Ionis Pharmaceuticals

36th Annual J.P. Morgan Healthcare Conference

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

January 2018

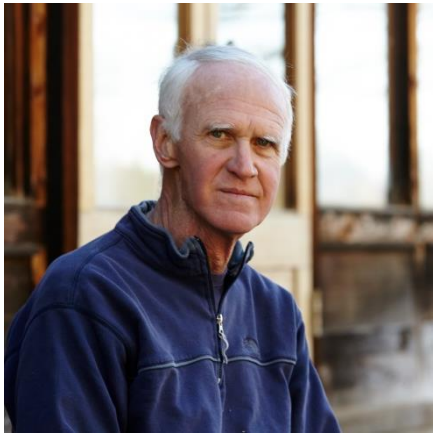
IONIS™ PHARMACEUTICALS

Forward Looking Language Statement

This presentation includes forward-looking statements regarding Ionis Pharmaceuticals' financial position and outlook, Ionis' business, the business of Akcea Therapeutics, Inc., and the therapeutic and commercial potential of Ionis' technologies and products in development, including SPINRAZA, inotersen and volanesorsen. 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 drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. 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, 2016, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

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 trademark of Ionis Pharmaceuticals, Inc. SPINRAZA® is a registered trademark of Biogen.

Revolutionizing Medicine. Saving Lives.



Key Achievements (1 of 2)

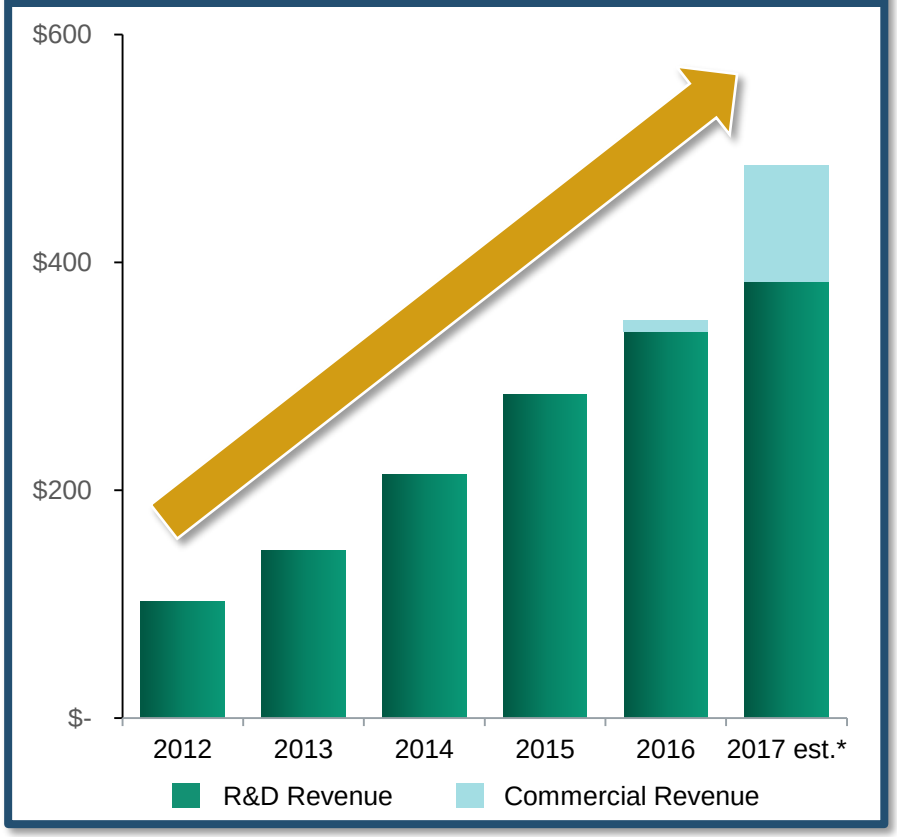
SPINRAZA	✓ On track to be one of the most successful rare disease drug launches
	✓ Approved in numerous markets globally, additional approvals anticipated
	✓ Continues to demonstrate increasing benefit across a broad range of SMA patients
	✓ Established collaboration to create new antisense oligonucleotides for SMA
	✓ Awarded prestigious Prix Galien Award
Volanesorsen	✓ On track to launch volanesorsen for FCS globally in mid-2018
	✓ Marketing applications accepted in the U.S., EU (Promising Innovative Medicine designation in UK) and Canada (Priority Review)
	✓ Enrolling expanded access program
	✓ Reported positive results from Phase 3 APPROACH study
Inotersen	✓ On track to launch inotersen for hATTR globally in mid-2018
	✓ NDA accepted for Priority Review (PDUFA date July 6, 2018); MAA submitted with Accelerated Assessment
	✓ Advancing expanded access program
	✓ Reported positive results from Phase 3 NEURO-TTR study
	✓ Initiated IONIS-TTR-L_{Rx} preclinical toxicology studies

Key Achievements (2 of 2)

Pipeline	✓ Reported positive and consistent data from multiple Generation 2+ LICA programs, including data with once-monthly dosing
	✓ Reported positive data from IONIS-STAT3-2.5$_{Rx}$ in combination with AZ's Imfinzi
	✓ Achieved dose-dependent reductions of mHTT in Huntington's patients with IONIS-HTT$_{Rx}$; Roche advancing clinical development
	✓ Initiated Phase 2 programs with AKCEA-APO(a)-L$_{Rx,}$ AKCEA-APOCIII-L$_{Rx}$ and AKCEA-ANGPTL3-L$_{Rx}$
	✓ Initiated study of IONIS-FXI$_{Rx}$ in patients with ESRD
	✓ Advanced 1st orally delivered antisense drugs under Janssen collaboration, earned $10M
	✓ Initiated study of IONIS-MAPT$_{Rx}$ in patients with Alzheimer's Disease
	✓ Added 8 new drugs to the pipeline
Business	✓ Significantly improved on financial guidance
	✓ Initiated collaboration for enhanced antisense oligonucleotides for SMA; Substantially improved economics
	✓ Generated more than $200M from Biogen in 2017
	✓ Licensed IONIS-HTT$_{Rx}$ to Roche, earning a $45M license fee; potential for $300M in milestones plus royalties
	✓ Advanced both IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$, generating $175M from Bayer
	✓ Entered collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$, valued at up to more than $1B
	✓ Completed Akcea IPO, raising greater than $180M

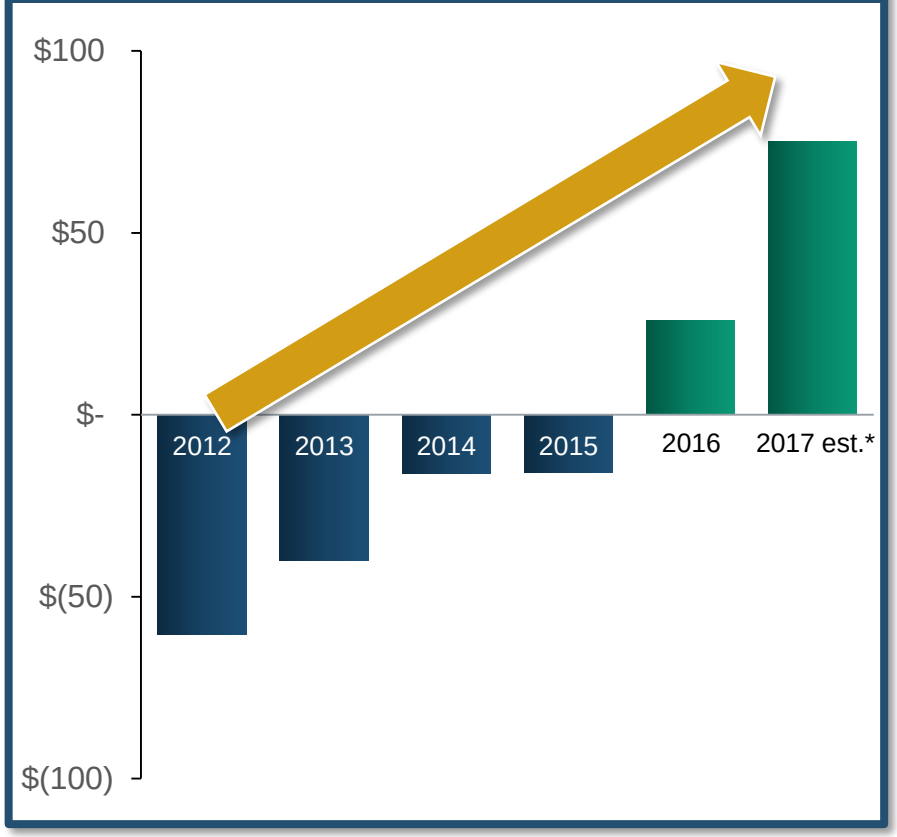
Significant Revenue Growth Supports Sustained Operating Profit

Revenue 2012 – 2017



Commercial Revenue Building Off a Solid Base of R&D Revenue

Operating Income** 2012 – 2017



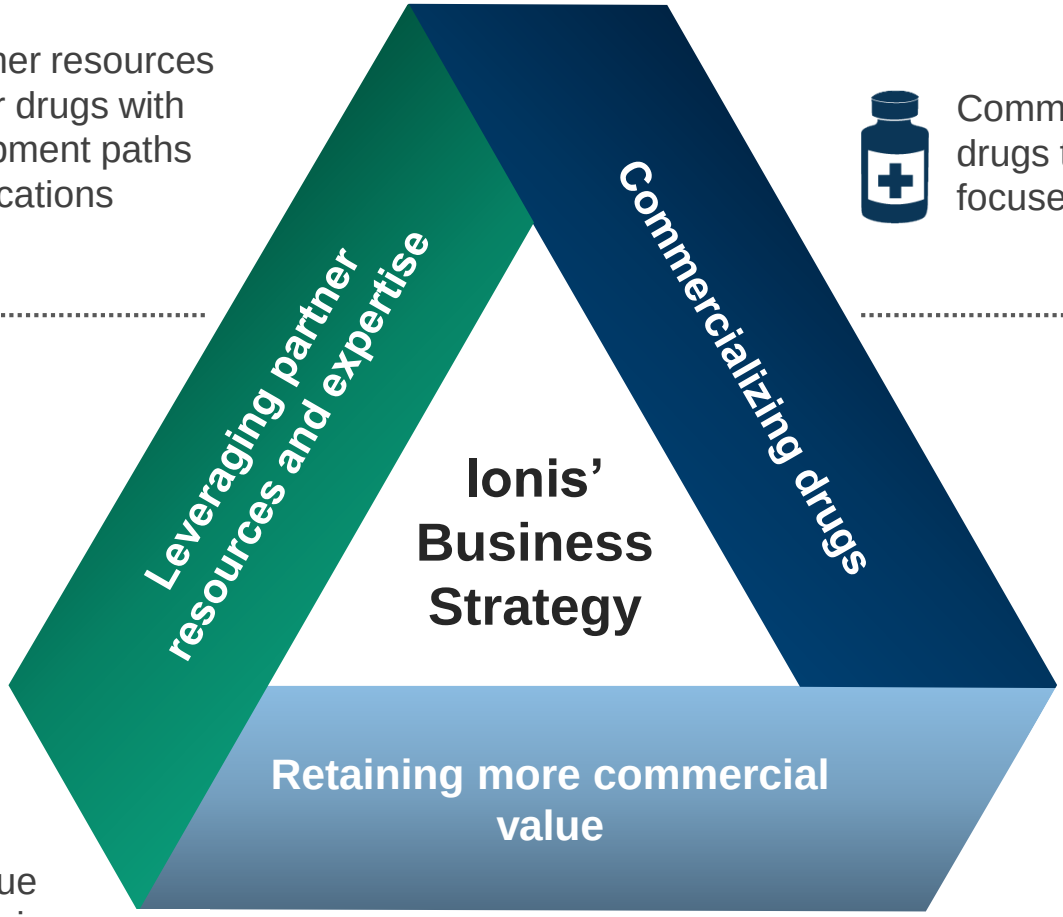
2 Consecutive Years of Operating Profit*

