IONIS®

A Genetic Medicines Company

J.P. Morgan Healthcare Conference

Brett P. Monia, Ph.D., Chief Executive Officer

January 11, 2023

Every Moment Matters...

in the Discovery, Development & Delivery of Life Transforming Genetic Medicines

Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, tofersen, Ionis' technologies, and Ionis' other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including 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, 2021, 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
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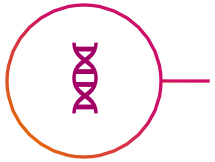
Advancing our Strategic Priorities

Deliver an abundance of genetic medicines to the market

Establish an integrated commercial organization



Expand and **diversify** the reach of our technology platform

Strengthen our financial foundation to support our strategic priorities

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2022 Achievements that Advanced Our Strategic Priorities (1 of 2)

Advanced Ionis Near-term Commercial Opportunities Towards the Market

- ✓ Delivered positive Phase 3 eplontersen NEURO-TTRansform data in ATTRv-PN
- ✓ Submitted eplontersen NDA for ATTRv-PN
- ✓ Strengthened Phase 3 eplontersen CARDIO-TTRansform study in ATTR-CM
- ✓ Completed enrollment in olezarsen Phase 3 BALANCE study in FCS, on track for data H2:2023
- ✓ Delivered positive longer-term donidalorsen Phase 2 OLE data in HAE

Advanced our Rich Late-stage Pipeline

- ✓ NDA and MAA for tofersen under review
- ✓ Delivered 9 positive late- and mid-stage data readouts
- ✓ Delivered positive bepirovirsen & IONIS-FB-L_{Rx} data, on track for Phase 3 starts in H1:23
- ✓ Completed enrollment in pelacarsen Phase 3 Lp(a) HORIZON study, on track for data in 2025

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2022 Achievements that Advanced Our Strategic Priorities (2 of 2)

Built our Commercial Organization

- ✓ Established commercialization strategy and near-term priorities
- ✓ Developed core capabilities to enable eplontersen, olezarsen and donidalorsen launches

Expanded and Diversified Our Technology

- ✓ Added gene editing capabilities through Metagenomi collaboration
- ✓ Advanced new programs using advanced medicinal chemistry approaches (e.g., muscle LICA & MsPA backbone) into preclinical development
- ✓ Initiated clinical development of SPINRAZA follow-on program in SMA

Strengthened Our Financial Foundation

- ✓ Executed royalty financing transaction, generating up to $1.1B to support investment in long term growth
- ✓ Executed sale leaseback transaction, valued at up to $400M

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Ionis' Near-term Commercial Opportunities with Aggregate Multibillion-dollar Potential[1,2]

UTILIZING ADVANCED LICA PLATFORM

Eplontersen

~500,000 patients
in 2 indications worldwide

Expected to **change the standard-of-care** for patients with TTR amyloidosis

First Potential Approval: **2023**

Estimated peak sales: **Multibillion**

Olezarsen

>3 million patients
in 2 indications in the US

Expected to be a **first-in-class** treatment for patients with severely elevated triglycerides

First Phase 3 Data: **2023**

Estimated peak sales: **>$1 Billion**

Donidalorsen

>20,000 patients
in the US and EU

Expected to be a **best-in-class** prophylactic treatment for patients with HAE[3]

Phase 3 Data: **2024**

Estimated peak sales: **>$500 Million**

1. Market data on file 2. Timing expectations and peak sales estimates are based on current assumptions and are subject to change. 3. Profile based on Phase 2 and OLE data

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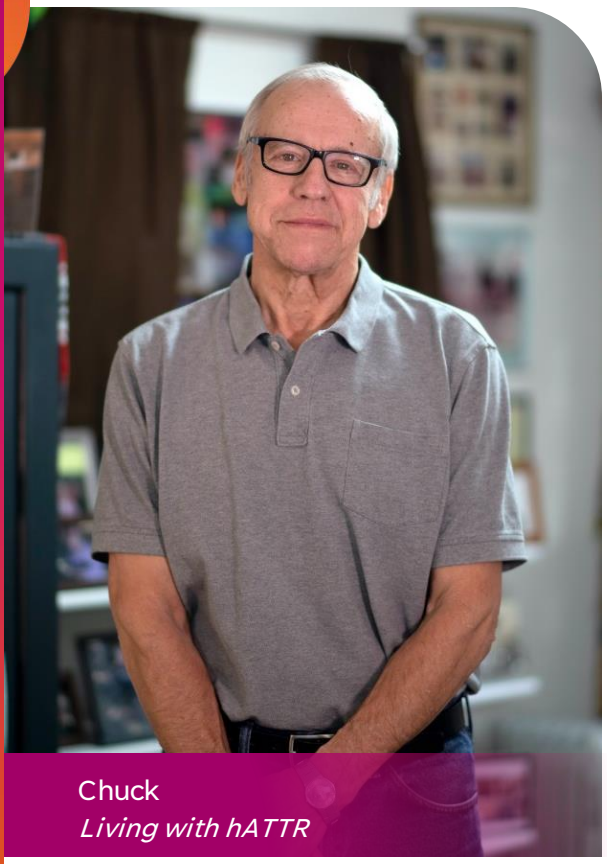
Eplontersen: ATTR Remains an Area of High Unmet Need

ATTR is a progressive and fatal disease caused by misfolded TTR protein aggregation in multiple tissues, including heart, nerve and GI tract, leading to rapid decline and poor quality of life



Chuck
Living with hATTR

Global Patient Segments
Expanding Patient Population

	Indication	Patients
	ATTR	~500K
Cardio	wtATTR	300K-500K
Cardio	ATTRv-CM	10K
Polyneuro	ATTRv-Mixed	30K
Polyneuro	ATTRv-PN	10K

