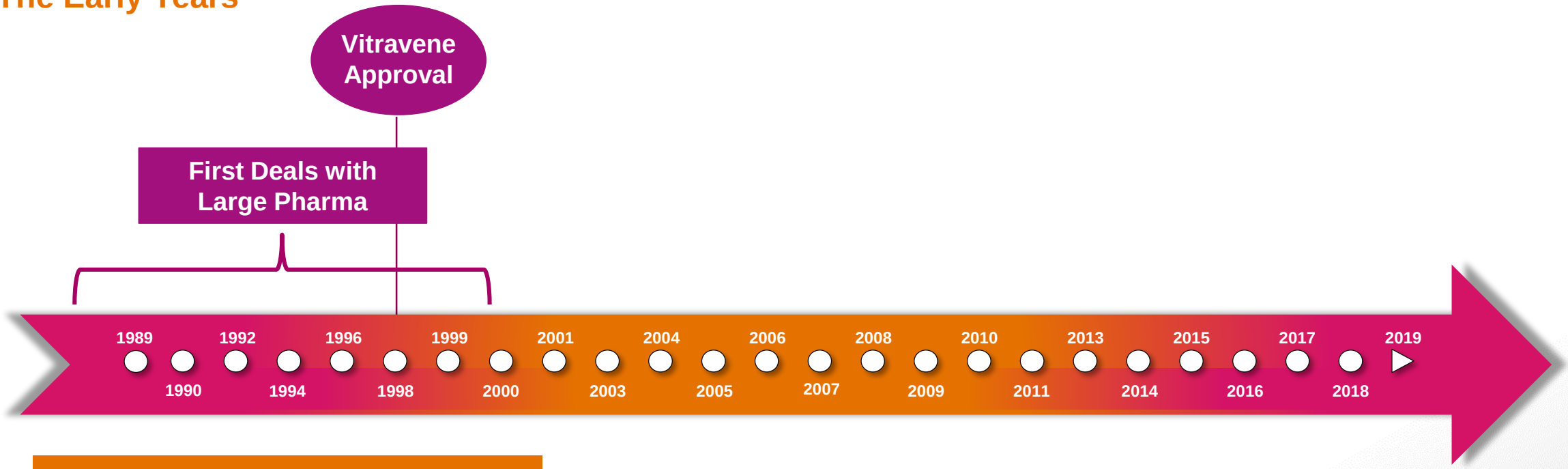
What we set out to create

- A small innovation-centered core organization
- A culture of "YES"
- A strategy to identify the optimal organizations to develop and commercialize each precious medicine in our pipeline
- Multiple sources of revenue