**Includes consensus estimate for Q4 2017, **Pro forma amounts*

Maximizing Potential Value of Ionis' Pipeline

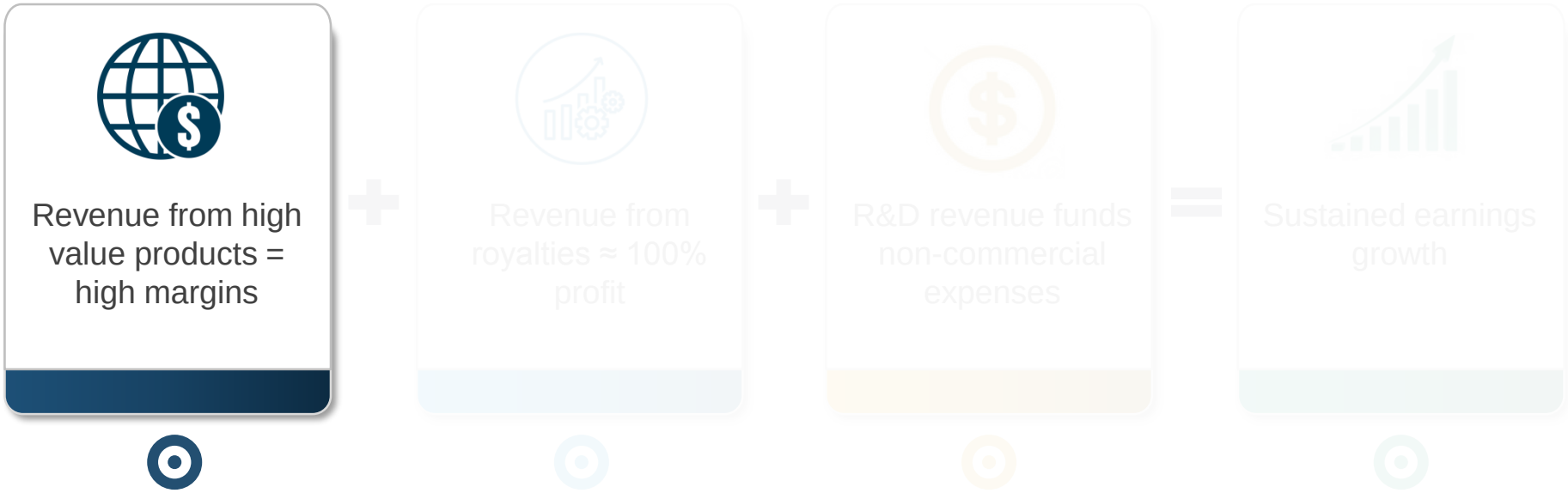
Leveraging partner resources and expertise for drugs with complex development paths and/or large indications

Commercializing drugs through highly focused subsidiaries



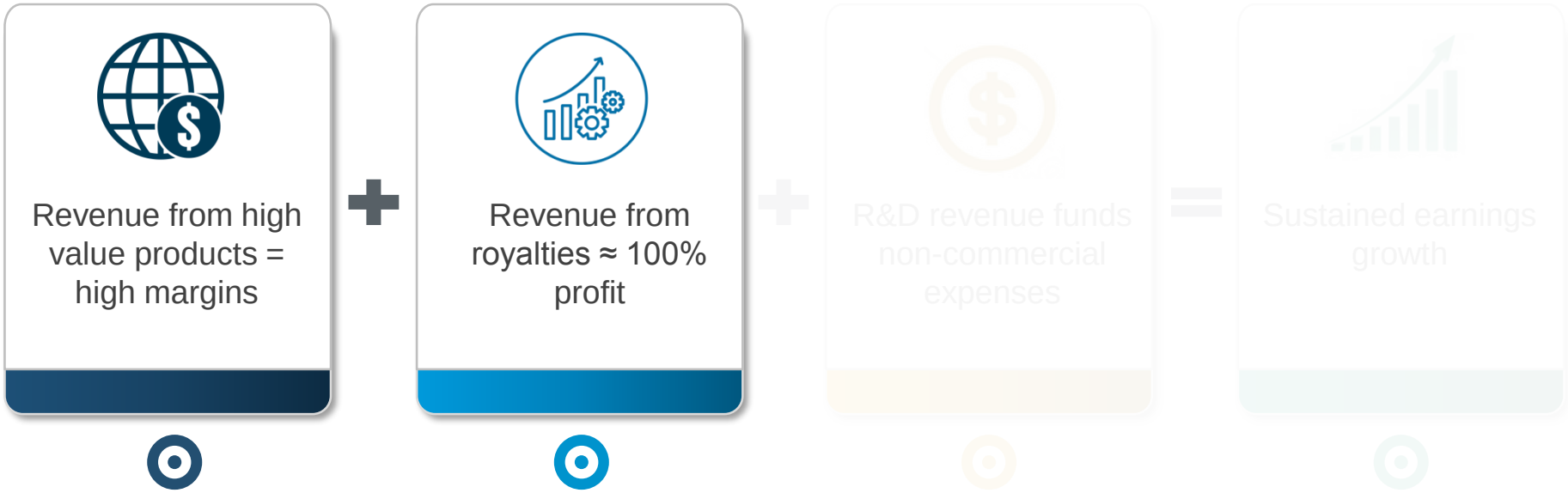
Retaining more commercial value for all our drugs in development

Commercial Revenue Has Potential to Drive Sustainable Earnings Growth



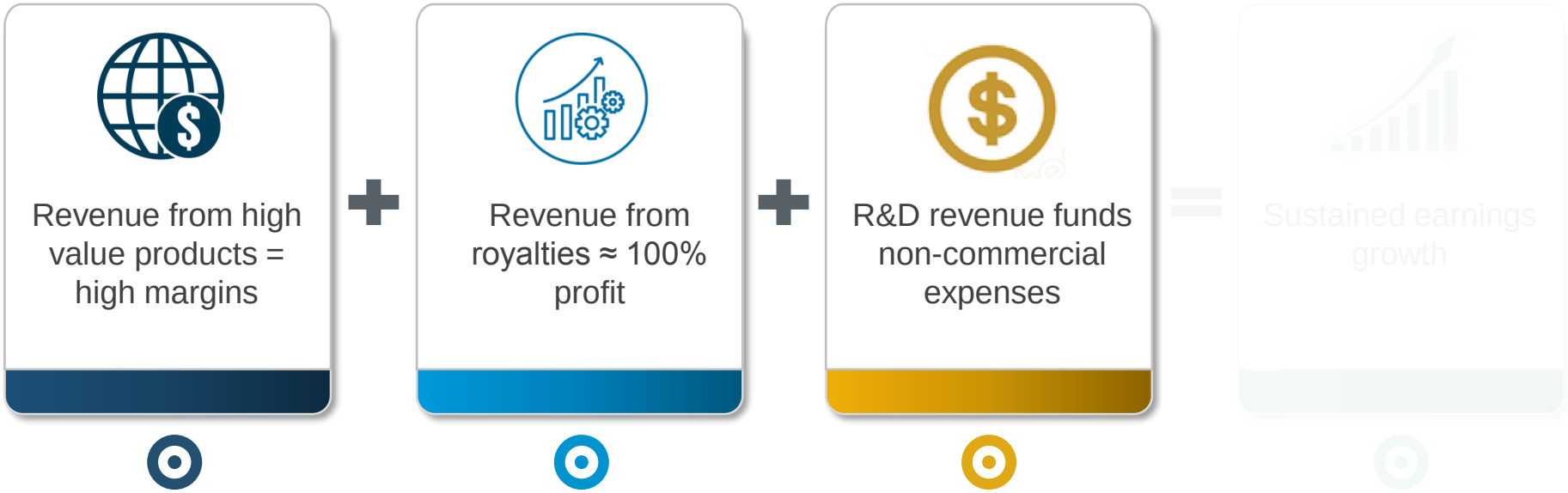
Growing commercial revenue building off a solid base of R&D revenue

