

# IONIS™

## 30 Years: Our Extraordinary Journey





# Prologue to an Exciting Future



# IONIS™

## Novel Business Model



Brian Birchler,  
1997

# 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**



# IONIS™

## An Even More Exciting Future

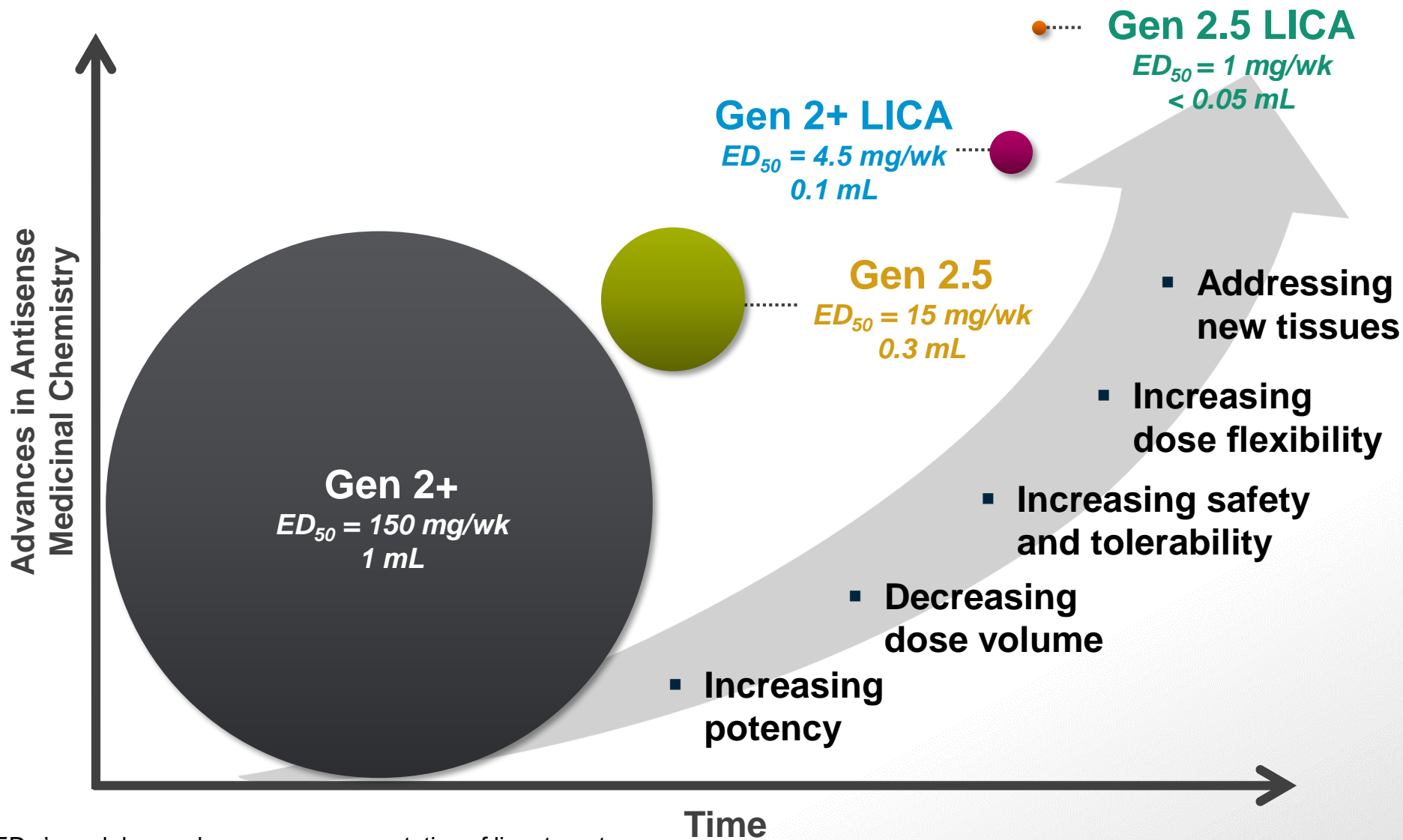




# IONIS<sup>TM</sup>

## Our Technology

# Advances in Our Technology Substantially Improve the Utility of Antisense Medicines



# 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	<b>\$1 Billion*</b>
Research term	6 years	<b>10 years</b>
Option timing	Clinical proof-of-concept	<b>Completion of IND-enabling studies</b>
Additional payments per typical program	Up to \$220M	<b>Up to \$270M</b>
Royalty rate	Low to mid teens	<b>Mid teens to twenty</b>
*Includes \$625 million for Ionis stock at 25% cash premium		



