



ISIS
PHARMACEUTICALS



Isis Pharmaceuticals

2015 Annual Shareholders Meeting

June 30, 2015

Forward Looking Language Statement

This presentation includes forward-looking statements regarding Isis Pharmaceuticals' financial position and outlook, Isis' business, and the therapeutic and commercial potential of Isis' technologies and products in development, including the commercial potential of KYNAMRO®, ISIS-TTR_{Rx}, ISIS-SMN_{Rx} and volanesorsen. Any statement describing Isis' 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. Isis' 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 Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2014, 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 press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Isis Pharmaceuticals, Inc. Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc. KYNAMRO® is a registered trademark of Genzyme Corporation.

Welcome Isis' Board of Directors



**Spencer Berthelsen,
MD, FACP**



Skip Klein



Fred Muto, Esq



Lynne Parshall, Esq



Breaux Castleman



Joe Wender



**Joseph Loscalzo,
MD, PhD**



The Year In Review



Isis' Pipeline Continues to Grow and Expand

Commercialized

KYNAMRO®	Homozygous FH
Alicaforsen	*Pouchitis
Vitravene®	CMV Retinitis

* Named Patient Supply

Phase 3

ISIS-TTR _{Rx}	TTR Amyloidosis
ISIS-SMN _{Rx}	Spinal Muscular Atrophy (Infants)
ISIS-SMN _{Rx}	Spinal Muscular Atrophy (Children)
Volanesorsen	FCS
Volanesorsen	Familial Partial Lipodystrophy
KYNAMRO®	Severe HeFH
Custirsen (OGX-011)	Prostate / Lung Cancer
Plazomicin	Severe Bacterial Infection

Phase 2

ATL1103	Acromegaly
ISIS-DMPK-2.5 _{Rx}	Myotonic Dystrophy 1

Phase 2 (cont.)

ISIS-APO(a) _{Rx}	Very High Lp(a)
ISIS-FXI _{Rx} (BAY 2306001)	Clotting Disorders
ISIS-GCGR _{Rx}	Diabetes
ISIS-GCCR _{Rx}	Diabetes
ISIS-PTP1B _{Rx}	Diabetes
Apatorsen (OGX-427)	Cancer
ISIS-STAT3-2.5 _{Rx} (AZD9150)	Cancer
ISIS-AR-2.5 _{Rx} (AZD5312)	Cancer
EXC 001 (PF-06473871)	Scarring
ATL1102	Multiple Sclerosis
RG-101	HCV

Phase 1

ISIS-GCCR _{Rx}	Cushing's Syndrome
ISIS-PKK _{Rx}	Hereditary Angioedema
RG-012	Alport Syndrome
ISIS-APO(a)-L _{Rx}	Very High Lp(a)
ISIS-FGFR4 _{Rx}	Obesity
ISIS-HBV _{Rx}	HBV

■ Severe & Rare ■ Cardiovascular
■ Metabolic ■ Cancer ■ Other

Preclinical

ISIS-HTT _{Rx}	Huntington's Disease
ISIS-BIIB3 _{Rx}	Neurodegenerative Disease
ISIS-BIIB4 _{Rx}	Neurodegenerative Disease
ISIS-RHO-2.5 _{Rx}	Autosomal Dominant Retinitis Pigmentosa
ISIS-GHR-L _{Rx}	Acromegaly
ISIS-AGT-L _{Rx}	Treatment-Resistant Hypertension
ISIS-ANGPTL3-L _{Rx}	Hyperlipidemia
ISIS-APOCIII-L _{Rx}	Severely High TGs
ISIS-TMPRSS6-L _{Rx}	β-Thalassemia
ISIS-DGAT2 _{Rx}	NASH
RG-125	NASH in Patients with Type 2 Diabetes
ISIS-GSK4-L _{Rx}	Ocular Disease
ISIS-GSK6-L _{Rx}	Antiviral

2014: A Year of Broad Success and Enhanced Value

Data Published in the New England Journal of Medicine



The NEW ENGLAND
JOURNAL of MEDICINE

Targeting APOC3 in the Familial Chylomicronemia Syndrome

Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D.,
Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S.,
Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D.,
Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D.,
and Joseph L. Witztum, M.D.