IONIS + AstraZeneca

Industry-leading experience in RNA therapeutics & in ATTR

Vast global-scale experience in commercialization of CVD medicines

Shared strategy to bring eplontersen to patients with ATTR around the globe

ATTR represents an estimated >$10B market opportunity worldwide[1]

1. Market data on file 2. peak sales estimates are based on current assumptions and are subject to change

Source: amyloidosis.org (https://amyloidosis.org/facts/familial/; https://amyloidosis.org/facts/wild-type/ NOTE: For illustrative purposes only. 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. Peak sales estimates are based on current assumptions and are subject to change

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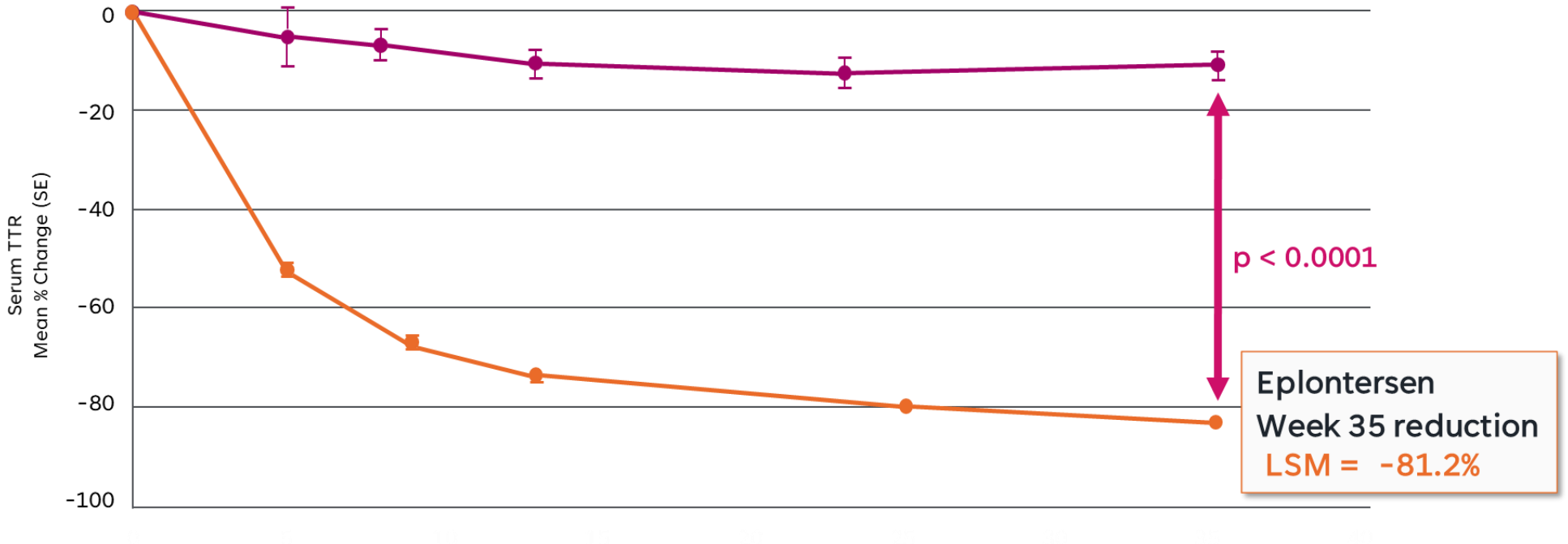
Eplontersen Demonstrated Competitive Therapeutic Profile in the Phase 3 NEURO-TTRansform Study (35-week Interim Analysis)

- Robust and consistent **reduction** in **TTR protein** levels
- Highly statistically significant and **clinically meaningful improvement** in **neuropathy** and **quality of life**
- Favorable **safety** and **tolerability** profile



Eplontersen: A Multibillion-Dollar Opportunity Positioned for US Approval This Year[1]

ATTRv POLYNEUROPATHY

neuro TTRansform

- Met co-primary + key secondary endpoints in Phase 3 (IA) with attractive safety and tolerability
- **NDA submission complete, FDA approval decision expected in 2023**
- **Plan to report Week 35 and Week 66 data in H1:2023**
- **On track for OUS filings in 2023**

ATTR CARDIOMYOPATHY

cardio TTRansform

- Most comprehensive ATTR-CM study to date
- Positioned to deliver most robust data in broad patient population
- **Full enrollment expected in 2023**
- **On track for data in H1:2025**

ATTR

TTRansform beyond

- Open-label extension studies in patients with ATTRv-PN and ATTR-CM enrolling
- Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function underway
- Additional profile-enhancing studies planned

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change.