Commercial Revenue Has Potential to Drive Sustainable Earnings Growth



Growing commercial revenue building off a solid base of R&D revenue

Commercial Revenue Has Potential to Drive Sustainable Earnings Growth

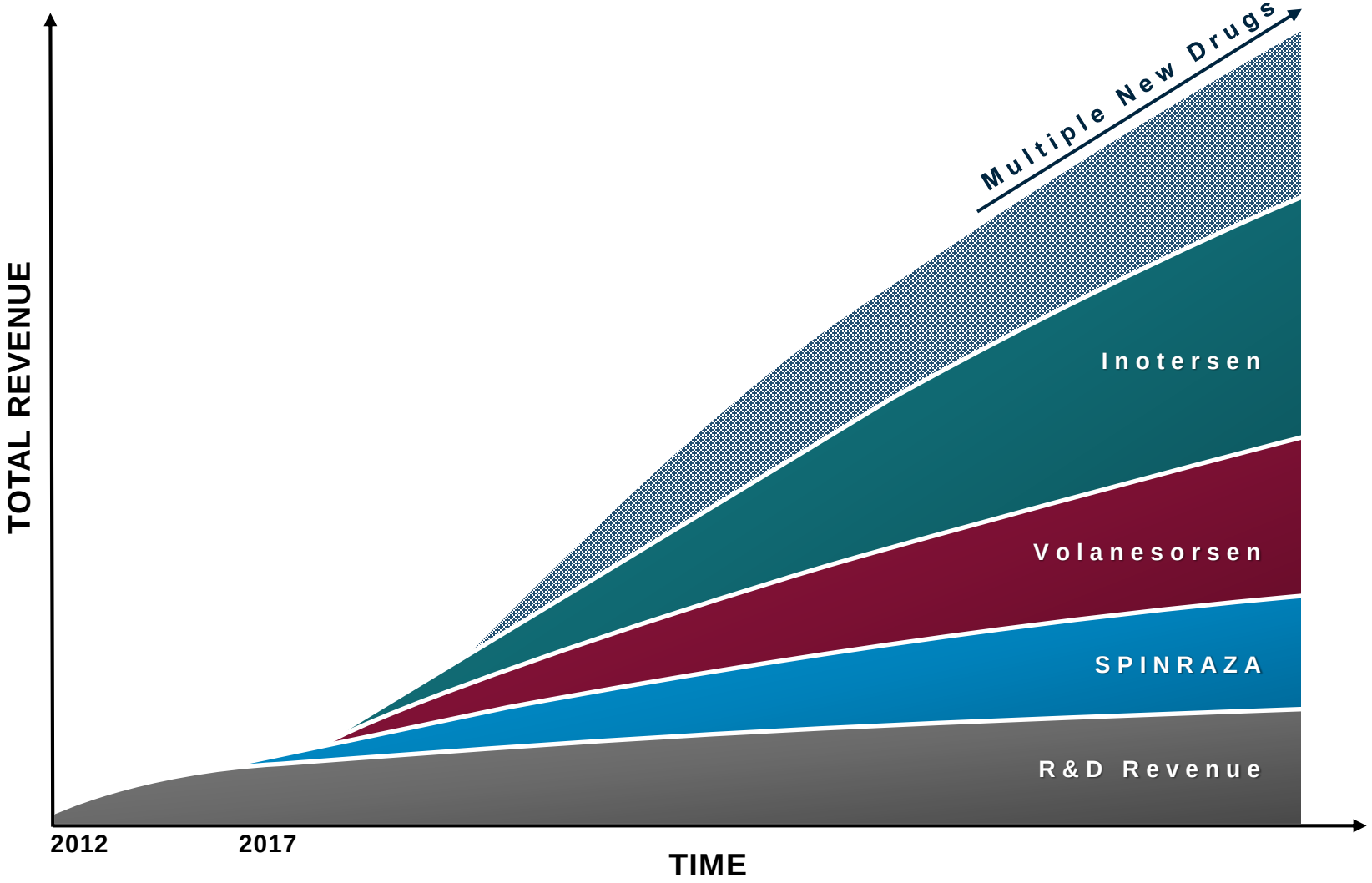


Growing commercial revenue building off a solid base of R&D revenue

Commercial Revenue Has Potential to Drive Sustainable Earnings Growth

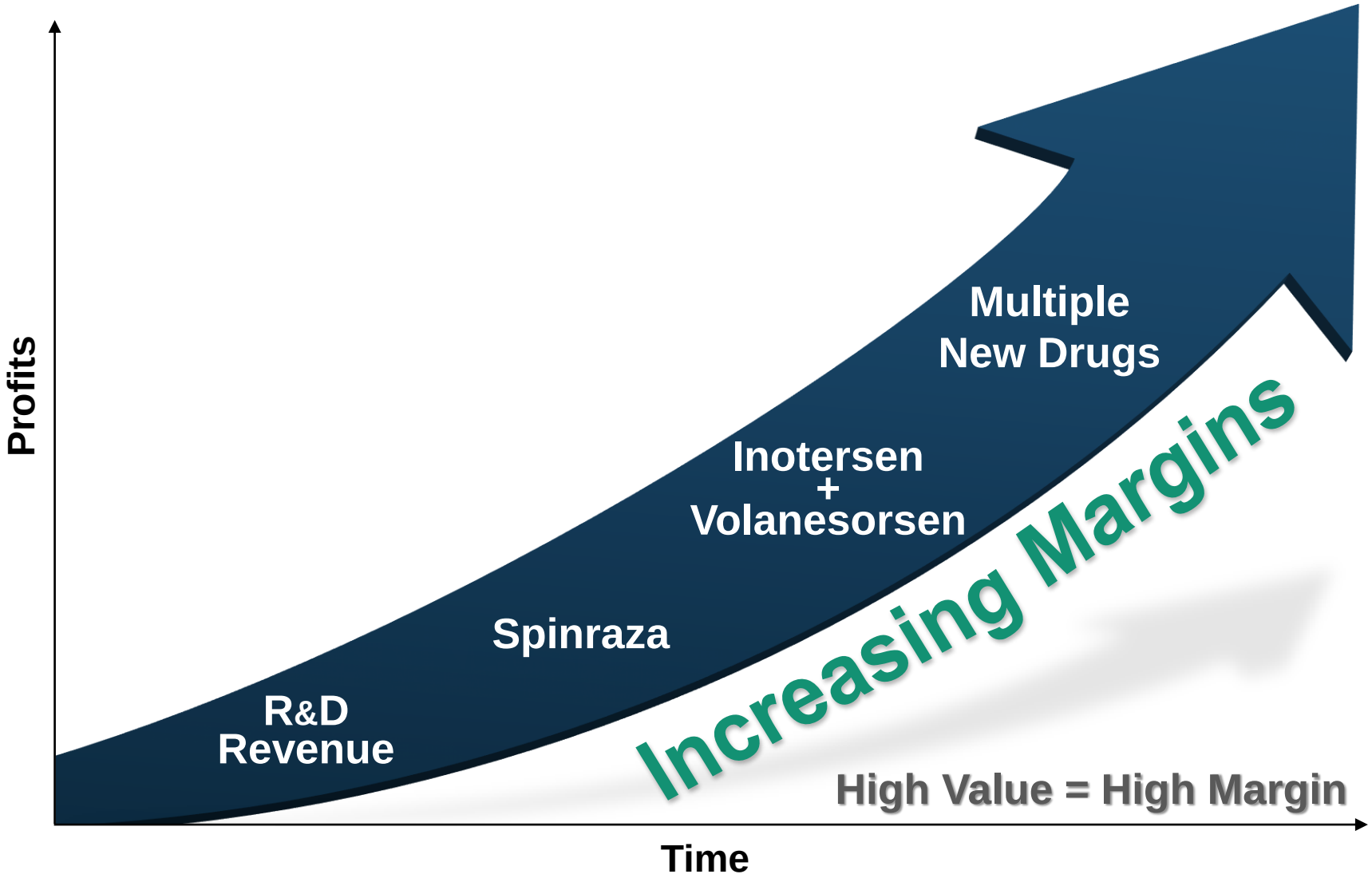
Growing commercial revenue building off a solid base of R&D revenue

Potential for Sustained Revenue Growth



Manageable expense structure

Increasing Commercial Participation Has Potential to Support Increasing Margins and Earnings Growth



Ionis: Multiple Medicines with Potential for Significant Commercial Value

SPINRAZA

A life-changing medicine commercialized for the treatment of spinal muscular atrophy

Volanesorsen

A potentially transformative medicine for patients with FCS and FPL with planned global launch in mid-2018

Inotersen

A potentially transformative medicine for patients with hATTR with planned global launch in mid-2018

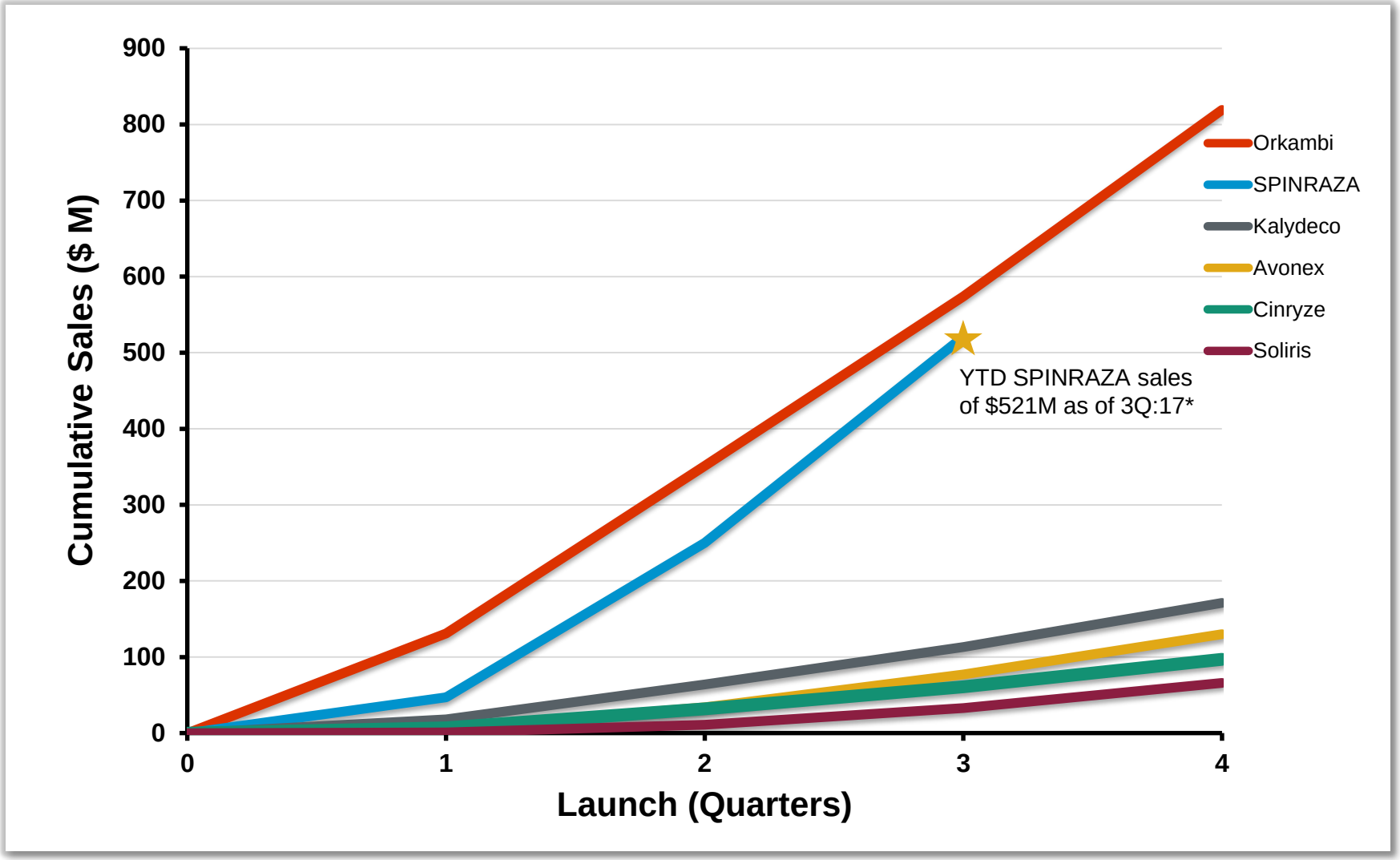
SPINRAZA: A Landmark Advance in the Treatment of Spinal Muscular Atrophy

