



J.P. Morgan Healthcare Conference 2022

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

January 12, 2022



Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), eplontersen, olezarsen, donidalorsen, 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, 2020 and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of this and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, “Ionis,” “Company,” “we,” “our,” and “us” refers to Ionis Pharmaceuticals and its subsidiaries.

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.

Executing on a Clear Vision to Become a Leading Fully Integrated Biotechnology Company

Positioned for Substantial Growth

Rich Mid- & Late-Stage Pipeline

Growing pipeline of potentially transformational medicines **advancing towards** the **market**

Technology Leadership

Our technology is advancing at an unprecedented pace, expanding our opportunities and **extending** our **leadership position**

Compelling Financial Profile

Ionis' strong financial position enables needed investments to support our vision and drive **substantial growth**

GROWTH



**Build
the Ionis
Commercial
Pipeline**



**Expand
&
Diversify
Technology**



**Deliver
Abundance of
New Medicines
To Market**



**Validated
Platform
Technology**



**Rich Mid- &
Late-Stage
Pipeline**



**Financial
Strength**



**Commitment to
Innovation
Leadership**



**Highly
Dedicated
Employees**

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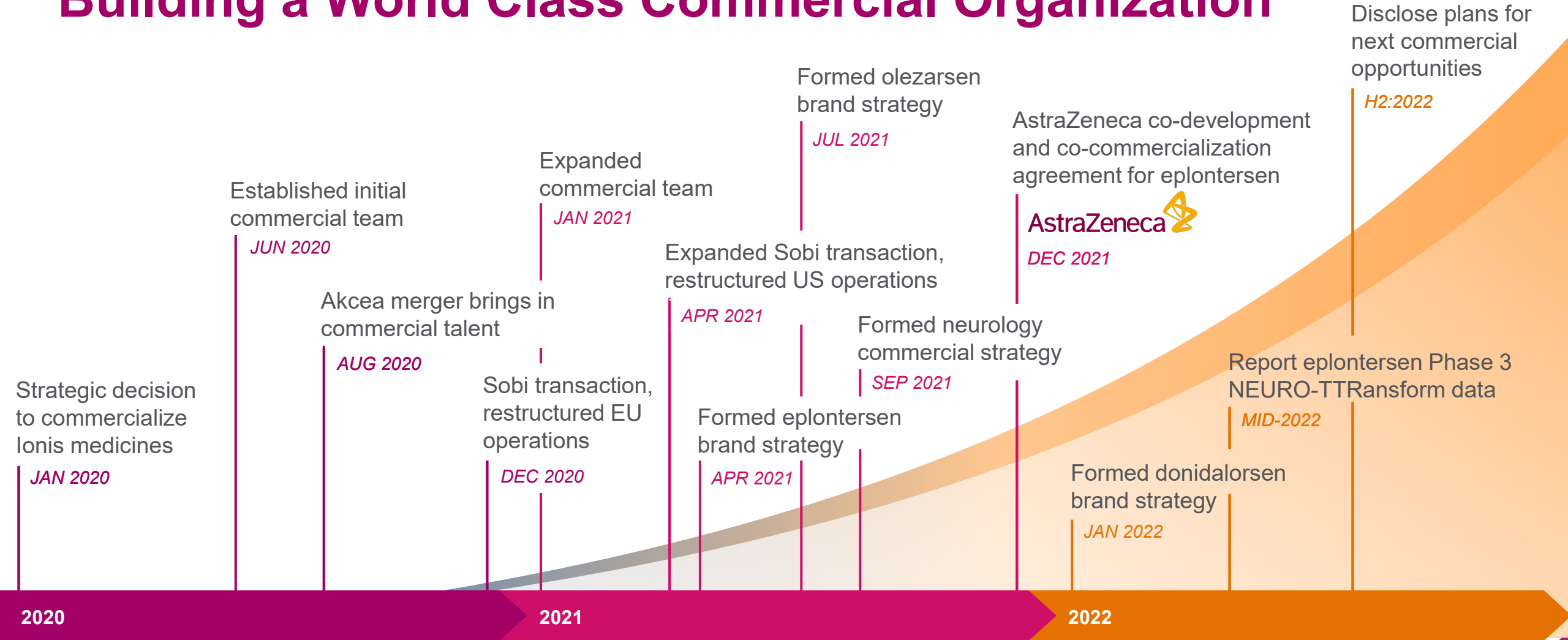
**Highly
Dedicated
Employees**