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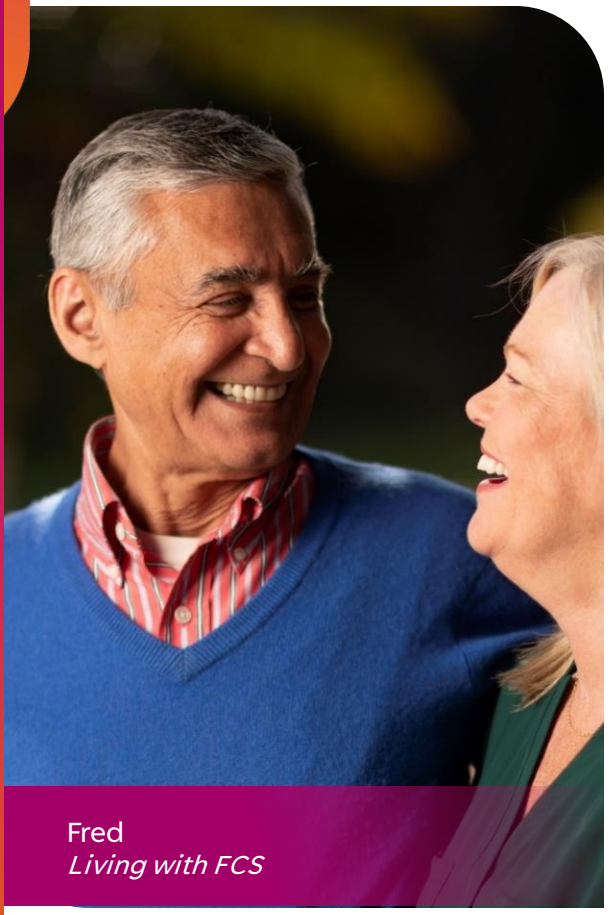
Olezarsen: Positioned to Address Diseases Associated with Severely Elevated Triglycerides



Fred
Living with FCS

Severely elevated triglycerides (TGs)

- Associated with acute, potentially fatal pancreatitis and atherosclerotic cardiovascular disease
- Endocrinology and cardiology guidelines recognize the risks of SHTG and recommend pharmacologic therapy
- Patients unable to achieve guideline recommended TG levels with current standard-of-care (High Unmet Need)

Indication	Peak Sales[2]
FCS SHTG	**>$1 Billion**

Familial chylomicronemia syndrome (FCS)

- Rare, genetically defined
- Significant risk for acute, potentially fatal pancreatitis
- ~1,500 US patients

Severe hypertriglyceridemia (SHTG): TG >500 mg/dL

- Significant risk for acute, potentially fatal pancreatitis
- Elevated risk for CVD
- >3 million US patients

1. Market data on file. 2. Peak sales estimates are based on current assumptions and are subject to change.

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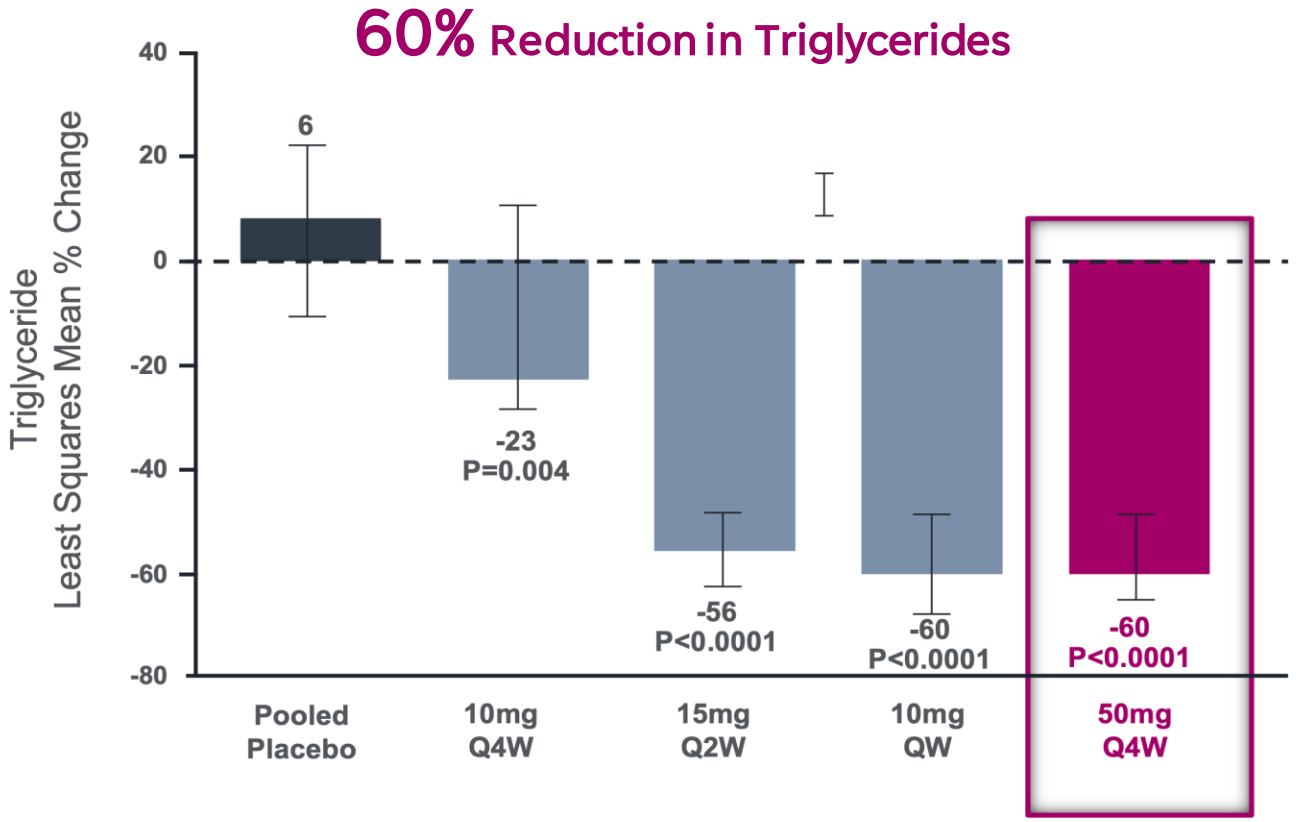
Olezarsen Represents a New Approach to Treating Diseases Caused by Severely Elevated Triglycerides