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Approved in global markets for the treatment of spinal muscular atrophy (SMA)

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

SPINRAZA is Positioned to be One of the Top Orphan Drug Launches in History



**As reported by Biogen*
Note: Sales data obtained from Biomedtracker or Company SEC filings

SPINRAZA Continues to Demonstrate Benefit Across a Broad Range of Patients with SMA[1]

- All infants in study were alive and none required permanent ventilation
- Most infants achieved motor milestones at the age expected for healthy infants

- Increased event-free survival vs. placebo
- Continued improvements in strength and function

- Stability or continued improvement in strength and function
- Some children gained or regained the ability to walk[2]

1. *Results from Phase 2 open-label studies in infantile-onset and later-onset SMA, Phase 3 ENDEAR study, Phase 3 CHERISH study, Phase 2 NURTURE study (NURTURE data cut-off date: October 31, 2016)*
2. *Results from CS2-CS12 analysis*

Discovering New, Enhanced Treatment Options for Patients Suffering with SMA

Ionis and Biogen are committed to bringing new, innovative therapies to market for the SMA community

Ionis and Biogen plan to work together to identify antisense oligonucleotides with enhanced properties

Ionis received a $25M upfront payment and is eligible to earn development and regulatory milestone payments

Ionis is eligible to earn tiered royalties on sales up to the mid twenty percent range

Creating a New Future for Patients with SMA and Their Families

SPINRAZA

- A fundamental advance in the treatment of patients with SMA
- A product of Ionis' antisense technology
- The epitome of precision medicine
- Potential for new therapies to enhance treatment options for patients with SMA

Ionis: Multiple Medicines with Potential for Significant Commercial Value

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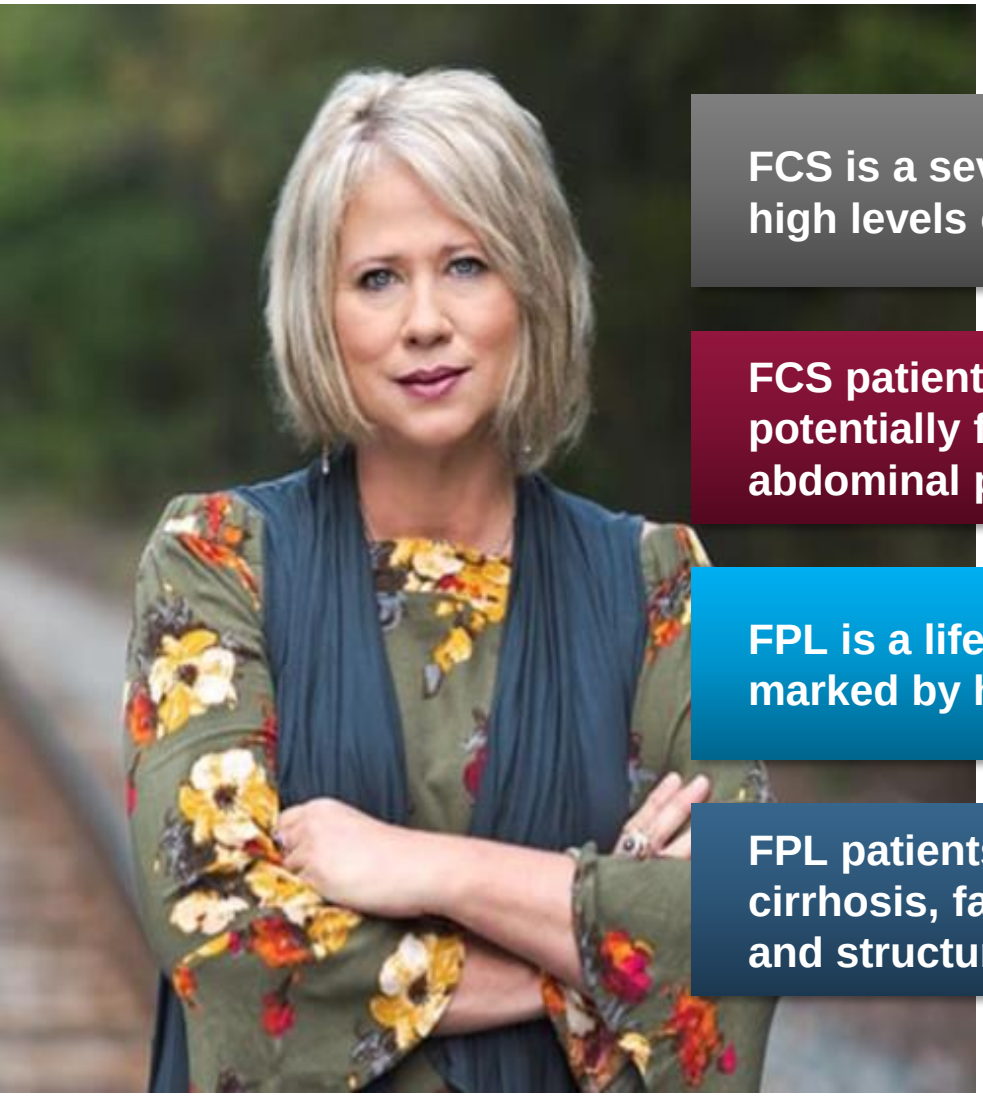
Inotersen

A potentially transformative medicine for patients with hATTR with planned global launch in mid-2018

FCS and FPL: Two Severe, Rare, Potentially Fatal Diseases with No Approved Therapies



FCS is a severe disease characterized by extremely high levels of triglycerides

FCS patients suffer from symptoms such as potentially fatal, acute pancreatitis and chronic abdominal pain

FPL is a life-threatening, genetic, fat storage disorder marked by high triglyceride levels

FPL patients suffer from hepatic steatosis and cirrhosis, fat deposits in organs, resistant diabetes, and structural heart disease

AKCEA THERAPEUTICS

Potential to Transform the Lives of Patients with FCS

Robust triglyceride lowering	Lower incidence of pancreatitis	Reduced abdominal pain
Sustained effect observed	Positive results across multiple studies	Monitorable and manageable side effect profile

volanesorsen

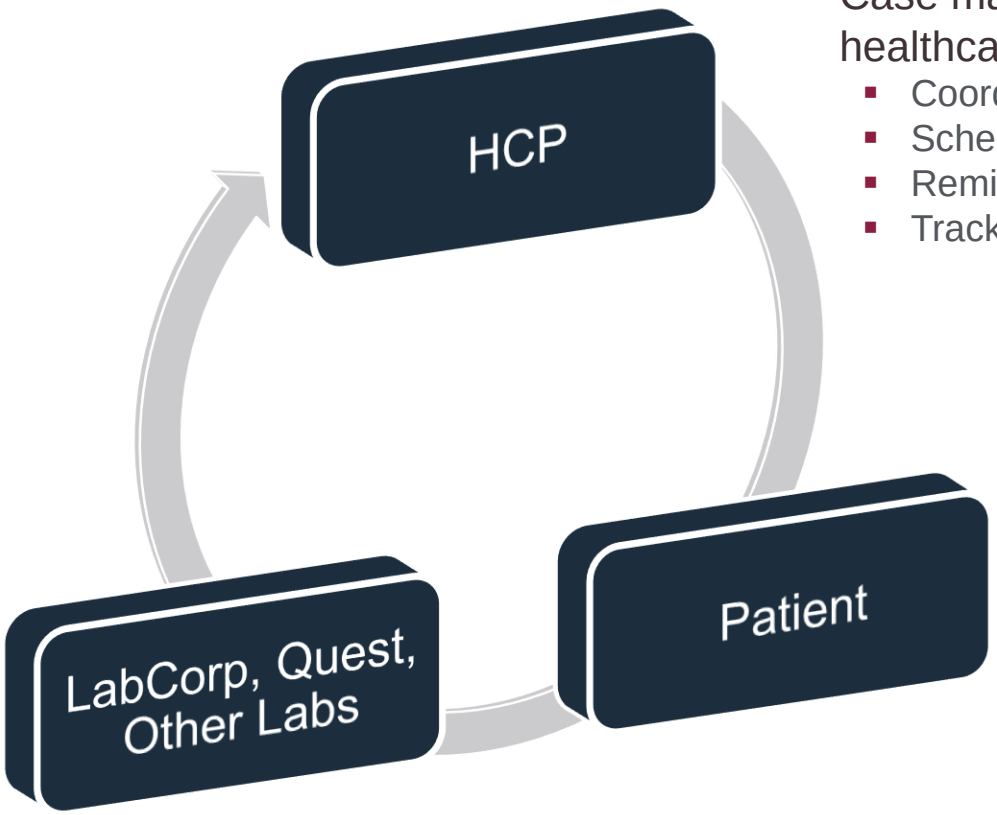
AKCEA THERAPEUTICS

Volanesorsen: On Track to Launch Globally in Mid-2018

- Engaging with physicians to better understand the burden of FCS and the need for a therapy
- Simplifying the diagnosis for patients with FCS
- Enrolling expanded access program
- Building a global commercial team and infrastructure
- Building a high-touch patient support program for successful start and retention
- Creating a broader, long-term, high triglyceride franchise with volanesorsen and LICA drugs

AKCEA THERAPEUTICS

Process for Monitoring and Managing Platelets Designed for Patient Convenience



Case managers provide support to patients and healthcare providers (HCPs) through:

- Coordinating lab orders with volanesorsen start forms
- Scheduling appointments
- Reminding the patient
- Tracking results

1 **Standing Order for Blood Draw**

2 **Patient Receives Blood Draw**

3 **Results Returned to HCP**

Wherever is most convenient:

- HCP office or local clinic
- Visiting phlebotomist
- LabCorp/Quest
- At home, potentially using novel TAP™ device

AKCEA THERAPEUTICS

Volanesorsen: Next Steps

Continue to enroll EAP

Potential approval and launch for the treatment of FCS in the U.S., EU and Canada in mid-2018

Commercialize worldwide, expand the triglyceride franchise with AKCEA-APOCIII-L_{Rx}

Complete the BROADEN study in FPL (early 2019)

Ionis: Multiple Medicines with Potential for Significant Commercial Value

SPINRAZA

A life-changing medicine commercialized for the treatment of spinal muscular atrophy