Realizing the Promise of our Innovative Products

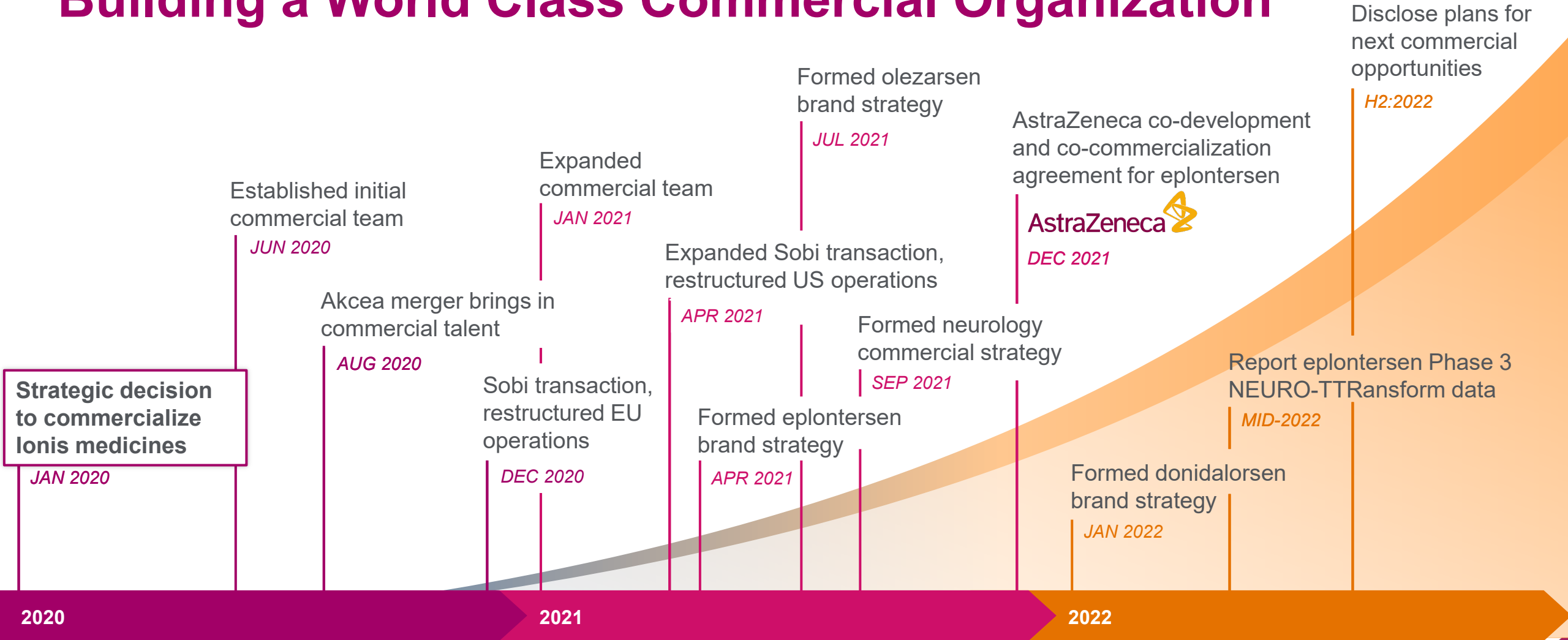
Commercial Strategy to Maximize Value for Patients and Shareholders

Go-to-Market Strategy	Disciplined Expansion Over Time	Partner Strategically
Focus on 2 core franchises – cardiovascular & neurology	Expand commercial pipeline beyond near-term assets	Out-license assets outside our core areas of focus and capabilities
Commercialize non-core assets with high PoS and attractive markets	Expand commercial infrastructure outside the U.S.	Co-commercialize where appropriate to enable greater patient access and availability
Commercialize medicines for both rare and broad indications	Build an agile commercial operating model	
Build U.S. commercial excellence		
Establish ex-U.S. distribution/commercial partners near-term		

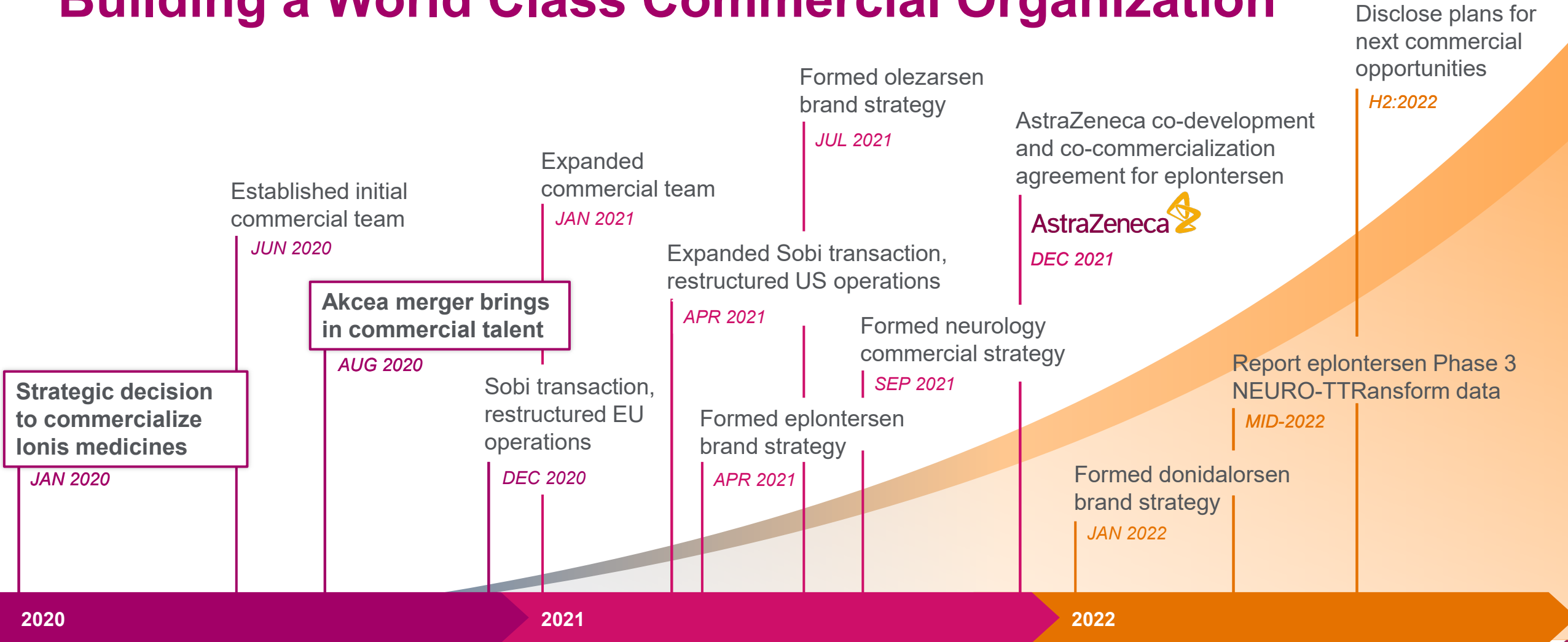
Building a World Class Commercial Organization