Olezarsen targets ApoCIII, key regulator of triglyceride metabolism in the blood



Phase 2 Study

- Dose-ranging, placebo-controlled study in 114 patients with CVD and TGs 200-500mg/dl
- Met primary endpoint of significant triglyceride reduction at 6 months
- Demonstrated favorable safety and tolerability profile
- Results support first-in-class and best-in-class TG lowering potential

Phase 3 Program

- Phase 3 studies in FCS and SHTG with 50mg and 80mg monthly dose underway
- Expected to demonstrate even greater TG reductions than in Phase 2

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Olezarsen is Positioned to Change the Standard of Care for Patients with Severely Elevated Triglycerides[1]

1. Market data on file.

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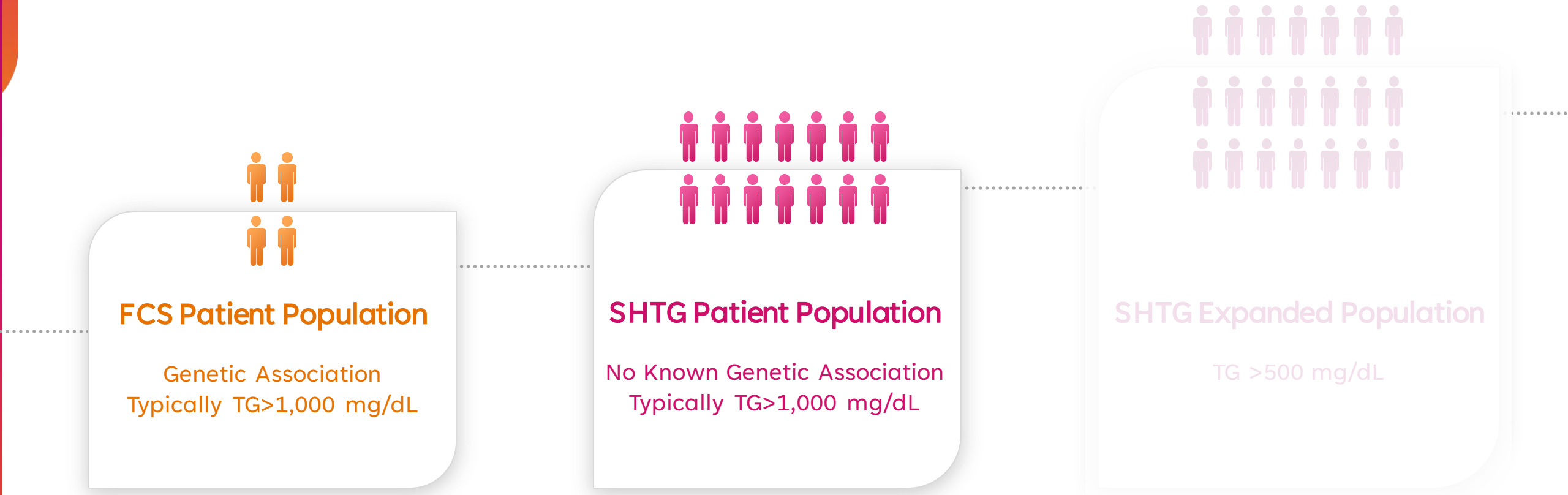
Olezarsen is Positioned to Change the Standard of Care for Patients with Severely Elevated Triglycerides[1]



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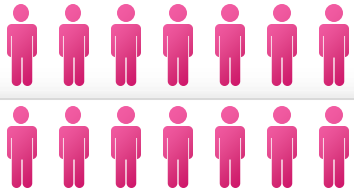
Olezarsen is Positioned to Change the Standard of Care for Patients with Severely Elevated Triglycerides[1]

FCS Patient Population

Genetic Association
Typically TG>1,000 mg/dL



SHTG Patient Population

No Known Genetic Association
Typically TG>1,000 mg/dL

SHTG Expanded Population

TG >500 mg/dL

- Immediate opportunity
- Highest risk for acute, potentially fatal pancreatitis
- CVD risk
- >$1B market opportunity[2]

1. Market data on file. 2. Peak sales estimates are based on current assumptions and are subject to change.

IONIS
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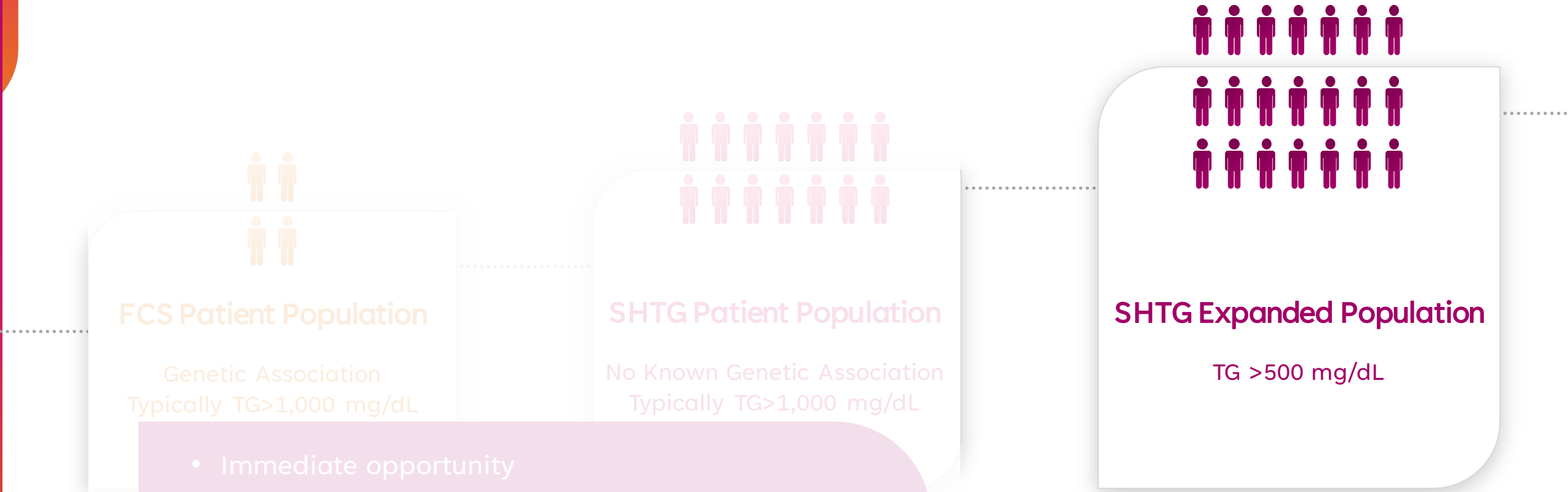
Olezarsen is Positioned to Change the Standard of Care for Patients with Severely Elevated Triglycerides[1]