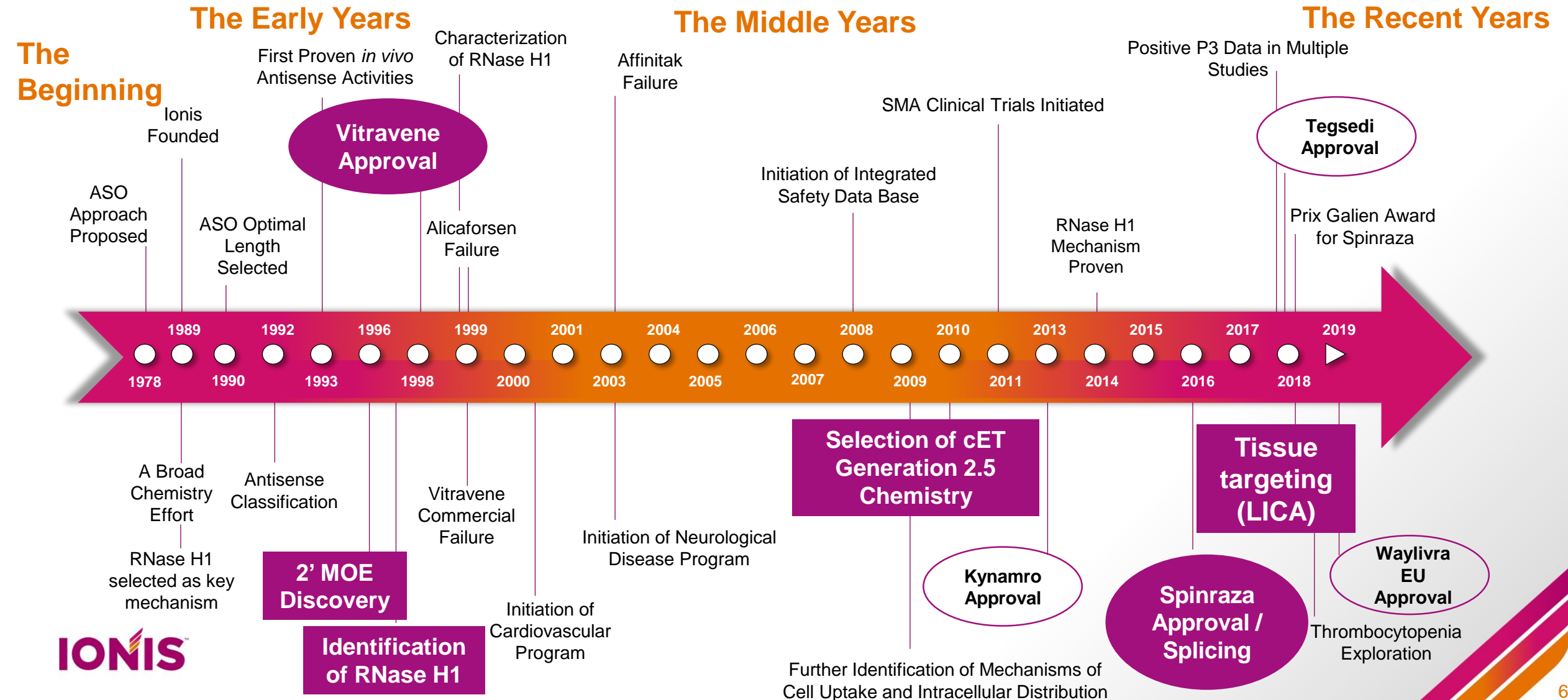
# Gen 2.5 Liver LICA

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 <sub>Rx</sub>	Cardiovascular disease	Large
AKCEA-APOCIII-L <sub>Rx</sub>	Cardiovascular disease	Large
IONIS-HBV-L <sub>Rx</sub>	Hepatitis B virus infection	Large
IONIS-FB-L <sub>Rx</sub>	Complement-mediated diseases	Large
IONIS-AGT-L <sub>Rx</sub>	Treatment-resistant hypertension	Large
IONIS-FXI-L <sub>Rx</sub>	Clotting disorders	Large
ION224	Nonalcoholic steatohepatitis	Large
IONIS-AZ4-2.5-L <sub>Rx</sub>	Cardiovascular disease	Potential for commercially attractive
ION839	Nonalcoholic steatohepatitis	oral delivery
AKCEA-ANGPTL3-L <sub>Rx</sub>	Metabolic disorders	Medium
IONIS-TTR-L <sub>Rx</sub>	Transthyretin amyloidosis	Medium
IONIS-TMPRSS6-L <sub>Rx</sub>	β-Thalassemia	Medium
IONIS-GHR-L <sub>Rx</sub>	Acromegaly	Small (Rare)
IONIS-PKK-L <sub>Rx</sub>	Hereditary angioedema	Small (Rare)

# Technology Timeline



# 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<sup>TM</sup>

## Where is Ionis today?

*Annette, living with Charcot  
Marie Tooth disease*





# 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<sup>1</sup>; Q1 2019 sales increased by 42% compared to Q1 2018
- Over 7,500 patients on treatment<sup>2</sup>
- Over 1,000 adult SMA patients on SPINRAZA in the U.S., accounted for 50% of new U.S. patient starts<sup>1</sup>
- Approved in >40 countries, including across Asia and Latin America, with reimbursement in >30 countries<sup>3</sup>

## 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



<sup>1</sup>As of March 31, 2019

<sup>2</sup>Includes patients in commercial setting, EAP and clinical trials

<sup>3</sup>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<sub>Rx</sub>) demonstrated trends towards clinical benefit in measures of disease in a Phase 1/2 study in SOD1-ALS patients
- IONIS-HTT<sub>Rx</sub> (RG6042) demonstrated sustained mHTT lowering through 9 months of treatment in the OLE
- Earned \$150 million when Novartis licensed AKCEA-APO(a)-L<sub>Rx</sub> based on positive Phase 2 data; initiation of Phase 3 cardiovascular outcomes study ongoing
- IONIS-DGAT2<sub>Rx</sub> 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<sub>Rx</sub> continued to progress towards pivotal program, which is on track to start in 2H 2019
- Initiated clinical studies with IONIS-GHR-L<sub>Rx</sub>, IONIS-C9<sub>Rx</sub>, IONIS-FXI-L<sub>Rx</sub>, IONIS-ENAC-2.5<sub>Rx</sub> and IONIS-AZ4-2.5-L<sub>Rx</sub>

# 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

# 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\*



# 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

— G R O W I N G R & D R E V E N U E —