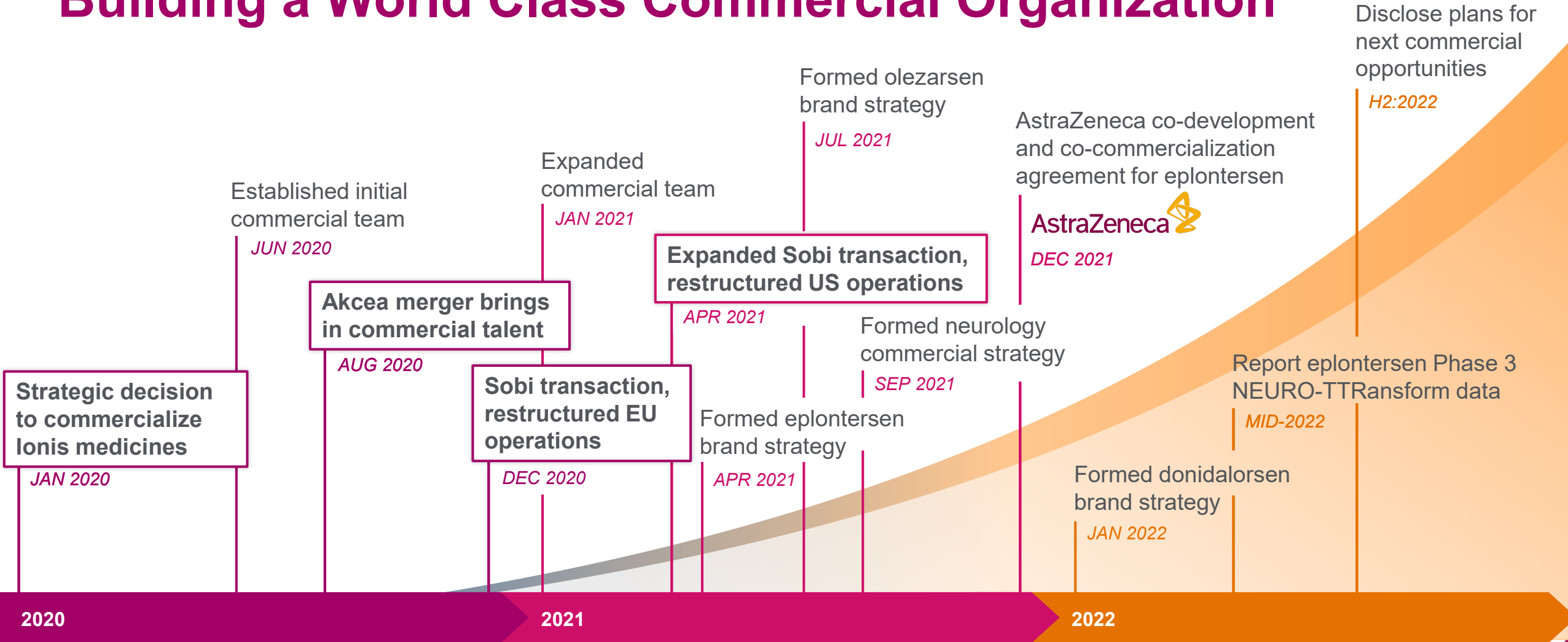
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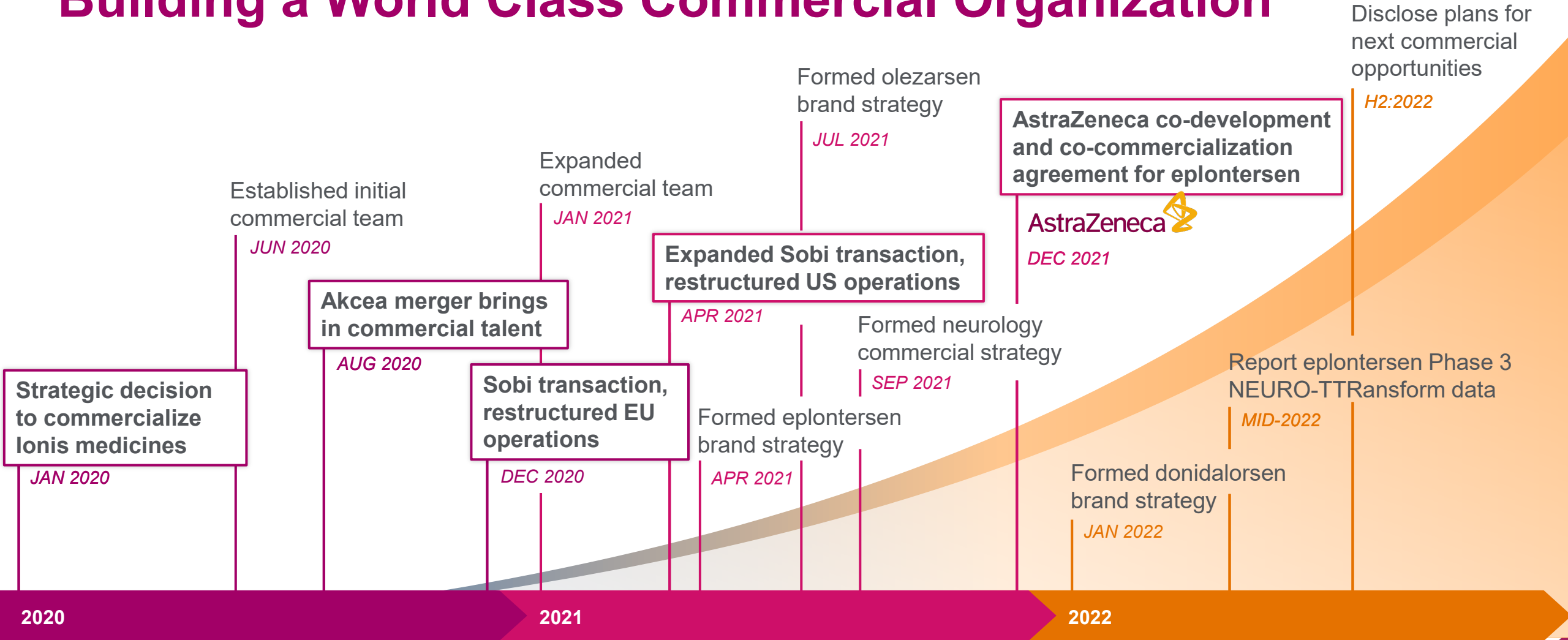
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