FCS Patient Population

Genetic Association
Typically TG>1,000 mg/dL

SHTG Patient Population

No Known Genetic Association
Typically TG>1,000 mg/dL

SHTG Expanded Population

TG >500 mg/dL

- Immediate opportunity
- Highest risk for acute, potentially fatal pancreatitis
- CVD risk
- >$1B market opportunity[2]

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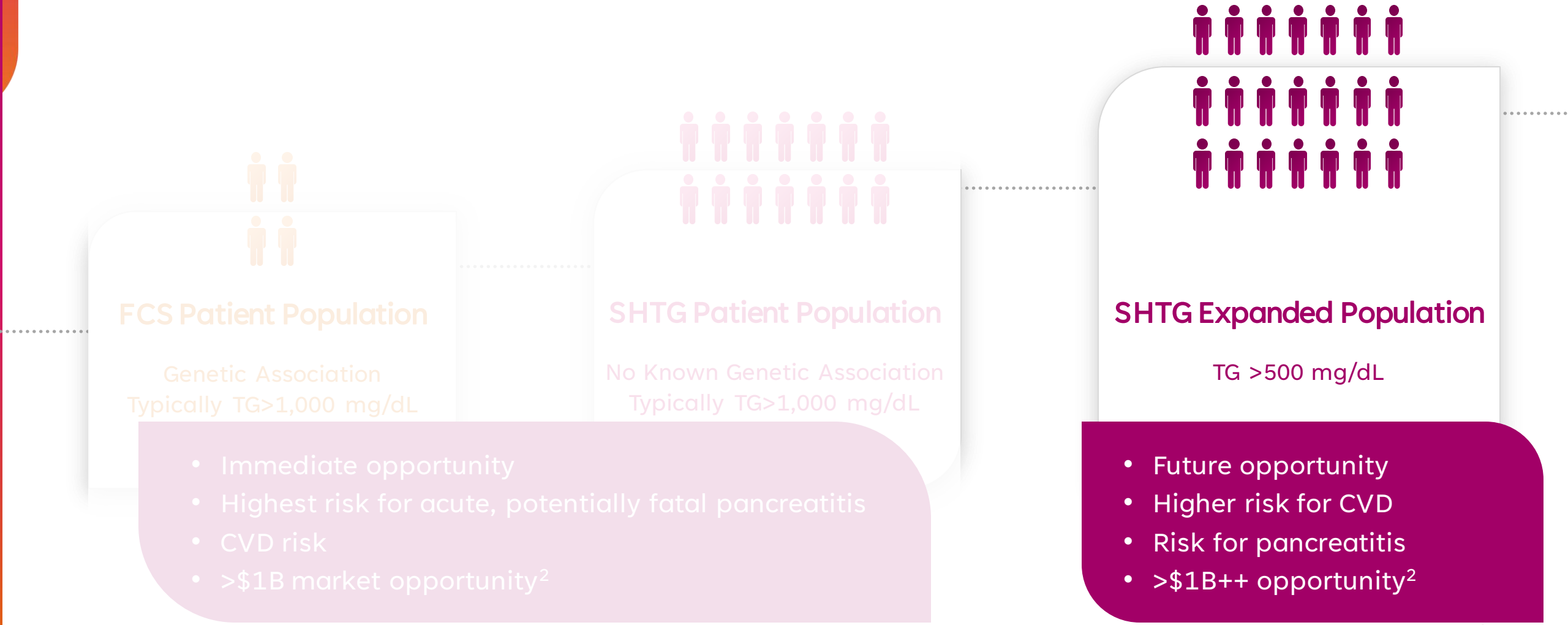
Olezarsen is Positioned to Change the Standard of Care for Patients with Severely Elevated Triglycerides[1]



FCS Patient Population

Genetic Association
Typically TG>1,000 mg/dL

- Immediate opportunity
- Highest risk for acute, potentially fatal pancreatitis
- CVD risk
- >$1B market opportunity[2]

SHTG Patient Population

No Known Genetic Association
Typically TG>1,000 mg/dL

SHTG Expanded Population

TG >500 mg/dL

- Future opportunity
- Higher risk for CVD
- Risk for pancreatitis
- >$1B++ opportunity[2]

1. Market data on file. 2. Peak sales estimates are based on current assumptions and are subject to change.

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Olezarsen Development Program Designed to Support a >$1 Billion Market Opportunity[1]

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

Balance
a familial chylomicronemia syndrome study

- FCS Phase 3 BALANCE study fully enrolled
- Phase 3 data expected H2:2023
- OLE progressing well
- Launch preparations underway

SEVERE HYPERTRIGLYCERIDEMIA (SHTG)