- **First study to demonstrate the key role apoC-III plays as a regulator of LPL-independent pathways of triglyceride TG metabolism**
 - apoC-III levels reduced up to 90%
 - TG levels reduced up to 86%
 - All FCS patients in study achieved TG levels <500 mg/dL with treatment



The NEW ENGLAND
JOURNAL of MEDICINE

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D.,
David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D.,
Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D., for
the FXI-ASO TKA Investigators

- **Seven-fold lower incidence of VTE in patients treated with 300 mg ISIS-FXI_{Rx} compared with enoxaparin-treated patients (4% vs. 30%)**
- **Demonstrates for the first time a clear dissociation between thrombosis and bleeding**

Broad Success and Enhanced Value

Clinical Study Initiations (2014 & 2015)

Drug	Indication	Phase	
ISIS-SMN_{Rx}	Spinal Muscular Atrophy (infants)	3	✓
ISIS-SMN_{Rx}	Spinal Muscular Atrophy (children)	3	✓
Volanesorsen	Familial Chylomicronemia Syndrome	3	✓
Plazomicin	Multi-drug Resistance	3	✓
ISIS-APO(a)_{Rx}	High Lp(a)	2	✓
ISIS-GCCR_{Rx}	Type 2 Diabetes	2	✓
Apatorsen (OGX-427)	Non-small Cell Lung Cancer	2	✓
ISIS-AR-2.5_{Rx} (AZD5312)	Cancer	2	✓
ISIS-DMPK-2.5_{Rx}	Myotonic Dystrophy Type I	1/2	✓
RG-101	Hepatitis C Virus	1/2	✓
ISIS-ANGPTL3_{Rx}	Healthy Volunteers	1	✓
ISIS-PKK_{Rx}	Healthy Volunteers	1	✓
ISIS-APO(a)-L_{Rx}	Healthy Volunteers	1	✓



completed milestone

Broad Success and Enhanced Value

Clinical Data Readouts (2014)

Drug	Indication	Phase
KYNAMRO	One and two-year MACE analysis	✓ 3
Custirsen (OGX-011)	Castration-resistant Prostate Cancer	✗ 3
ISIS-SMN_{Rx}	Spinal Muscular Atrophy (infants)	✓ 2
ISIS-SMN_{Rx}	Spinal Muscular Atrophy (children)	✓ 2
Volanesorsen	High to Severely High Triglycerides (monotherapy)	✓ 2
Volanesorsen	High to Severely High Triglycerides (add on to fibrates)	✓ 2
Volanesorsen	High Triglycerides and Type 2 Diabetes	✓ 2
*Volanesorsen	Familial Chylomicronemia Syndrome	✓ 2
ATL 1103	Acromegaly	✓ 2
†ISIS-FXI_{Rx}	Thrombosis in Total Knee Replacement	✓ 2
ISIS-CRP_{Rx}	Atrial Fibrillation	✓ 2
ISIS-GCGR_{Rx}	Type 2 Diabetes	✓ 2
ISIS-EIF4E_{Rx}	Prostate Cancer, Lung Cancer	✗ 2
ISIS-STAT3-2.5_{Rx} (AZD9150)	Liver Cancer	✓ 2
Apatorsen (OGX-427)	Bladder Cancer	✓ 2
iCo-007	Diabetic Macular Edema	✗ 2
RG-101	Hepatitis B Virus	✓ 1/2
ISIS-APO(a)_{Rx}	Healthy Volunteers	✓ 1

✓ Positive study

✗ Negative study

*Gaudet, D. et al. (2014) *NEJM*. 371, 2200-2206.

† Buller, H. et al. (2014) *NEJM*. published online December 7, 2014.

Broad Success and Enhanced Value

Clinical Data Readouts (2015)

Drug	Indication	Phase
<i>ISIS-TTR_{Rx}</i>	Familial Amyloid Polyneuropathy	✓ OLE
<i>ISIS-SMN_{Rx}</i>	Spinal Muscular Atrophy (infants) update	✓ 2
<i>ISIS-SMN_{Rx}</i>	Spinal Muscular Atrophy (children) update	✓ 2
<i>ISIS-PTP1B_{Rx}</i>	Type 2 Diabetes	✓ 2
<i>ISIS-STAT3-2.5_{Rx}</i>	Lymphoma	✓ 2
<i>ISIS-PKK_{Rx}</i>	Healthy Volunteers	✓ 1
<i>ISIS-ANGPTL3_{Rx}</i>	Healthy Volunteers	✓ 1