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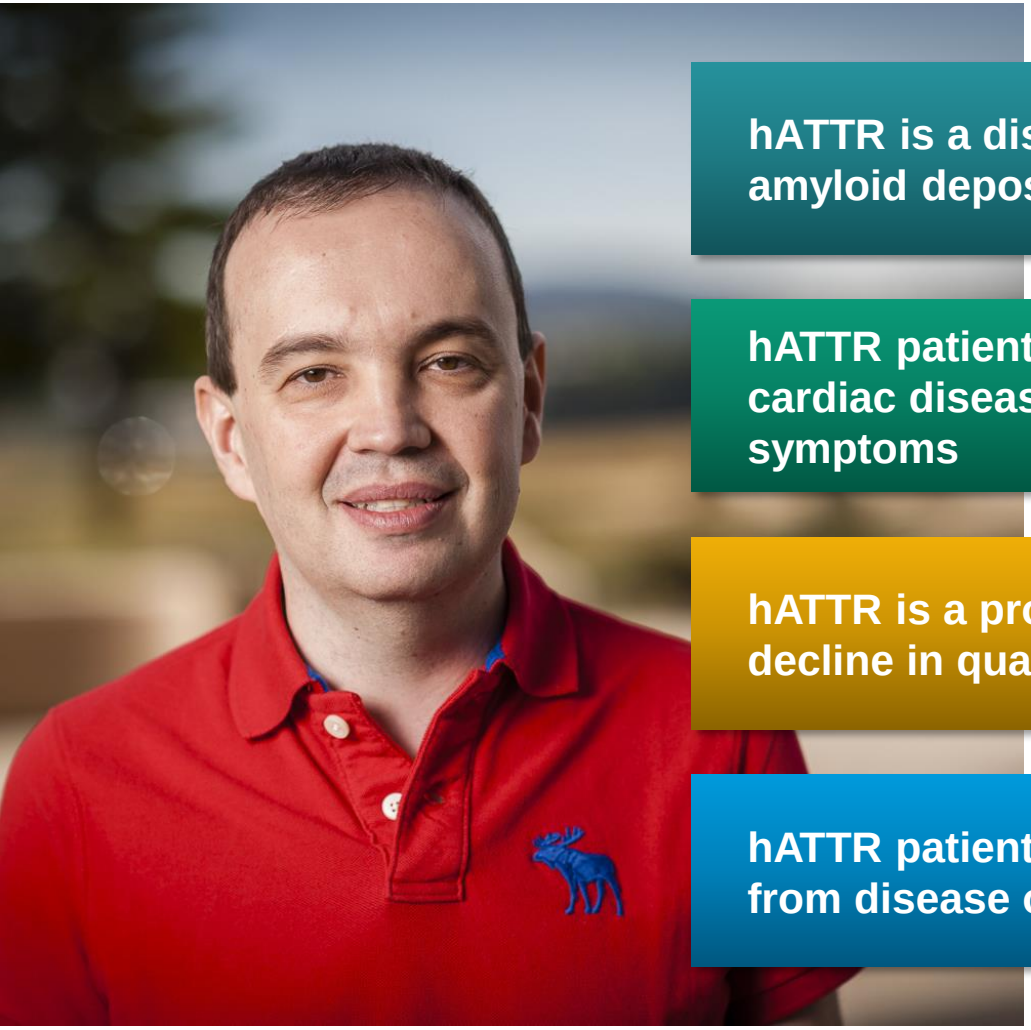
A potentially transformative medicine for patients with FCS and FPL with planned global launch in mid-2018

Inotersen

A potentially transformative medicine for patients with hATTR with planned global launch in mid-2018

hATTR: A Devastating, Progressive, and Fatal Disease With High Unmet Medical Need



hATTR is a disease marked by the formation of TTR amyloid deposits leading to multi-organ failure

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

hATTR is a progressive disease resulting in a rapid decline in quality of life

hATTR patients have a 3 – 15 year life expectancy from disease onset

Potential to Reduce the Burden of Disease

Early benefit in quality of life & disease measures	**Sustained benefit in quality of life & disease measures**	**Improvement in measures of quality of life**
Once weekly, subcutaneous, self administration	**Potential for increased independence**	**Monitorable and manageable side effect profile**

inotersen

Potential to Transform the Lives of Patients with hATTR

Inotersen: On Track to Launch Globally in Mid-2018

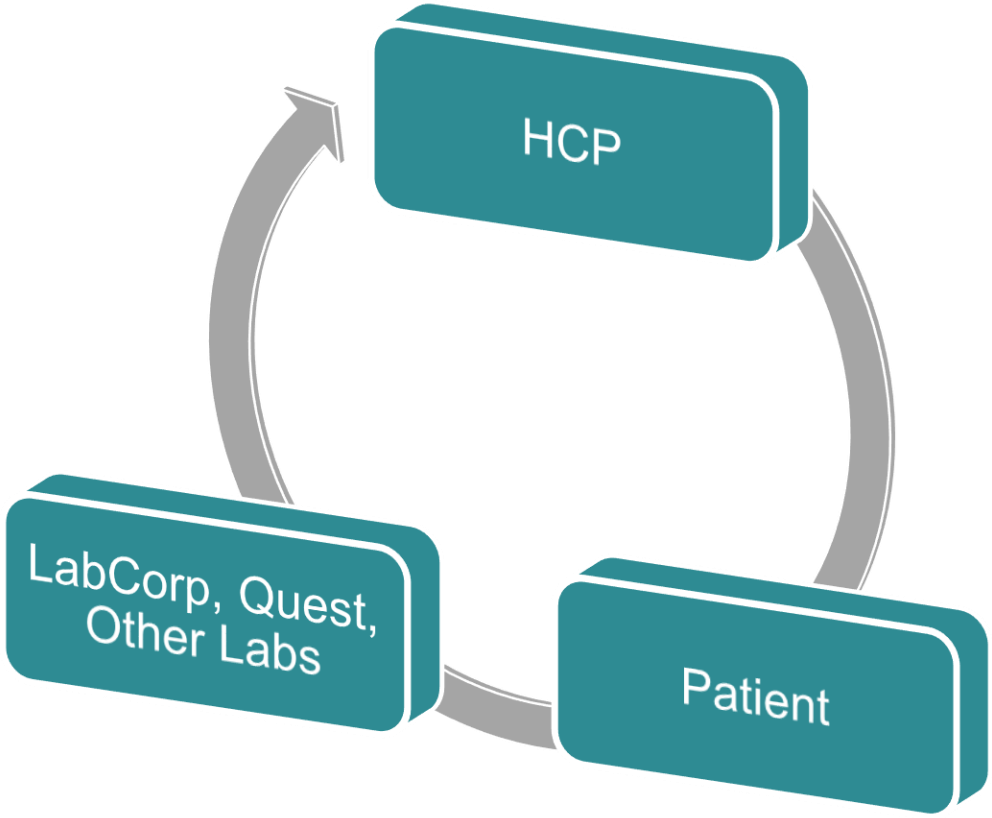
- Engaging With Physicians and Patients to Better Understand Need and Preference
- Building Disease Awareness Programs
- Building High-touch Patient Support Programs
- Advancing Expanded Access Program
- Creating a Broad Long-term ATTR Franchise with Enhanced LICA Follow on

Process for Monitoring and Managing Platelets Designed for Patient Convenience

1 **Standing Order for Blood Draw**

2 **Patient Receives Blood Draw**

3 **Results Returned to HCP**



Wherever is most convenient:

- HCP office or local clinic
- Visiting phlebotomist
- LabCorp/Quest
- At home, potentially using novel TAP™ device

Case managers provide support to patients and healthcare providers (HCPs) through:

- Coordinating lab orders with inotersen start forms
- Scheduling appointments
- Reminding the patient
- Tracking results

Inotersen: Next Steps

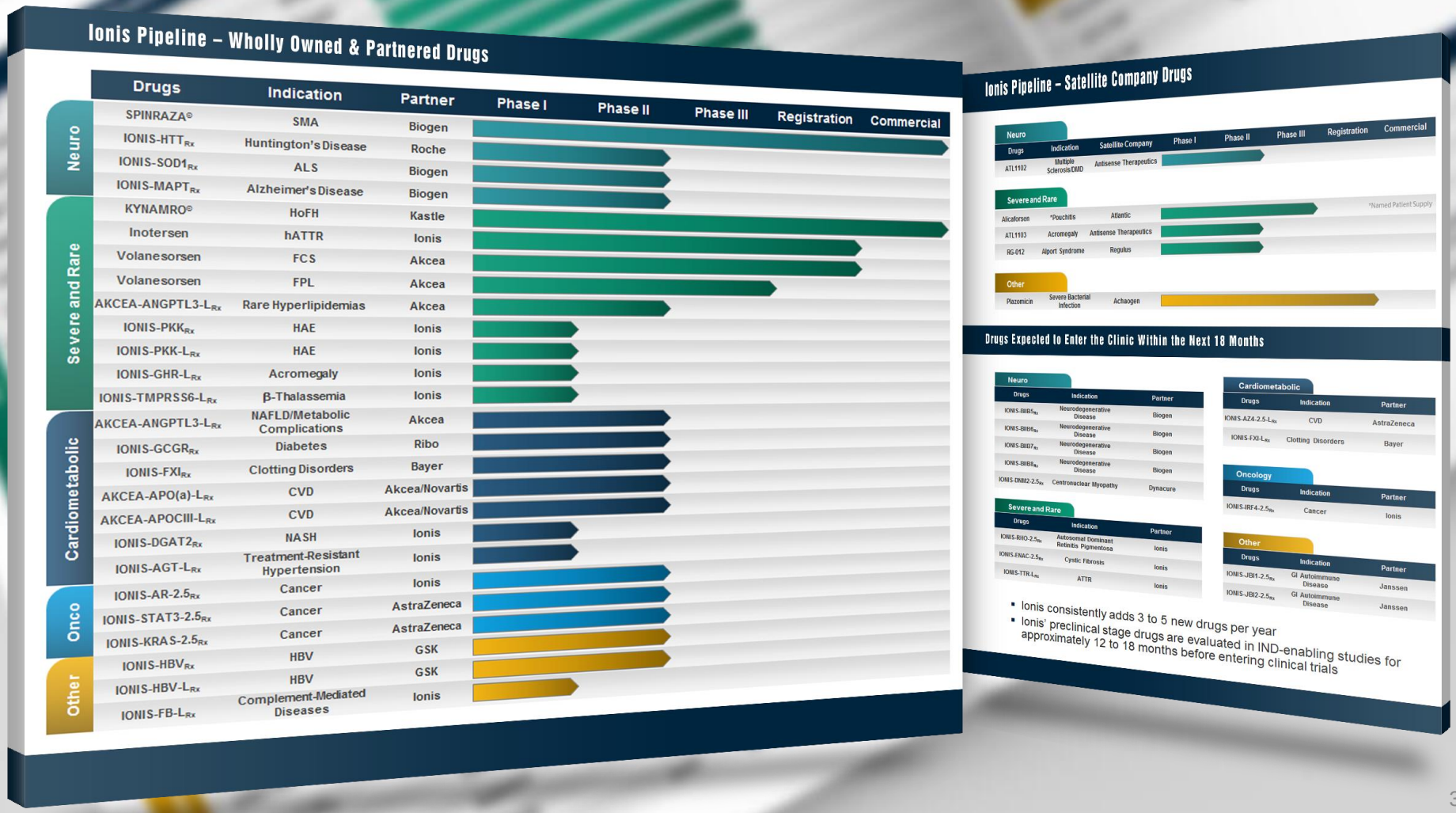
Maximize commercial success of inotersen through potential partnership and co-commercialization