CORE
a hypertriglyceridemia study

- SHTG Phase 3 study enrolling well
- First pivotal study in large SHTG population

CORE2
a hypertriglyceridemia study

- Confirmatory pivotal study enrolling
- Supportive of registration

ESSENCE Plus

- ESSENCE study in patients with mild TGs and CVD risk
- Strengthens safety database necessary for approval
- Additional profile enhancing studies underway

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change

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Donidalorsen: Positioned to be a Best-in-Class HAE Prophylactic

Sydney
Living with HAE

Hereditary Angioedema (HAE)

- Rare genetic disease
- Severe and potentially fatal swelling of the arms, legs, face and throat

Donidalorsen

- Targets the prekallikrein pathway, the root cause of HAE

>20K

Patients in the United States and Europe suffering from HAE[1]

Indication	Peak Sales[2]
HAE	**>$500 Million**

1. Market data on file. 2. Peak sales estimates are based on current assumptions and are subject to change.

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Donidalorsen Demonstrated a Best-in-Class HAE Prophylactic Profile in Phase 2 and OLE[1]

- **Rapid** and **sustained** reductions in HAE attacks in Phase 2 study (17 weeks)
- **Sustained** reductions in HAE attacks in patients treated for 1 year
- **Robust efficacy** with **monthly** self-administration sc dosing (auto-injector)
- **Favorable safety** and **tolerability** profile in patients treated for more than 1 year

Phase 2

97%

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

Open-label Extension

>99%

Mean attack-free study days
(through week 57)

1. Best-in-class potential based on results from Phase 2 study and Phase 2 OLE of donidalorsen

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Donidalorsen Phase 3 Development Program Designed to Replicate Robust Phase 2 and OLE Results[1]

Hereditary Angioedema

OASIS

- Positive Phase 2 and OLE data presented
- Phase 3 study on track for full enrollment this year
- Phase 3 data expected 2024

OASIS plus

- SWITCH study underway in patients previously treated with other prophylactic therapies
- Phase 3 OLE study underway in patients who have completed OASIS

Potential to demonstrate best-in-class HAE prophylactic profile

1. Timing expectations based on current assumptions and subject to change

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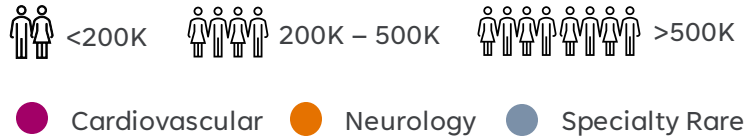
Rich Late-Stage Pipeline

Positioned to Deliver Steady Cadence of New Drugs to the Market



		Indication	Prevalence[1]	Program Status[2]	Next Event[2]
Tofersen	Biogen	SOD1-ALS		NDA and MAA under review	US, EU approval (2023)
		Presymptomatic SOD1-ALS		ATLAS Study underway	Ph3 data (TBD)
Eplontersen	IONIS AstraZeneca	ATTRv-PN		NDA submitted	Full data (2023) OUS submissions (2023) US approval (2023)
		ATTR-CM		Full enrollment expected 2023	Ph3 data (2025)
Olezarsen	IONIS	FCS		Fully enrolled	Ph3 data (2023)
		SHTG		Ph3 program underway	Ph3 data (2024)
Donidalorsen	IONIS	HAE		Full enrollment expected 2023	Ph3 data (2024)
ION363	IONIS	FUS-ALS		Ph3 study enrolling well	Ph3 data (2025)
Pelacarsen	NOVARTIS	Lp(a) CVD		Fully enrolled, profile-enhancing studies underway	Ph3 data (2025)

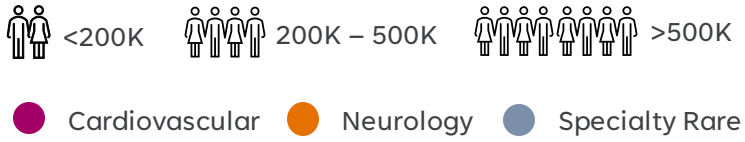
Bepirovirsen (gsk) and IONIS-FB-L_{Rx} (Roche) expected to enter Phase 3 pipeline in H1:23[2]

1. Market data on file. 2. Timing expectations are based on current assumptions and are subject to change.

IONIS A Genetic Medicines Company

Rich Late-Stage Pipeline

Positioned to Deliver Steady Cadence of New Drugs to the Market



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Eplontersen	IONIS AstraZeneca	ATTRv-PN		NDA submitted	Full data (2023) OUS submissions (2023) US approval (2023)
		ATTR-CM		Full enrollment expected 2023	Ph3 data (2025)
Olezarsen	IONIS	FCS		Fully enrolled	Ph3 data (2023)
		SHTG		Ph3 program underway	Ph3 data (2024)
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Bepirovirsen (gsk) **and IONIS-FB-L_{Rx}** (Roche) **expected to enter Phase 3 pipeline in H1:23[2]**

1. Market data on file. 2. Timing expectations are based on current assumptions and are subject to change.

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Positioned to Deliver a Steady Cadence of New Approved Products[1]