IONIS

Business Model & Strategy Timeline

The Early Years

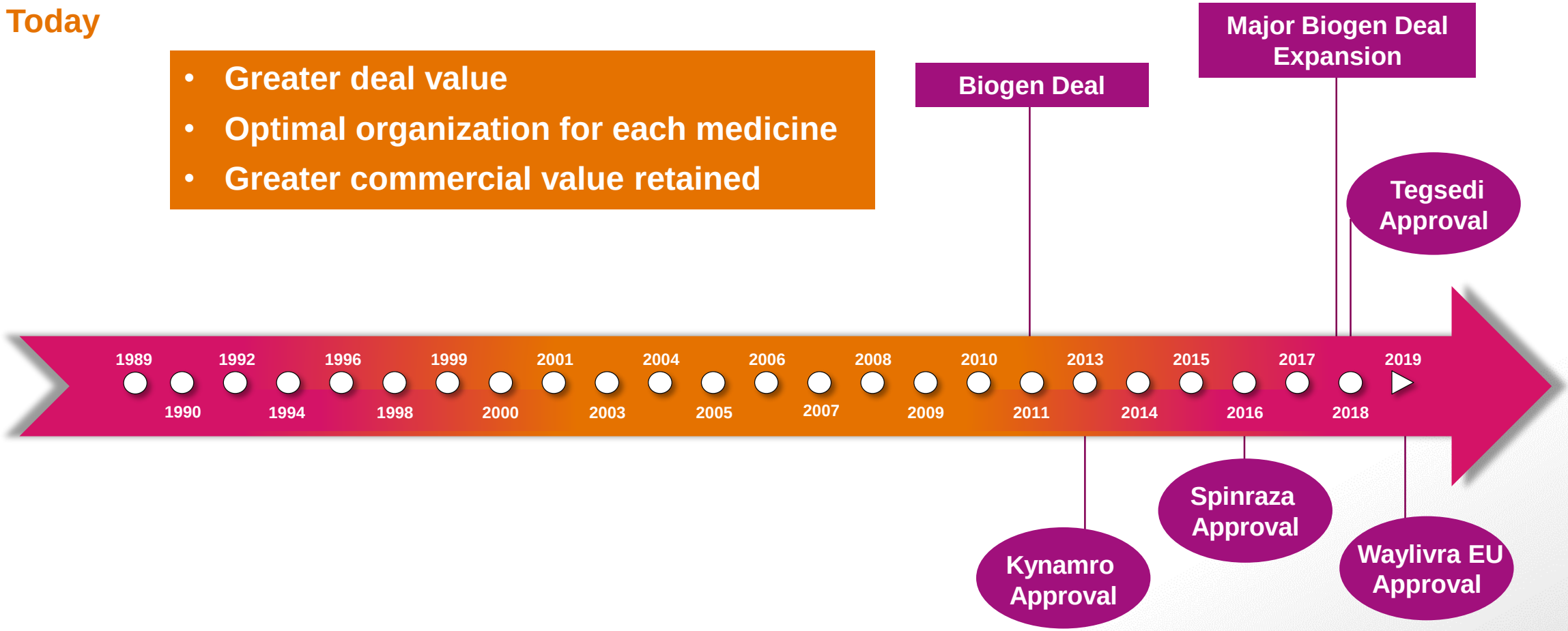


- Cash
- Access to resources
- Validate our technology

Business Model & Strategy Timeline

Today

- Greater deal value
- Optimal organization for each medicine
- Greater commercial value retained

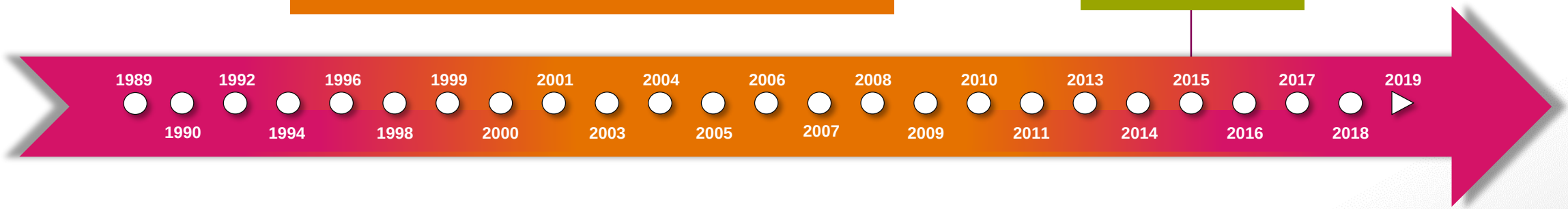


Business Model & Strategy Timeline

Akcea: Our First Commercial Affiliate

- 2 commercial medicines
- 6 first-in-class medicines advancing
- ~ $2 billion market capitalization
- Well funded to accomplish goals

Akcea Founded



2018 Biogen Collaboration

An Example of the Significantly Increasing Value of our Technology

	2013 Strategic Neurology Collaboration	2018 Strategic Neurology Collaboration
Upfront payment	$100 Million	**$1 Billion***
Research term	6 years	**10 years**
Option timing	Clinical proof-of-concept	**Completion of IND-enabling studies**
Additional payments per typical program	Up to $220M	**Up to $270M**
Royalty rate	Low to mid teens	**Mid teens to twenty**

*Includes $625 million for Ionis stock at 25% cash premium

IONIS

The Antisense Advantage: The Ionis Business Model and Technology Have Resulted in a Proven, Efficient Platform for Creating New Medicines