Advance expanded access program

Potential approval and launch for the treatment of patients with hATTR in the U.S. and EU in mid-2018

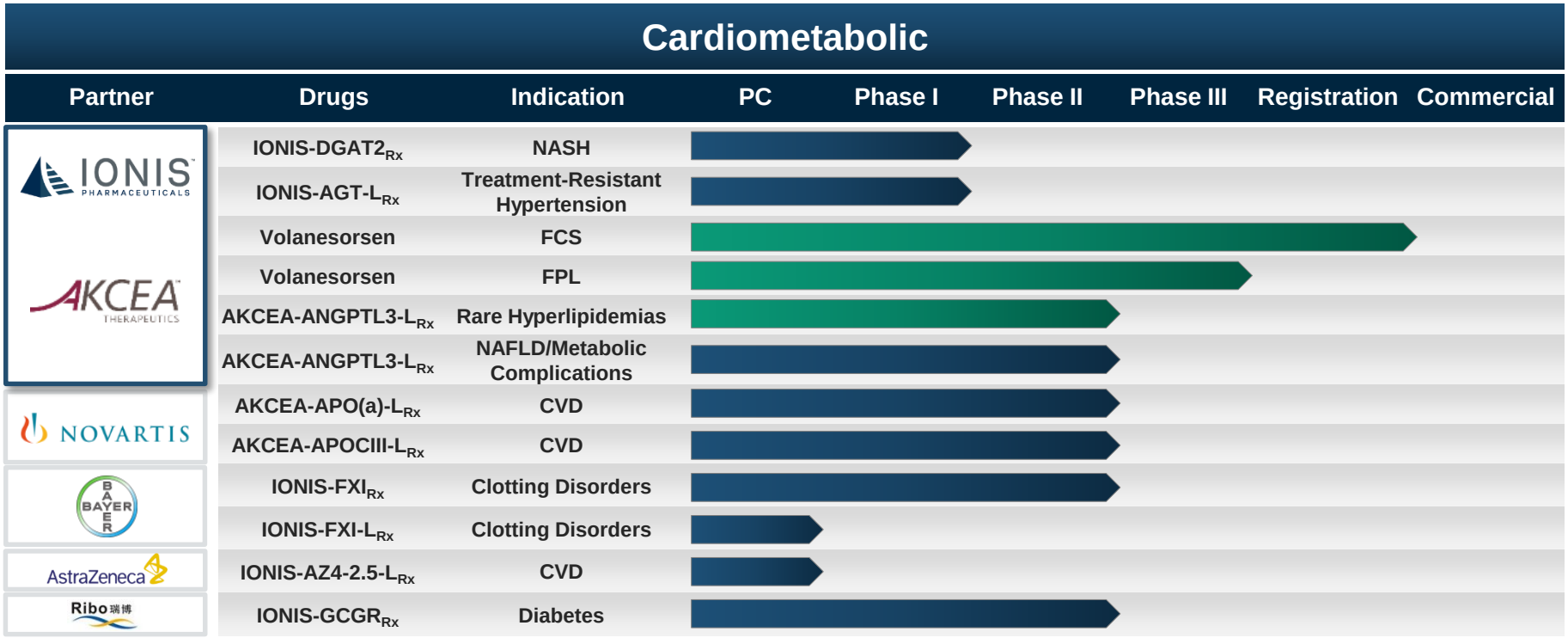
Initiate Phase 1 study with IONIS-TTR-L_{Rx} in 2H:2018 with plan to expand franchise

Our Pipeline of 42 Drugs is Mature, Broad, and Diverse with the Potential to Transform the Lives of Patients



Ionis Wholly Owned Pipeline

Cardiometabolic Pipeline: Addressing Unique Targets for Cardiometabolic Disease



Cardiometabolic Pipeline: Addressing Unique Targets for Cardiometabolic Disease

Key programs with near-term events

Wholly Owned

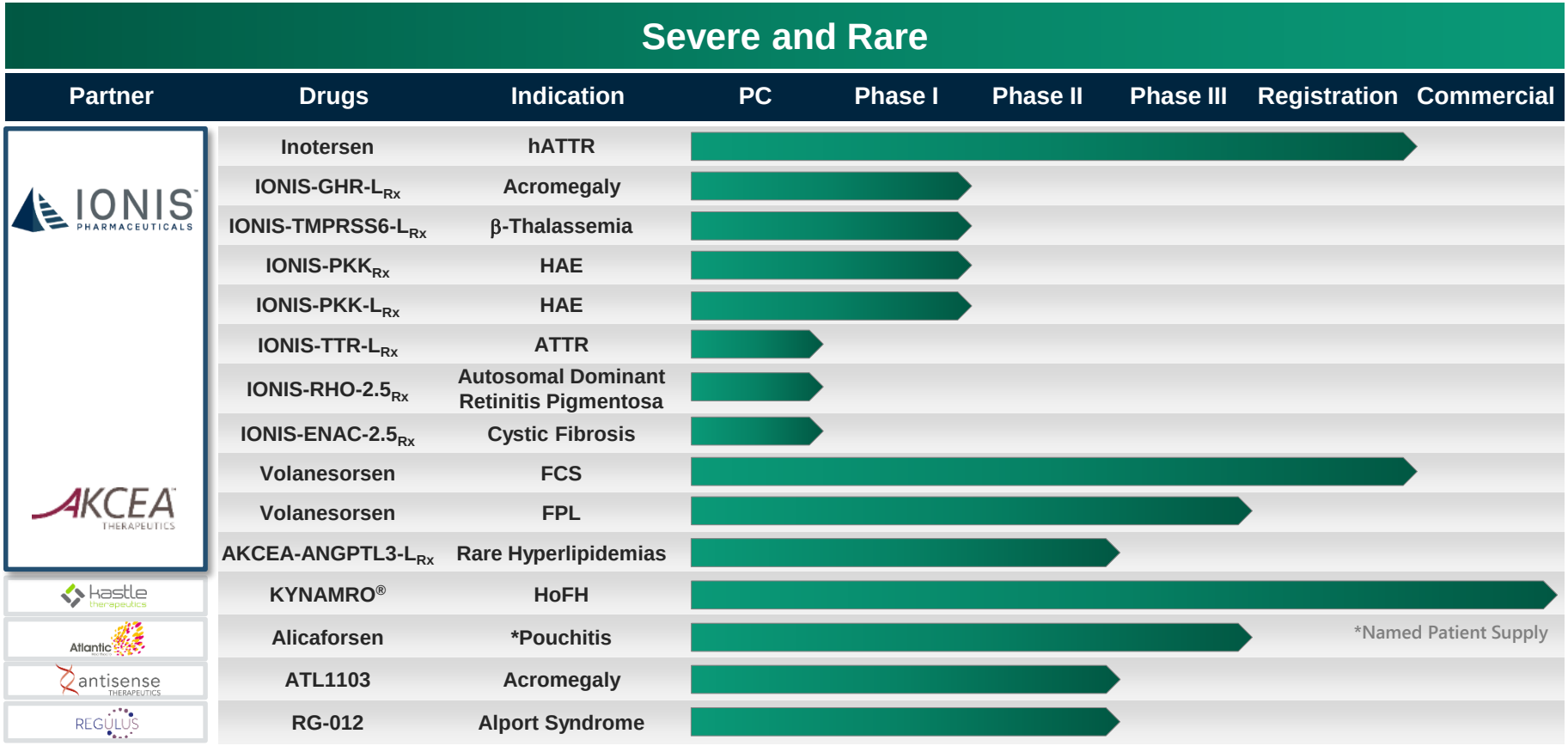
Drug	Indication	Event
Volanesorsen	FCS	▪ Launch in U.S., EU and Canada
AKCEA-APO(a)-L_{Rx}	High Lp(a) with CV Risk	▪ Report Phase 2 data
AKCEA-ANGPTL3-L_{Rx}	NAFLD/Metabolic complications	▪ Report Phase 2 data

Partnered

Drug	Indication	Event
IONIS-FXI-L_{Rx}	Clotting Disorders	▪ Initiate Phase 1 study

Severe and Rare Pipeline: Addressing Diseases with High Unmet Medical Need

Severe and Rare



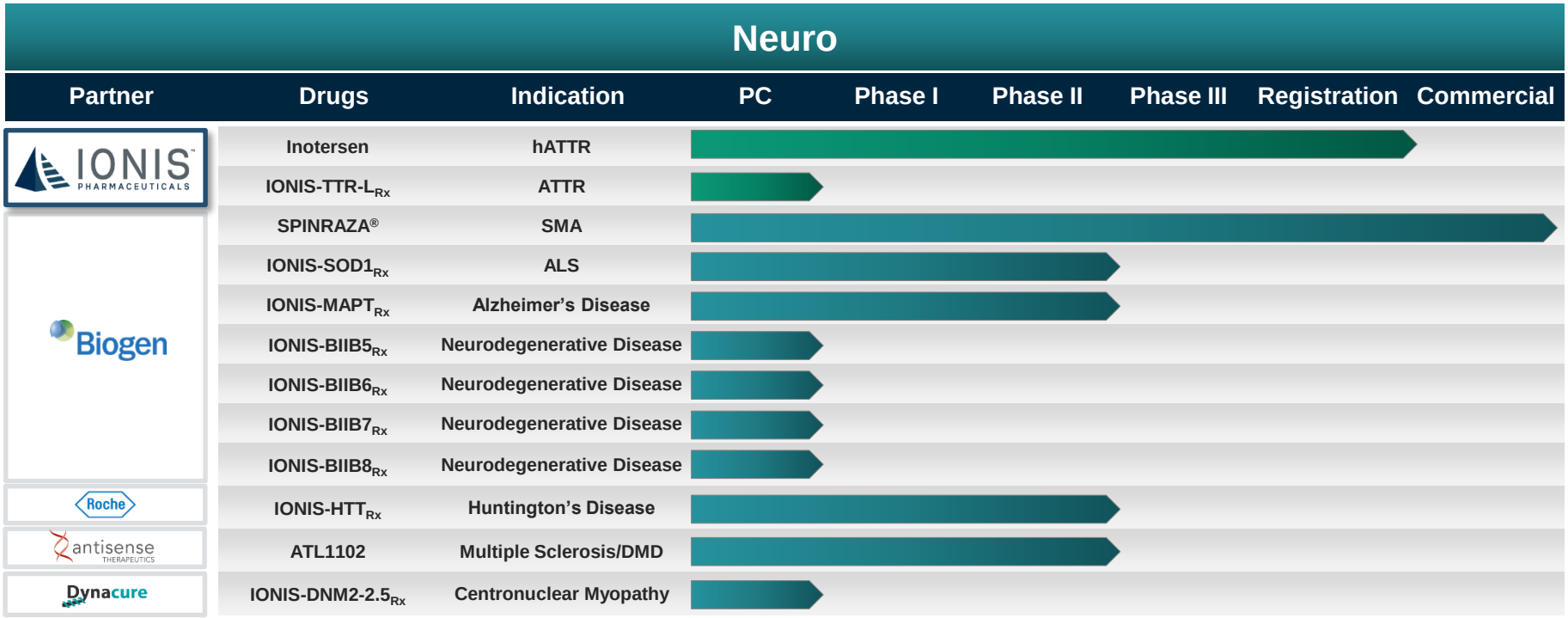
Severe and Rare Pipeline: Addressing Diseases with High Unmet Medical Need