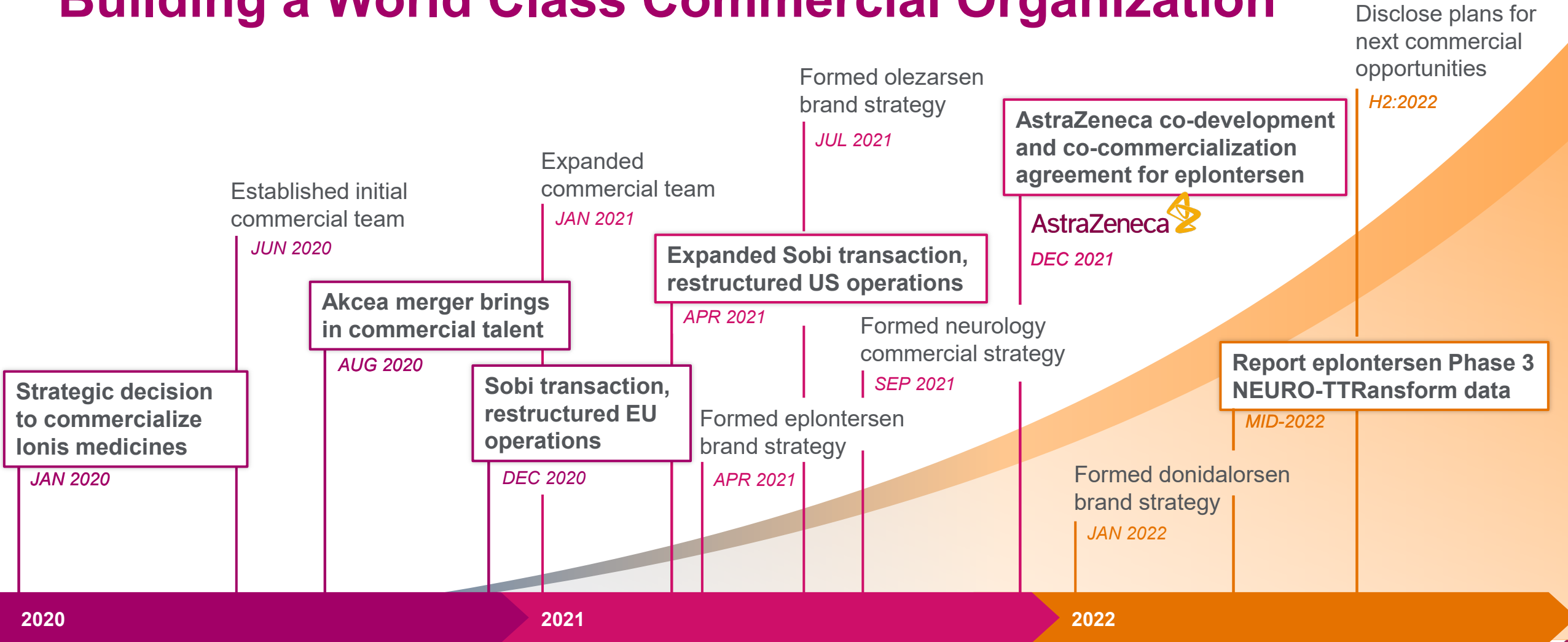
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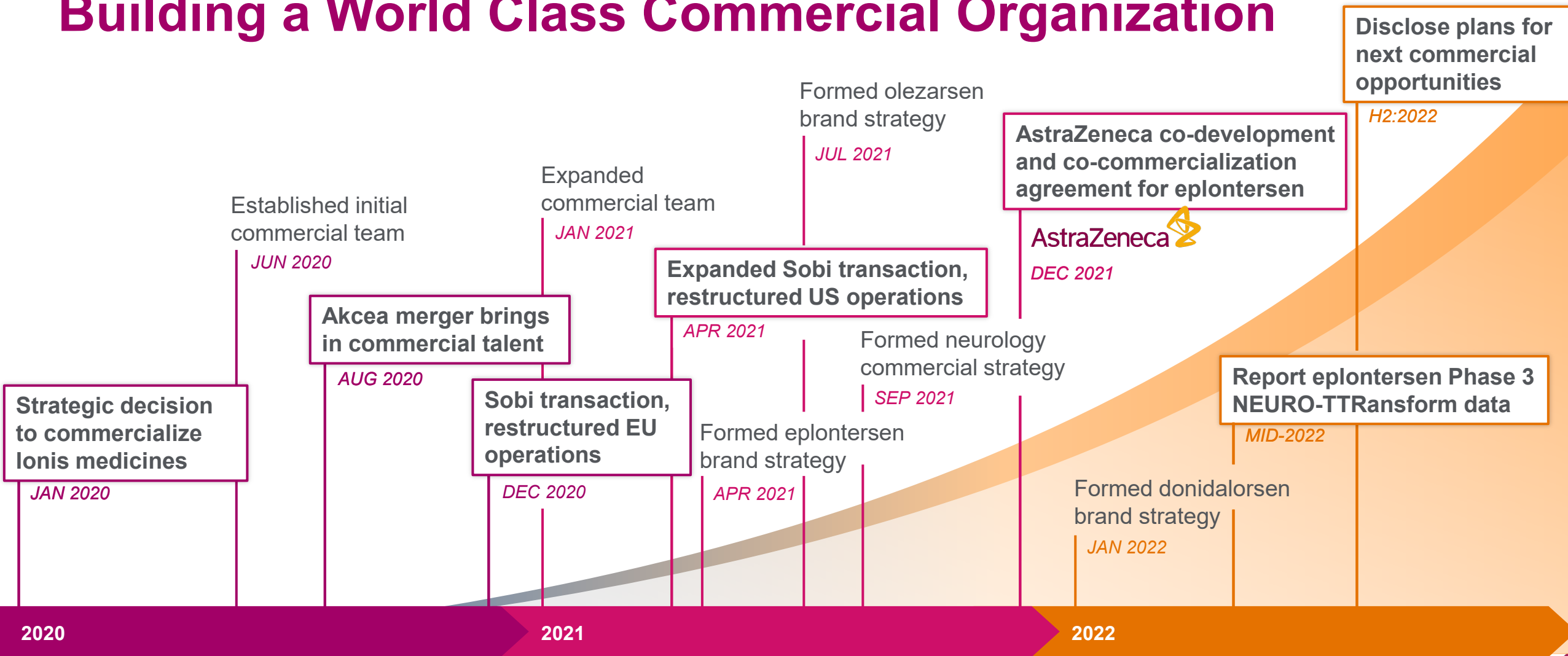
Building a World Class Commercial Organization