Positive study



Negative study

Isis' Business Model



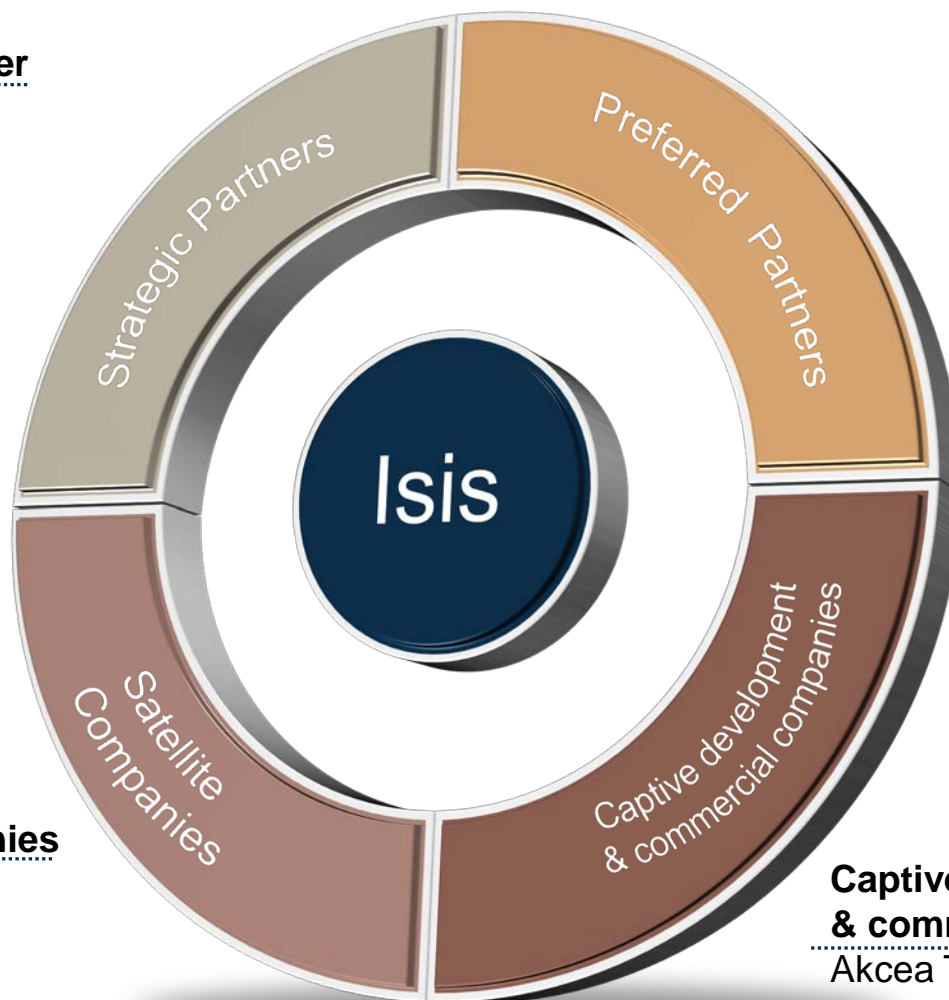
Strategic Partner

Biogen – CNS



Satellite Companies

Regulus
Achaogen
ATL
OncoGenex
Atlantic



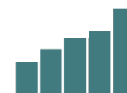
Preferred Partners and Licensee

GSK
AstraZeneca
Roche
Janssen (J&J)
Bayer



Captive development & commercial company