Key programs with near-term events

Wholly Owned

Drug	Indication	Event
Volanesorsen	FCS	▪ Launch in U.S., EU and Canada
Inotersen	hATTR	▪ Launch in U.S. and EU
AKCEA-ANGPTL3-L_{Rx}	Rare Hyperlipidemias	▪ Report Phase 2 data
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia	▪ Report Phase 1 data
IONIS-GHR-L_{Rx}	Acromegaly	▪ Initiate Phase 2 study
IONIS-ENAC-2.5_{Rx}	Cystic Fibrosis	▪ Initiate Phase 1 study

Neuro Pipeline: Addressing Large and Rare Opportunities with Partnered and Wholly Owned Drugs



Ionis Wholly Owned Drug Candidates Expected 2018 - 2019

IONIS PHARMACEUTICALS

Indication
Lafora Disease
Alexander Disease
Charcot-Marie-Tooth

Neuro Pipeline: Addressing Large and Rare Opportunities with Partnered and Wholly Owned Drugs

Key programs with near-term events

Wholly Owned

Drug	Indication	Event
Inotersen	hATTR	▪ Launch in U.S. and EU
IONIS	Charcot-Marie-Tooth	▪ Enter development
IONIS	Alexander Disease	▪ Enter development
IONIS	Lafora Disease	▪ Enter development (2019)

Partnered

Drug	Indication	Event
IONIS-HTT_{Rx}	Huntington's Disease	▪ Report Phase 1/2 data
IONIS-$SOD1_{Rx}$	ALS	▪ Report Phase 1/2 data
Biogen to advance 2 additional drugs into the clinic		

Oncology / Other Pipeline: Addressing Novel Targets for Unmet Needs in Cancer and Other Diseases

Oncology / Other

Partner	Drugs	Indication	PC	Phase I	Phase II	Phase III	Registration	Commercial
IONIS PHARMACEUTICALS	IONIS-AR-2.5$_{Rx}$	Cancer						
	IONIS-FB-L$_{Rx}$	Complement-Mediated Diseases						
	IONIS-IRF4-2.5$_{Rx}$	Cancer						
ACHAOGEN	Plazomicin	Severe Bacterial Infection						
AstraZeneca	IONIS-STAT3-2.5$_{Rx}$	Cancer						
	IONIS-KRAS-2.5$_{Rx}$	Cancer						
gsk	IONIS-HBV$_{Rx}$	HBV						
	IONIS-HBV-L$_{Rx}$	HBV						
janssen	IONIS-JBI1-2.5$_{Rx}$	GI Autoimmune Disease						
	IONIS-JBI2-2.5$_{Rx}$	GI Autoimmune Disease						

Oncology / Other Pipeline: Addressing Novel Targets for Unmet Needs in Cancer and Other Diseases

Key programs with near-term events

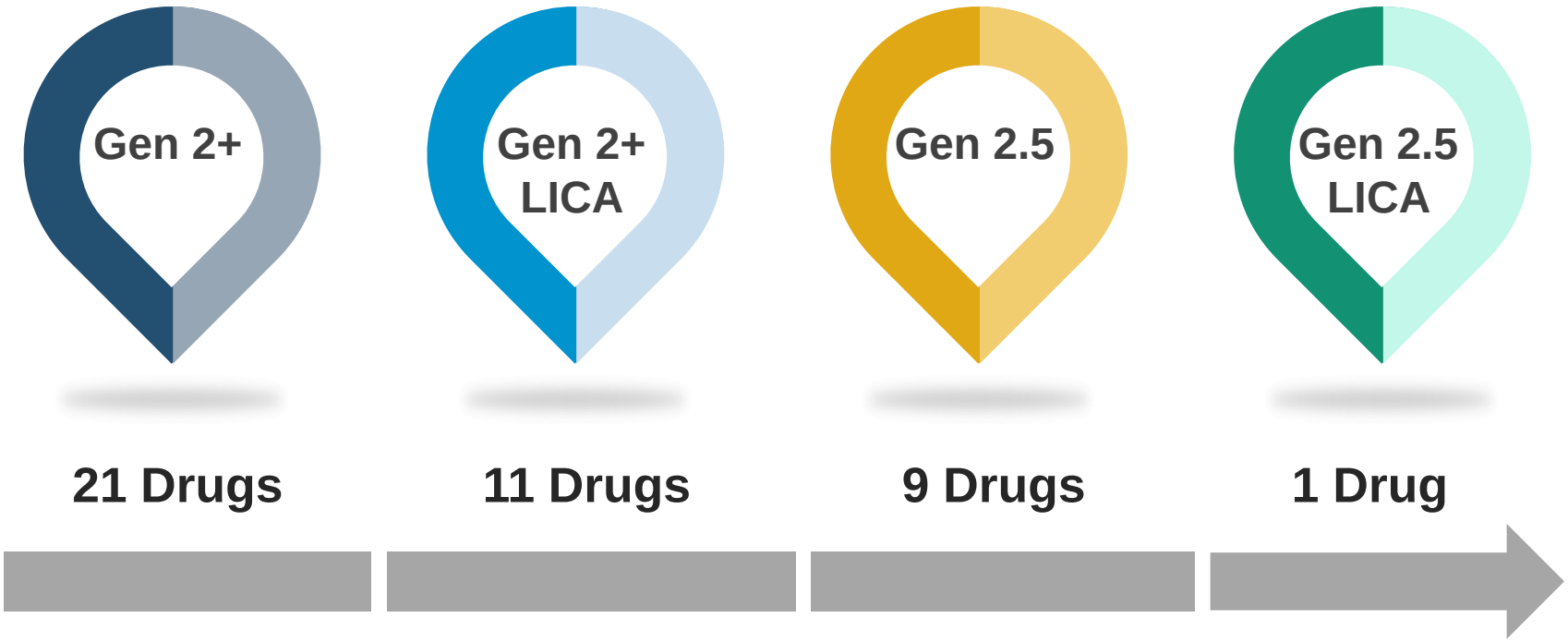
Wholly Owned

Drug	Indication	Event
IONIS-FB-L_{Rx}	Complement-Mediated Diseases	▪ Initiate Phase 2 study

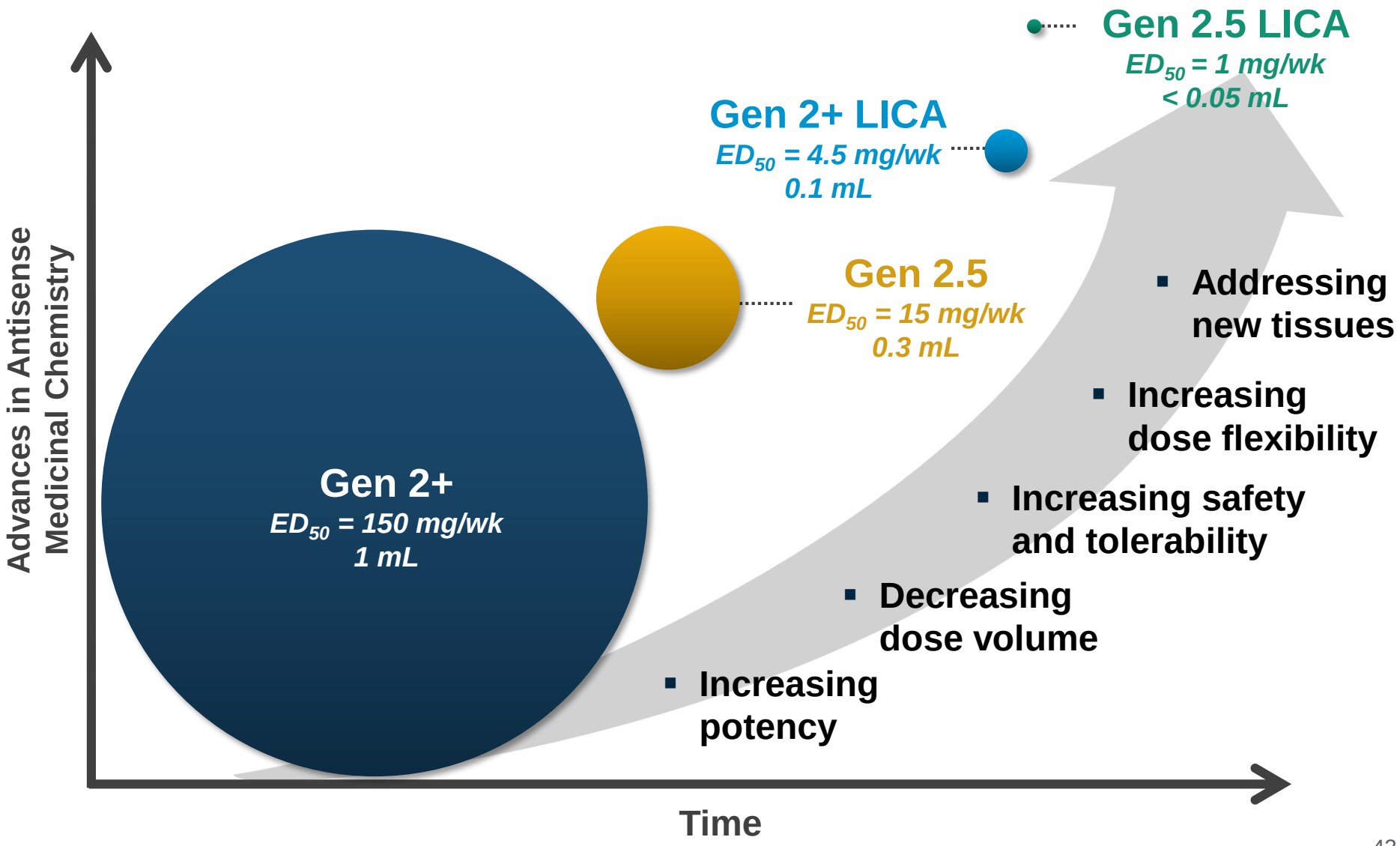
Partnered

Drug	Indication	Event
IONIS-STAT3-2.5_{Rx}	Cancer	▪ Initiate Phase 2/3 study
Plazomicin	Severe Bacterial Infection	▪ Launch in the U.S.