Building a World Class Commercial Organization









Building a World Class Commercial Organization



Eplontersen + Olezarsen + Donidalorsen

3 Near-term Opportunities with Aggregate Multibillion-dollar Potential^{1,2}

Eplontersen TTR Amyloidosis	Olezarsen Severe TGs	Donidalorsen HAE
<p>~300,000-500,000 patients in 2 indications worldwide</p> <p>First Phase 3 data readout: 2022</p> <p>Potential to change the standard-of-care for patients with TTR amyloidosis</p> <p>Estimated peak sales: </p>	<p>>3 million patients in 2 indications in the US</p> <p>First Phase 3 data readout: 2023</p> <p>Potential first-in-class treatment for patients with elevated triglycerides</p> <p>Estimated peak sales: </p>	<p>>20,000 patients in the US and EU</p> <p>Phase 3 data readout: 2024</p> <p>Potential best-in-class prophylactic treatment for patients with HAE</p> <p>Estimated peak sales: </p>
<p>Estimated peak sales:  <1 Billion  >1 Billion  Multibillion</p>		

Realizing the Potential of our Near-Term Commercial Opportunities

Eplontersen TTR Amyloidosis	Olezarsen Severe TGs	Donidalorsen HAE
<p>Large and growing patient population with high unmet medical need</p> <p>Highly attractive LICA drug profile</p> <p>Leverages AstraZeneca's global scale, leadership in cardiovascular disease</p> <p>Two Phase 3 studies underway; largest & potentially most informative ATTR-CM study</p>	<p>Significant need for more effective treatments to manage high TGs</p> <p>LICA drug with potential best-in-class profile and first-mover advantage</p> <p>Targets master regulator of TG levels & independent CV risk factor (APOCIII)</p> <p>Two Phase 3 studies underway</p>	<p>Significant need for prophylactic treatments with improved efficacy, tolerability and convenience</p> <p>Differentiated LICA drug with potential best-in-class profile</p> <p>Potential to switch patients from standard of care to donidalorsen</p> <p>Phase 3 study underway</p>

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Building on our Technology Leadership in RNA-Targeted Therapeutics

Recent Advancements to Enhance Drug Profiles



WHERE WE ARE

- ✓ Combine liver LICA medicines with medicinal chemistry advancements
 - e.g. Gen 2.5 chemistry + liver LICA PCSK9
- ✓ Enable potential best-in-class muscle LICA
- ✓ Enhance stability and duration with MsPA backbone chemistry for systemic & local applications
- ✓ Extend dosing interval for local applications (CNS/IT dosing) through medicinal chemistry
 - e.g. SMA follow-on, new chemistry enabling longer duration, less frequent dosing