IONIS

1 medicine / 11 employees

TRADITIONAL PHARMA

1 medicine / >1,000 employees

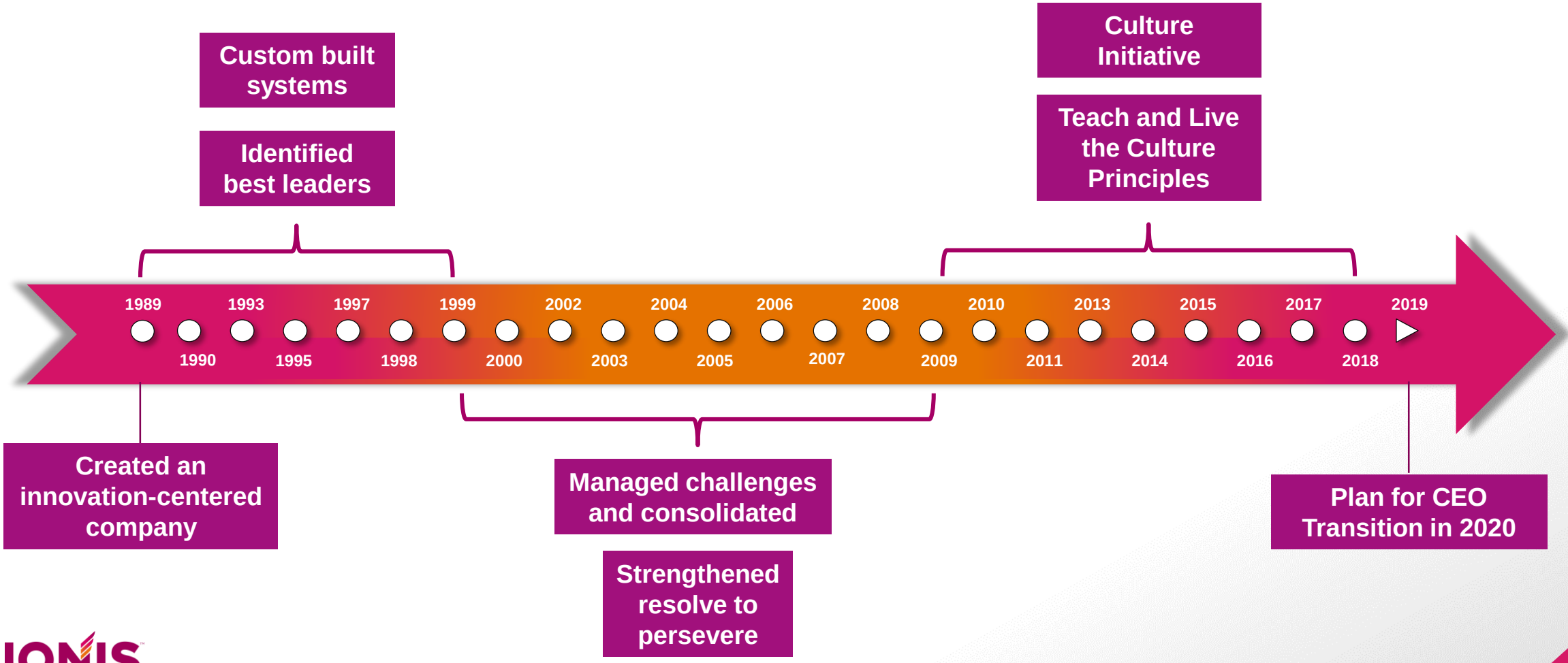
The Ionis Culture

Culture Timeline

The Early Years

The Middle Years

Today




“Because we can transform
the treatment of a disease,
we will always choose YES.
No patient ever got better
with a no.”