- Cardiovascular
- Neurology
- Specialty Rare
- Other Medicines

SPINRAZA
Spinal Muscular Atrophy

TEGSEDI
ATTRv polyneuropathy

WAYLIVRA
FCS & FPL

TODAY

1. Timing expectations are based on current assumptions and are subject to change.

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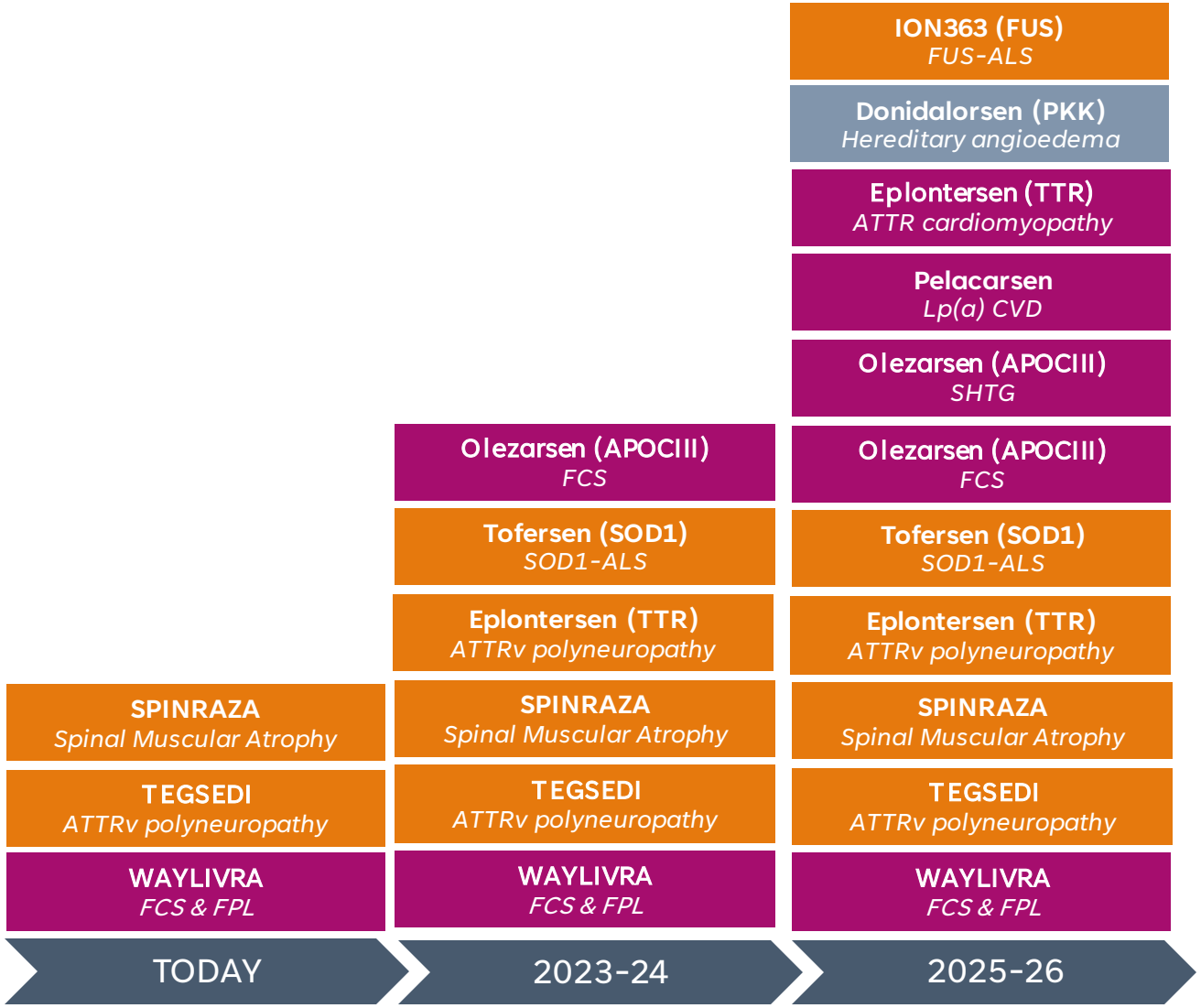
Positioned to Deliver a Steady Cadence of New Approved Products[1]