Building on our Technology Leadership in RNA-Targeted Therapeutics

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Adding Value for Tomorrow's Medicines



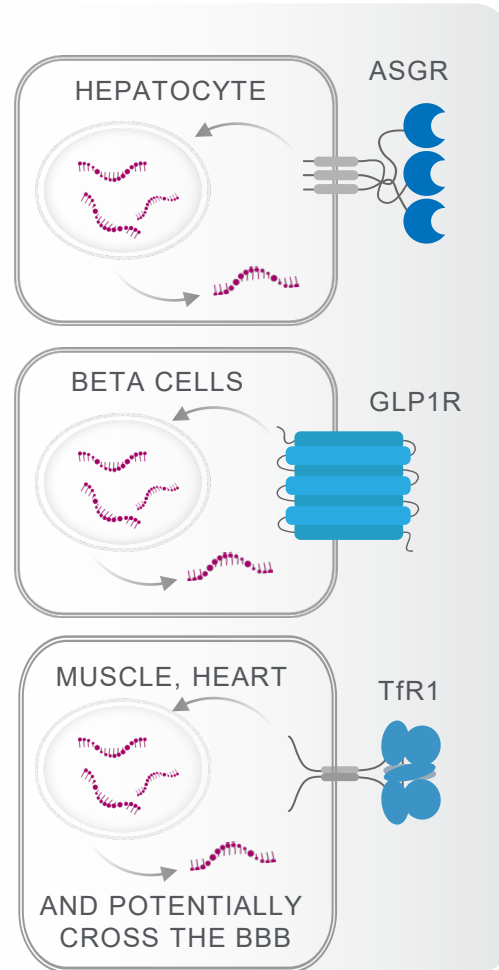
WHERE WE ARE GOING

- Develop additional LICA chemistries to improve potency, therapeutic index, enable new organs and target new disease areas
- Further optimize medicinal chemistry for CNS applications
- Penetrate blood-brain-barrier
- Optimize new routes of delivery through medicinal chemistry (e.g., pulmonary, ocular)

Ionis LICA Platform Continues to Expand

Multiple Tissues

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



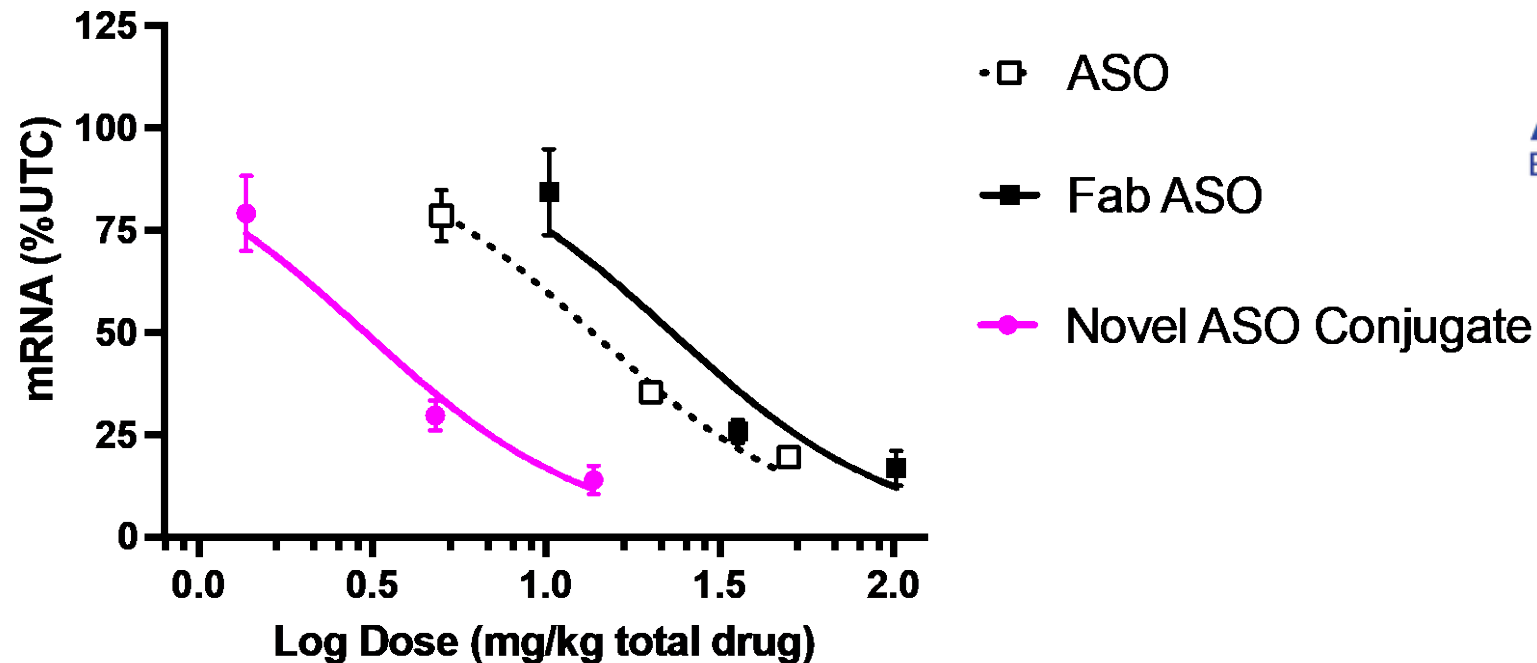
Multiple Ligands

- Carbohydrates
- Traditional peptides
- Antibodies and FAB fragments
- Constrained peptides & small protein mimics