Coupling a More Efficient Technology Platform to a Tailored Business Model

Ever-growing competitive advantage

Large and growing commercial opportunities

- Most Direct Route from Gene to Patient
- Higher Success Rate
- Efficient Infrastructure
- Optimal Approach for Each Medicine

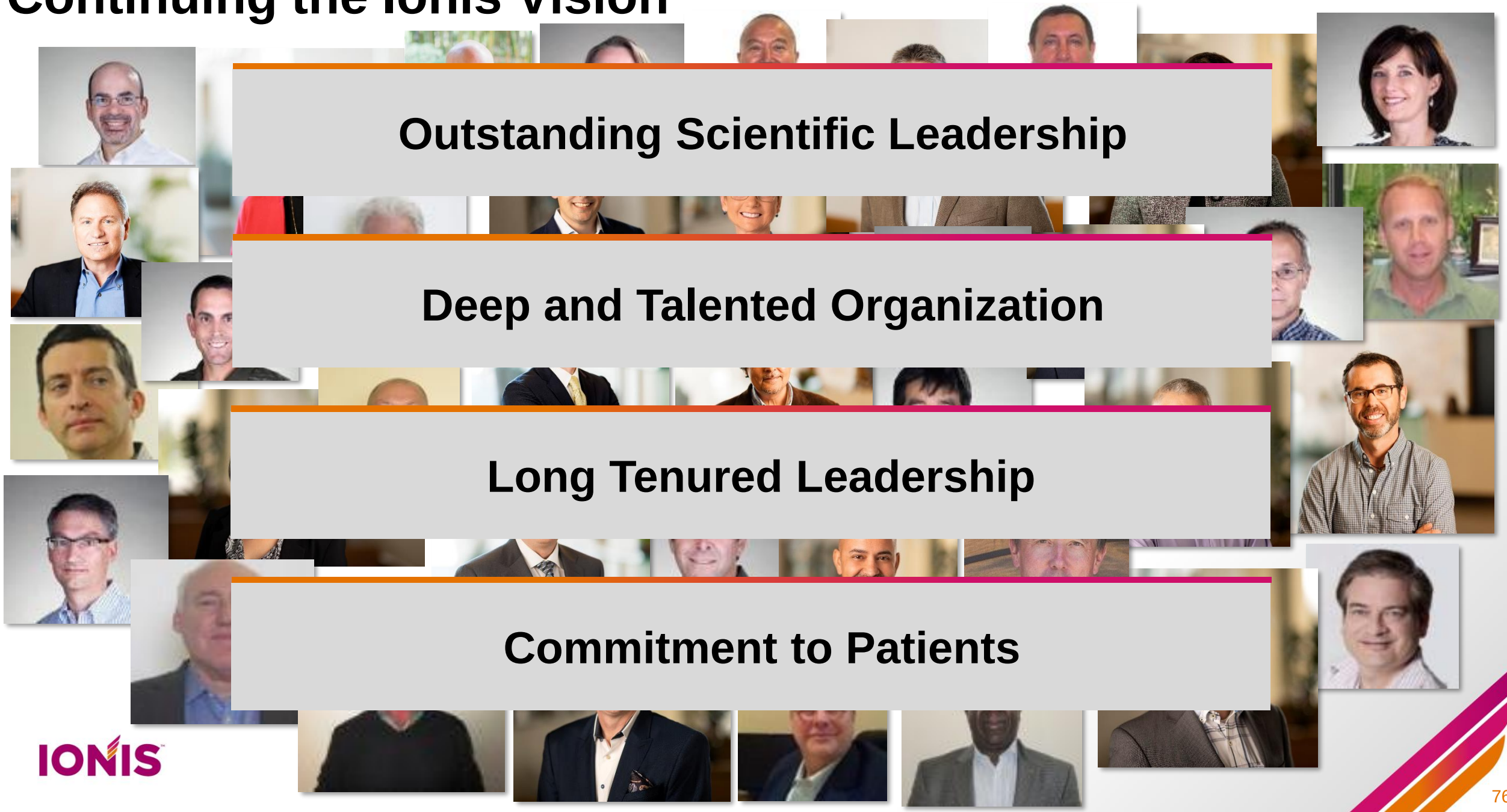
Creating growing value for patients and shareholders

IONIS

An Even More Exciting Future

Image: Charlie Neuman

Continuing the Ionis Vision



Outstanding Scientific Leadership

Deep and Talented Organization

Long Tenured Leadership

Commitment to Patients

Ionis: A Force For Life

IONIS™

A FORCE FOR LIFE