- Cardiovascular
- Neurology
- Specialty Rare
- Other Medicines

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IONIS
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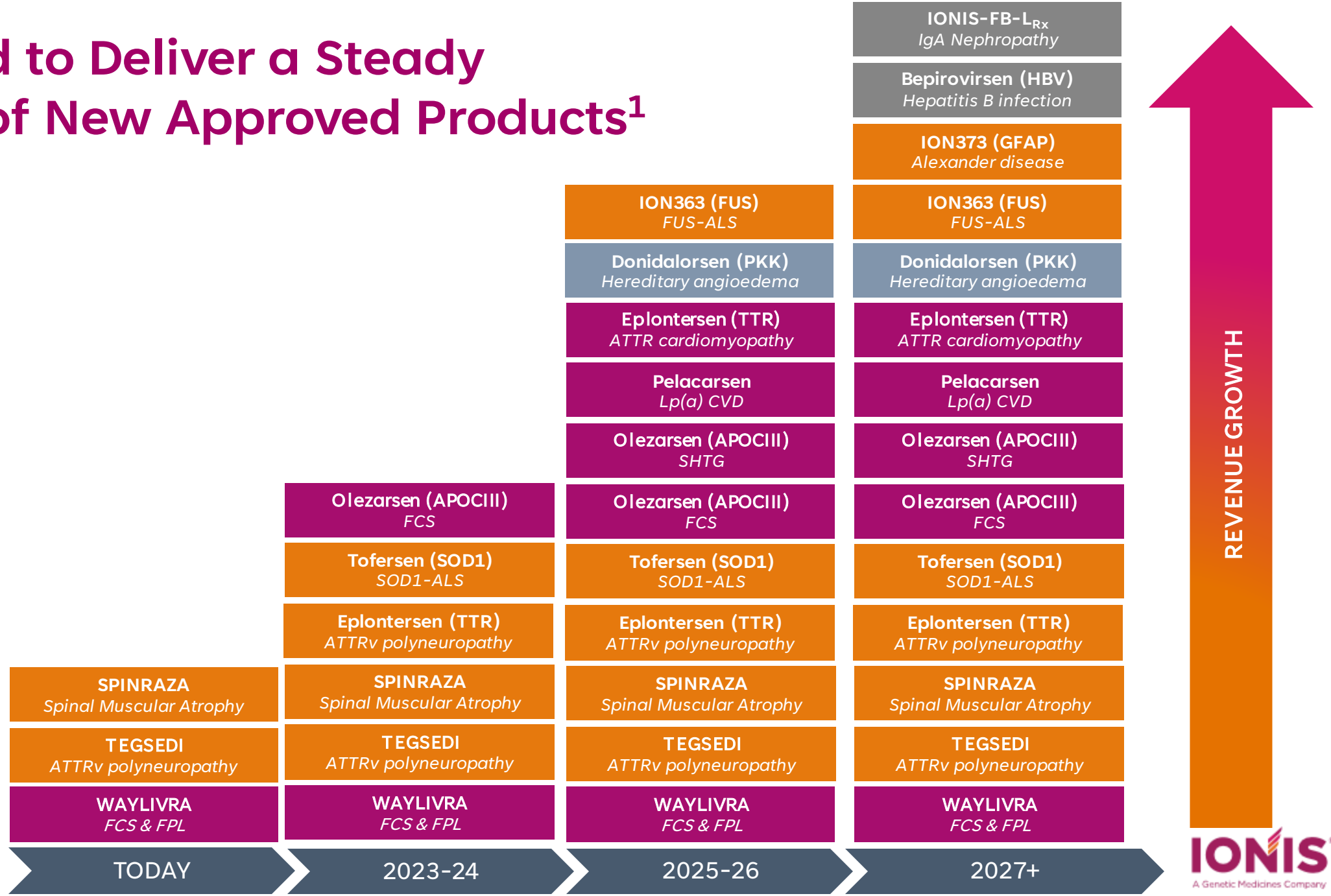
Positioned to Deliver a Steady Cadence of New Approved Products[1]



- Cardiovascular
- Neurology
- Specialty Rare
- Other Medicines

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IONIS
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Technology Advancements Build on our Leadership Position in Genetic Medicine

Recent Advancements to Enhance Drug Profiles

WHERE WE ARE

- Further optimized medicinal chemistry for CNS applications
- Advanced muscle LICA program into preclinical development
- Advanced new MsPA backbone chemistry with enhanced duration into preclinical development

Adding Value for Tomorrow's Medicines

WHERE WE ARE GOING

- Solve delivery across blood-brain-barrier
- Advance additional muscle LICA (bicycle) programs into development
- Advance new routes of delivery
- Advance new targets utilizing gene editing technology (Metagenomi partnership)

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Royalty Pharma Agreement Further Strengthens Ionis' Financial Foundation[1]

Royalty monetization transaction valued up to >$1.1B Underscores substantial upside potential for SPINRAZA & pelacarsen

$500M
Upfront

Up to **$625M**
in additional pelacarsen milestone payments

- Enables Ionis to:
  - Achieve commercial readiness for multiple late-stage programs
  - Deliver new genetic medicines to the market by further advancing a deep and innovative pipeline
- Royalty Pharma receives minority interest in SPINRAZA and pelacarsen royalties
- Ionis maintains the ability to participate in significant upside with majority royalty interest in both products and retains all development, regulatory and commercial milestones for pelacarsen

1. See SEC filing for additional details.

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Foundation of Financial Strength for Sustainable Growth

Financial Strength + **Accelerating Investments** + **Sustained Delivery of New Marketed Products**

- Significant financial resources with **~$2.5 billion in cash**[1]
- **Multiple revenue sources** with diverse margin profiles
- **Strategic transactions** provided even greater financial strength

- **Advancing** new medicines to the market
- **Building** our commercial organization
- **Expanding** and diversifying our technology
- **Scaling** our infrastructure

1. Pro forma cash based on 2022 cash guidance of ~$2 billion and recent transactions.

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Key Value Driving Events in 2023[1]

Regulatory Actions

- **Tofersen:** FDA approval decision, SOD1-ALS
- **Tofersen:** EU approval decision, SOD1-ALS
- **Eplontersen:** FDA approval decision, ATTRv-PN
- **Eplontersen:** OUS filings, ATTRv-PN

Clinical Achievements

- **Eplontersen:** Phase 3, NEURO-TTRansform 35-week & 66-week data, ATTRv-PN
- **Olezarsen:** Phase 3, BALANCE study data, FCS
- **Eplontersen:** Phase 3, CARDIO-TTRansform full enrollment, ATTR-CM
- **Donidalorsen:** Phase 3, OASIS full enrollment, HAE

Phase 3 Initiations

- **Bepirovirsen:** Phase 3 initiation, chronic HBV
- **IONIS-FB-L_{Rx}:** Phase 3 initiation, IgA nephropathy

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

IONIS A Genetic Medicines Company

Thoughtful Corporate Responsibility in Everything We Do

Second Annual Corporate Responsibility Report Published in December 2022

Well-positioned to **accelerate growth** through success across our business

Numerous attractive near-term product opportunities **rapidly approaching market**

Growing & advancing **Phase 3 pipeline**

Sustained delivery of **numerous new product opportunities** for rare and broad indications

Research, development & commercial **fully integrated**

Expanded and **diversified technology** with new capabilities extending our **leadership** in **genetic medicine**

REALIZING OUR VISION TO BE THE

Leader in Genetic Medicine

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IONIS®

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Every Moment Matters...

in the Discovery, Development & Delivery of Life Transforming Genetic Medicines