Ionis is Building a Potentially Best-In-Class Chemical Platform for Muscle Targeting Therapeutics

Transferrin-Receptor (TFR1) Targeting with Lower-Molecular Weight Conjugates

bicycle
therapeutics



Aro
BIOTHERAPEUTICS

- Lower-molecular weight TFR1 Conjugates Offer Several Advantages for Drug Development
 - Focus is on Conjugate Optimization for Heart & Skeletal Muscle Targets

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Two Leading Therapeutic Franchises

Cardiovascular



Addressing major cardiovascular disease risk factors

4

Ongoing Phase 3 studies

Eplontersen • Olezarsen • Pelacarsen

9

Medicines in clinical development

- 4 in Phase 2
- 2 in Phase 1

Neurological



Addressing major neurological diseases

3

Ongoing Phase 3 studies

Eplontersen • ION363 (FUS-ALS) • Tofersen

11

Medicines in clinical development

- 8 in Phase 2

Emerging Specialty-Rare Pipeline



Rich Phase 3 Pipeline

6 Medicines for 8 Indications



		Phase 3 Data ¹	Prevalence ²
Tofersen	SOD1-ALS	2021	~1.4K patients in G7 countries
Eplontersen	hATTR polyneuropathy	2022	>40K patients worldwide
Olezarsen	FCS	2023	~3-5K patients worldwide
Eplontersen	ATTR cardiomyopathy	2024	~300-500K patients worldwide
Olezarsen	SHTG	2024	>3M patients in US
Donidalorsen	HAE	2024	>20K patients in US and EU
ION363	FUS-ALS	2024	~350 patients in G7 countries
Pelacarsen	Lp(a) CVD	2025	>8M patients worldwide

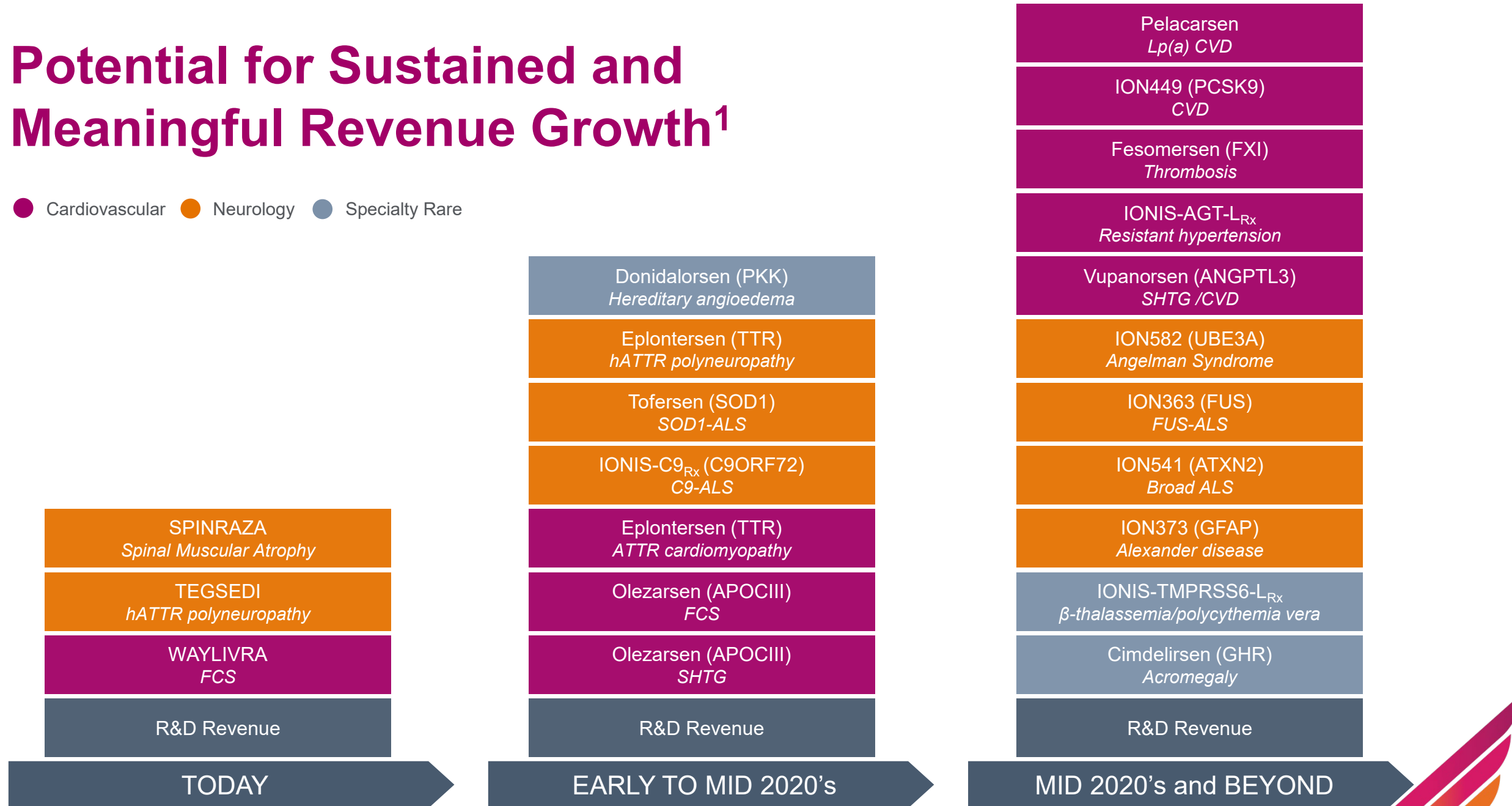
● Cardiovascular ● Neurology ● Specialty Rare