Advances in our Technology Should Enable Us to Create Future Transformative Medicines



Advances in Our Technology Substantially Improve the Utility of Antisense Drugs

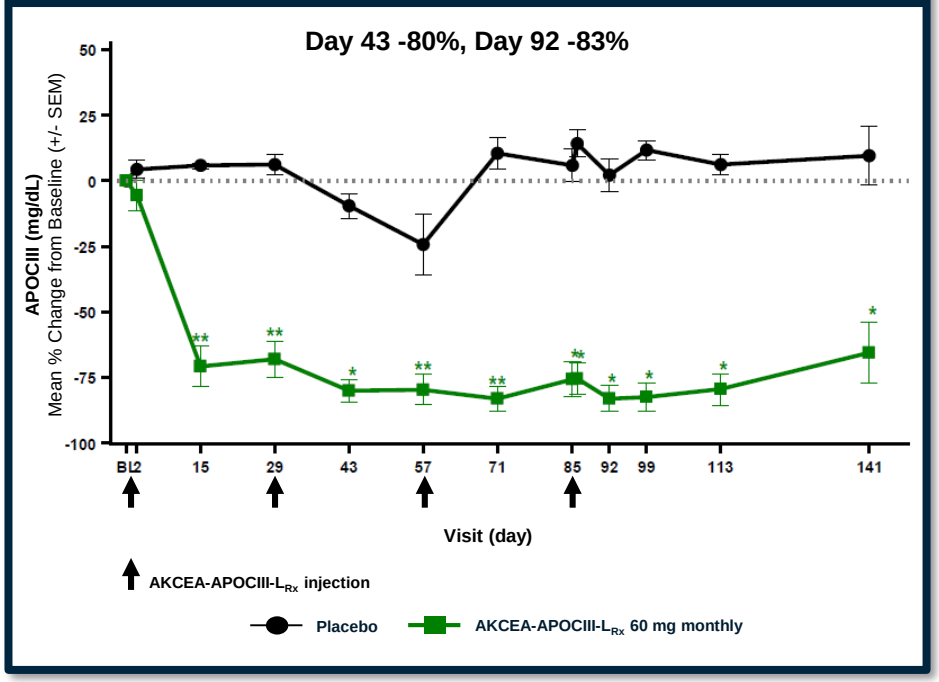


ED_{50}'s and dose volumes are representative of liver targets

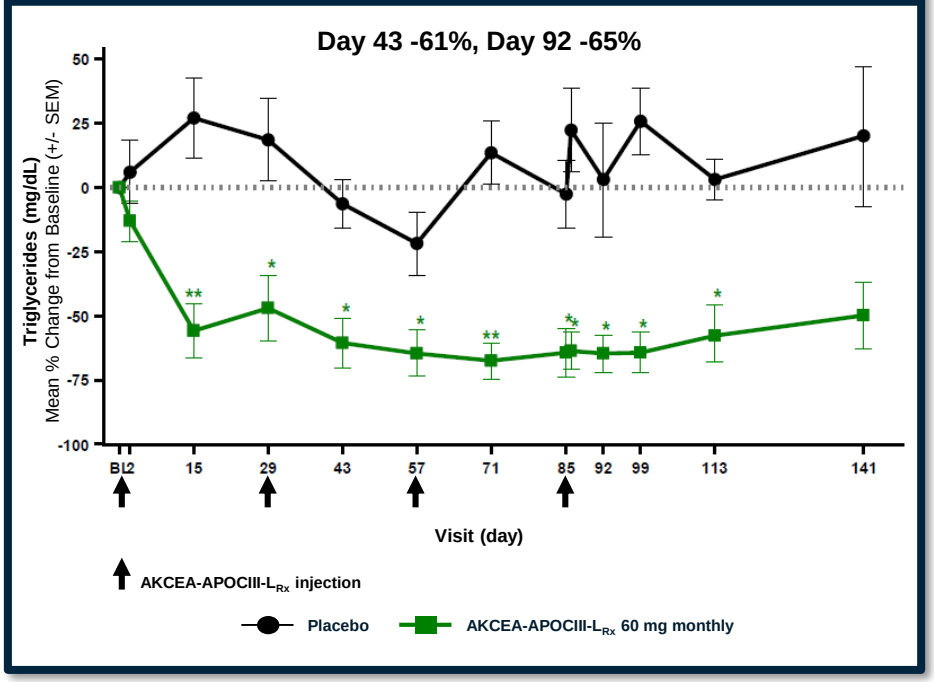
Monthly or Less Frequent Dosing of LICA Drugs Results in Sustained Target Reduction

Clinical data on 5 LICA drugs demonstrate consistent performance

Mean % Reduction in ApoCIII Following Four Monthly Doses of AKCEA-APOCIII-L_{Rx}



Mean % Reduction in TGs Following Four Monthly Doses of AKCEA-APOCIII-L_{Rx}



Note: Monthly multiple-dose cohorts, N=10; Exact Wilcoxon Rank Sum Test: *p ≤ 0.05 vs. placebo, **p ≤ 0.01 vs. placebo

Advances in Ionis Technology are Translating into Tangible Value in the Pipeline Today

12 LICA Drugs in Pipeline

Drugs	Indication	Current Phase	Clinical POC Data
AKCEA-APO(a)-L_{Rx}	CVD	Ph. 2	✓
AKCEA-ANGPTL3-L_{Rx}	Mixed Dyslipidemias	Ph. 2	✓
AKCEA-APOCIII-L_{Rx}	CVD	Ph. 2	✓
IONIS-HBV-L_{Rx}	HBV	Ph. 2	✓
IONIS-FB-L_{Rx}	Complement-Mediated Diseases	Ph. 1	✓
IONIS-AGT-L_{Rx}	Treatment-Resistant Hypertension	Ph. 1	2018
IONIS-GHR-L_{Rx}	Acromegaly	Ph. 1	2018
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia	Ph. 1	2018
IONIS-PKK-L_{Rx}	HAE	Ph. 1	2018
IONIS-TTR-L_{Rx}	ATTR	PC	2019
IONIS-FXI-L_{Rx}	Clotting Disorders	PC	2019
IONIS-AZ4-2.5-L_{Rx}	CVD	PC	2019

Severe & Rare Cardiometabolic Other

Key Upcoming Milestones in 2018

5 **Drugs Potentially On the Market**

6 **Phase 2 Readouts**

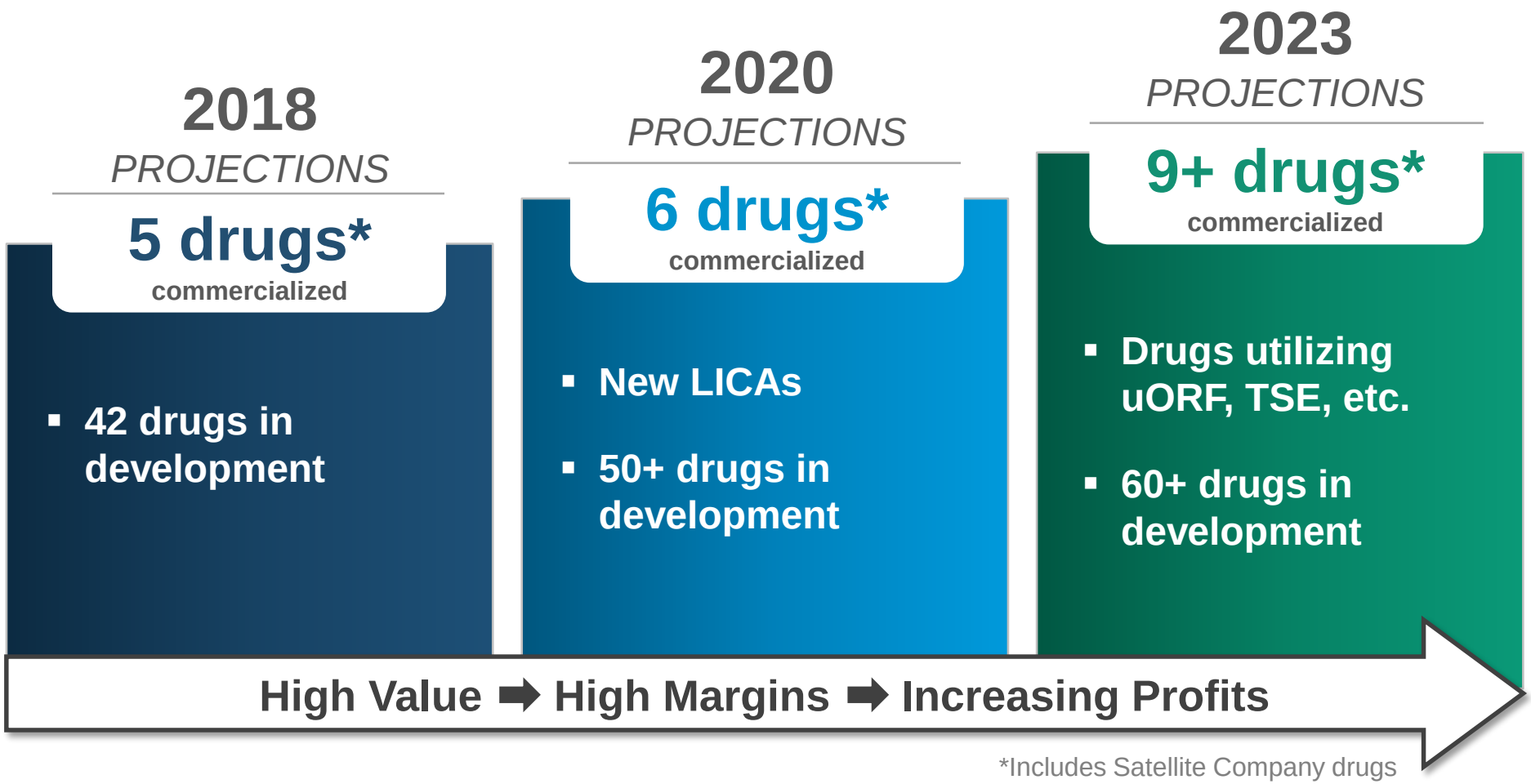
- AKCEA-APO(a)-L_{Rx}
- AKCEA-ANGPTL3-L_{Rx}
- IONIS-$DGAT2_{Rx}$
- IONIS-HTT_{Rx}
- IONIS-$SOD1_{Rx}$
- IONIS-PKK_{Rx}

5 **Phase 2 Initiations**

- IONIS-STAT3-2.5_{Rx}
- IONIS-GHR-L_{Rx}
- IONIS-FB-L_{Rx}
- IONIS-AR-2.5_{Rx}
- IONIS-KRAS-2.5_{Rx}

Multiple POC Initial Clinical Trial Readouts

Ionis' Future Focused on Continuing Growth Trajectory



*Includes Satellite Company drugs

Revolutionizing Medicine. Saving Lives.