Mid- and Late-Stage Pipeline

		MID-STAGE (Phase 1/2 - Phase 2)	LATE-STAGE (Phase 3)	COMMERCIAL RIGHTS
Eplontersen	hATTR polyneuropathy		●	Cost-sharing & royalty bearing
Olezarsen (APOCIII)	FCS		●	Global
Eplontersen	ATTR cardiomyopathy		●	Cost-sharing & royalty bearing
Olezarsen (APOCIII)	SHTG		●	Global
Pelacarsen	Lp(a) CVD		●	Milestones & up to low 20% royalties
Donidalorsen (PKK)	Hereditary angioedema		●	Global
ION363 (FUS)	FUS/ALS		●	Global
Tofersen	SOD1-ALS		●	Milestones & up to mid-teen royalties
Vupanorsen (ANGPTL3)	SHTG/CVD	●		Milestones & up to low 20% royalties
ION449 (PCSK9)	CVD	●		Milestones & up to low teen royalties
Fesomersen (FXI)	Clotting disorders	●		Milestones & up to high 20% royalties
IONIS-AGT-L _{Rx}	Treatment-resistant hypertension	●		Global
ION373 (GFAP)	Alexander disease	●		Global
IONIS-MAPT _{Rx}	Alzheimer's disease	●		Milestones & up to mid-teen royalties
IONIS-C9 _{Rx}	C9-ALS	●		Milestones & up to mid-teen royalties
ION541 (ATXN2)	Broad ALS	●		Milestones & up to mid-teen royalties
ION464 (SNCA)	MSA & Parkinson's disease	●		Milestones & up to mid-teen royalties
ION859 (LRRK2)	Parkinson's disease	●		Milestones & up to mid-teen royalties
ION582 (UBE3A)	Angelman syndrome	●		Milestones & up to mid-teen royalties
IONIS-TMPRSS6-L _{Rx}	b-thalassemia/polycythemia vera	●		Global
Cimdelirsen (GHR)	Acromegaly	●		Global

Potential for Sustained and Meaningful Revenue Growth¹

● Cardiovascular ● Neurology ● Specialty Rare



Financial Strength to Drive Substantial Growth

Strong Financial Foundation

- Well capitalized with ~\$2 billion in cash¹
- **Multiple sources of revenue** with diverse margin profiles

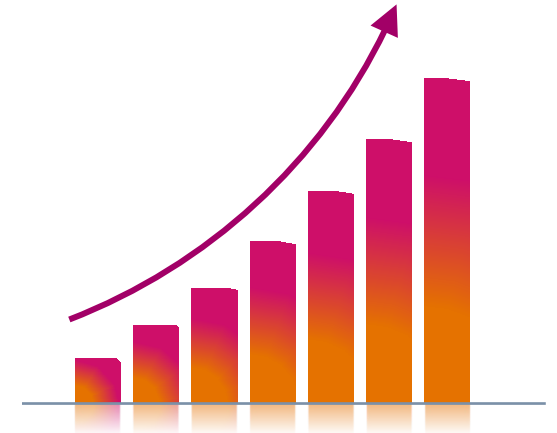


Accelerating Investments

- **Building** the Ionis commercial pipeline
- **Expanding** and diversifying our technology
- **Delivering** new medicines to the market



Substantial Growth



Key 2022 Catalysts¹

Data Readouts

- **Eplontersen**: Phase 3 hATTR polyneuropathy
- **ION449 (PCSK9-L)**: Phase 2b, CVD
- **Fesomersen (FXI-L)**: Phase 2b, thrombosis
- **AGT-L_{Rx}**: Phase 2b, TRH
- **Donidalorsen**: Phase 2 LTE, HAE
- **C9_{Rx}**: Phase 2, C9-ALS
- **Cimdelirsen (GHR-L)**: Phase 2, acromegaly (monotherapy)

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Regulatory Filings

- **Eplontersen**: hATTR polyneuropathy regulatory filing

Key 2022 Catalysts¹

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Regulatory Filings

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Technology Advancements

- ✔ **SMA**: advance follow-on program²
- **Muscle LICA**: advance into preclinical development²
- **MsPA Backbone**: advance into preclinical development²

Study Initiations

- ✔ **TMPRSS6-L_{Rx}**: Phase 2, polycythemia vera
- **MAPT_{Rx}**: Phase 2, Alzheimer's disease
- **ION904 (AGT-2.5-L)**: Phase 2, TRH
- **ION717 (PRNP)**: Phase 1/2, Prion disease

Thoughtful Corporate Responsibility in Everything We Do

Inaugural Corporate Responsibility Report Published in December 2021



Building a Leading Fully-Integrated Biotechnology Company

Well-positioned to accelerate growth & maximize success across all aspects of our business

Numerous **attractive product opportunities** rapidly approaching market

Growing & advancing **Phase 3 pipeline**

On track to becoming a leading **fully-integrated research, development & commercial organization**

Technology advancements are extending our leadership position & expanding our therapeutic capabilities

2022 promises to be a catalyst rich year for all Ionis stakeholders

IONIS[®]

A Force for Life