Akcea Therapeutics:
Isis' wholly owned subsidiary



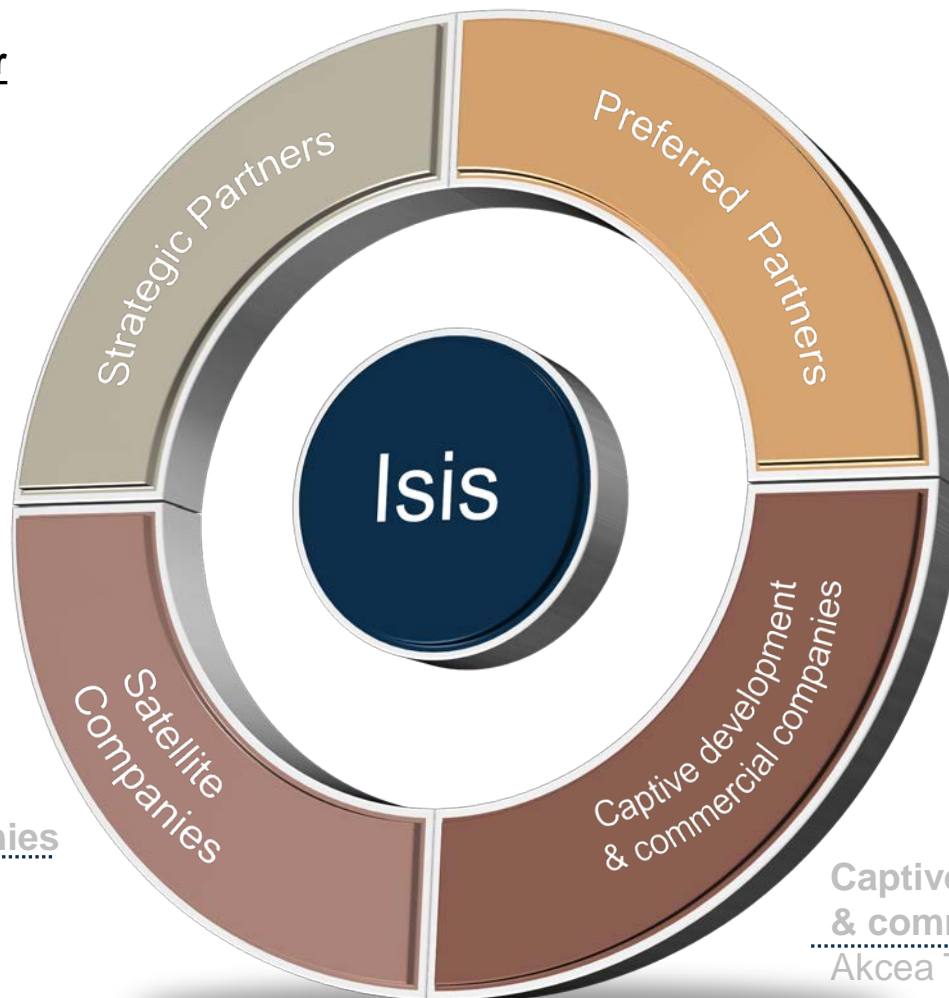
Isis' Business Model



Strategic Partner
Biogen – CNS



Satellite Companies
Regulus
Achaogen
ATL
OncoGenex
Atlantic



**Preferred Partners
and Licensee**

GSK
AstraZeneca
Roche
Janssen (J&J)
Bayer



**Captive development
& commercial company**
Akcea Therapeutics:
Isis' wholly owned subsidiary



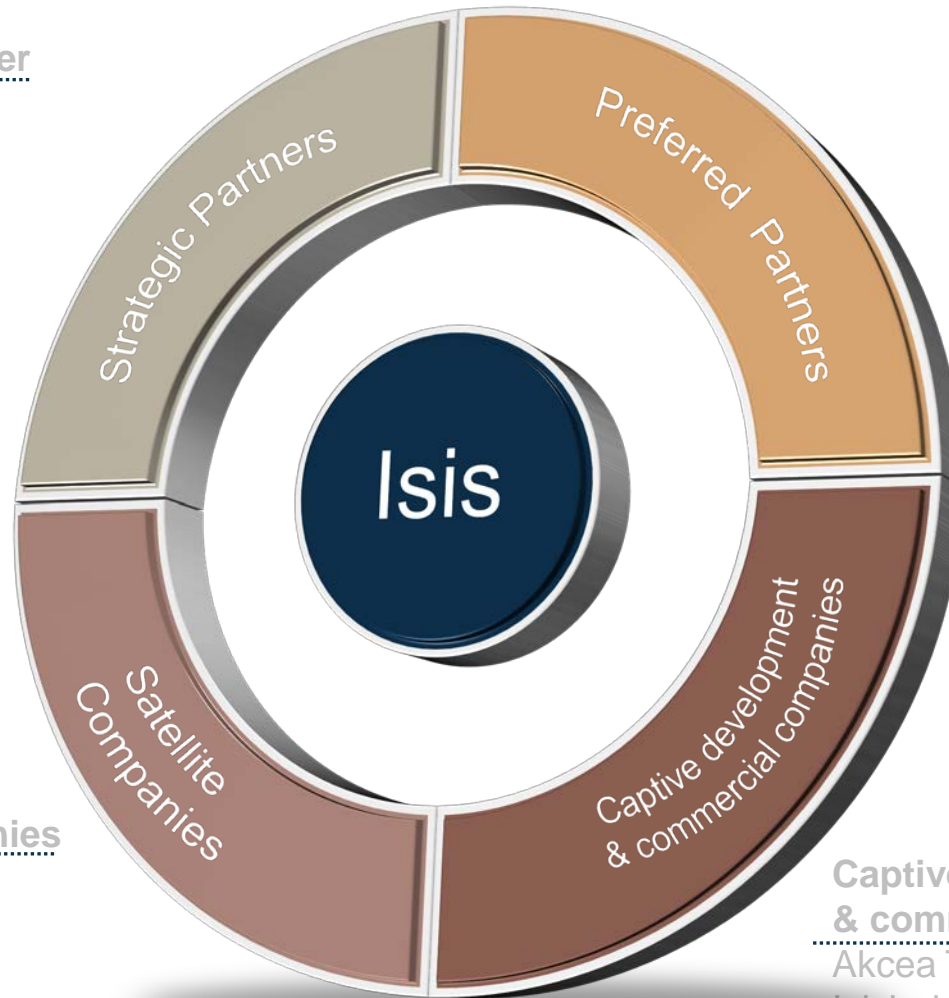
Isis' Business Model



Strategic Partner
Biogen – CNS



Satellite Companies
Regulus
Achaogen
ATL
OncoGenex
Atlantic

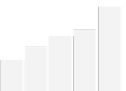


**Preferred Partners
and Licensee**

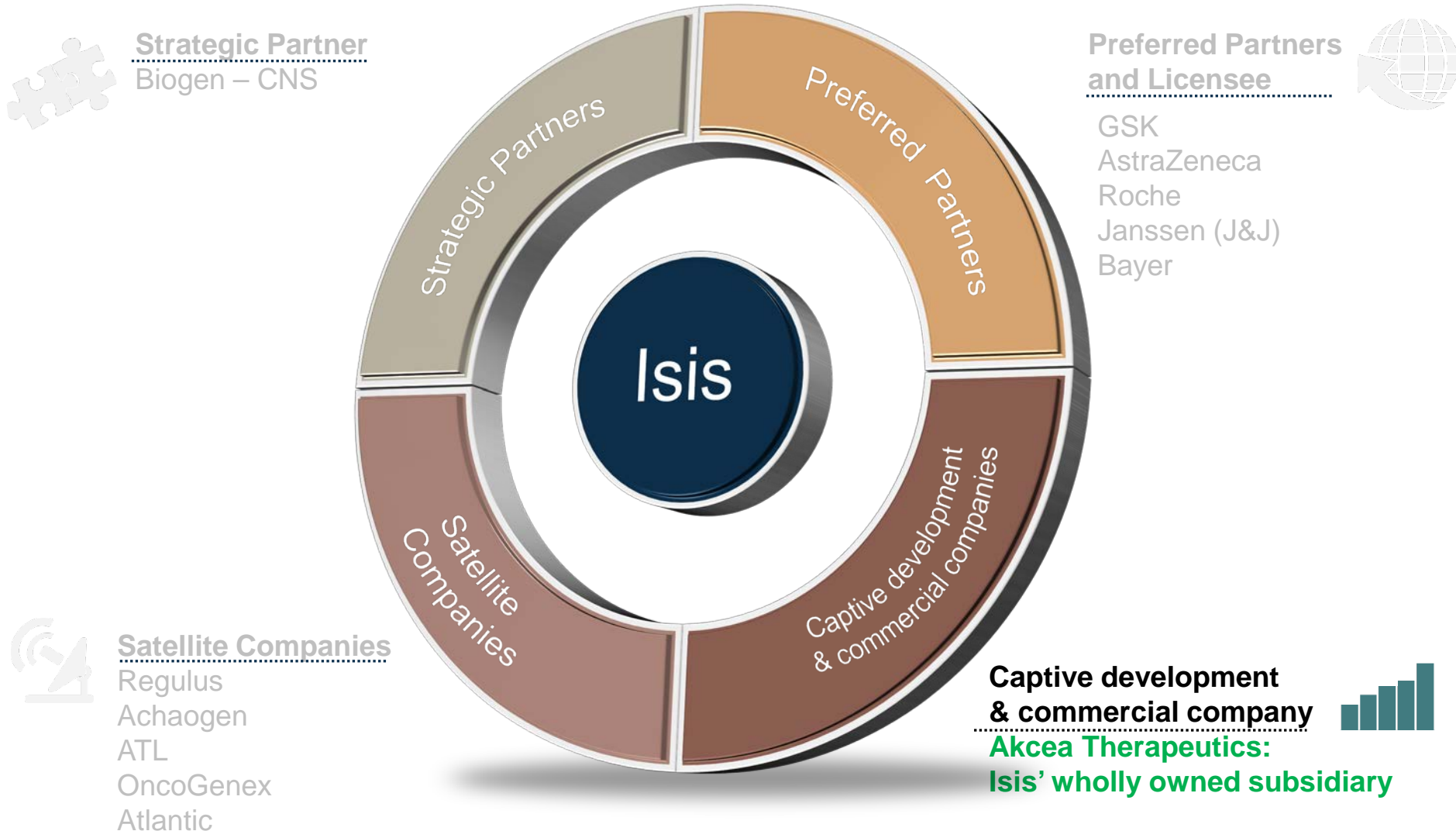
GSK
AstraZeneca
Roche
Janssen (J&J)
Bayer



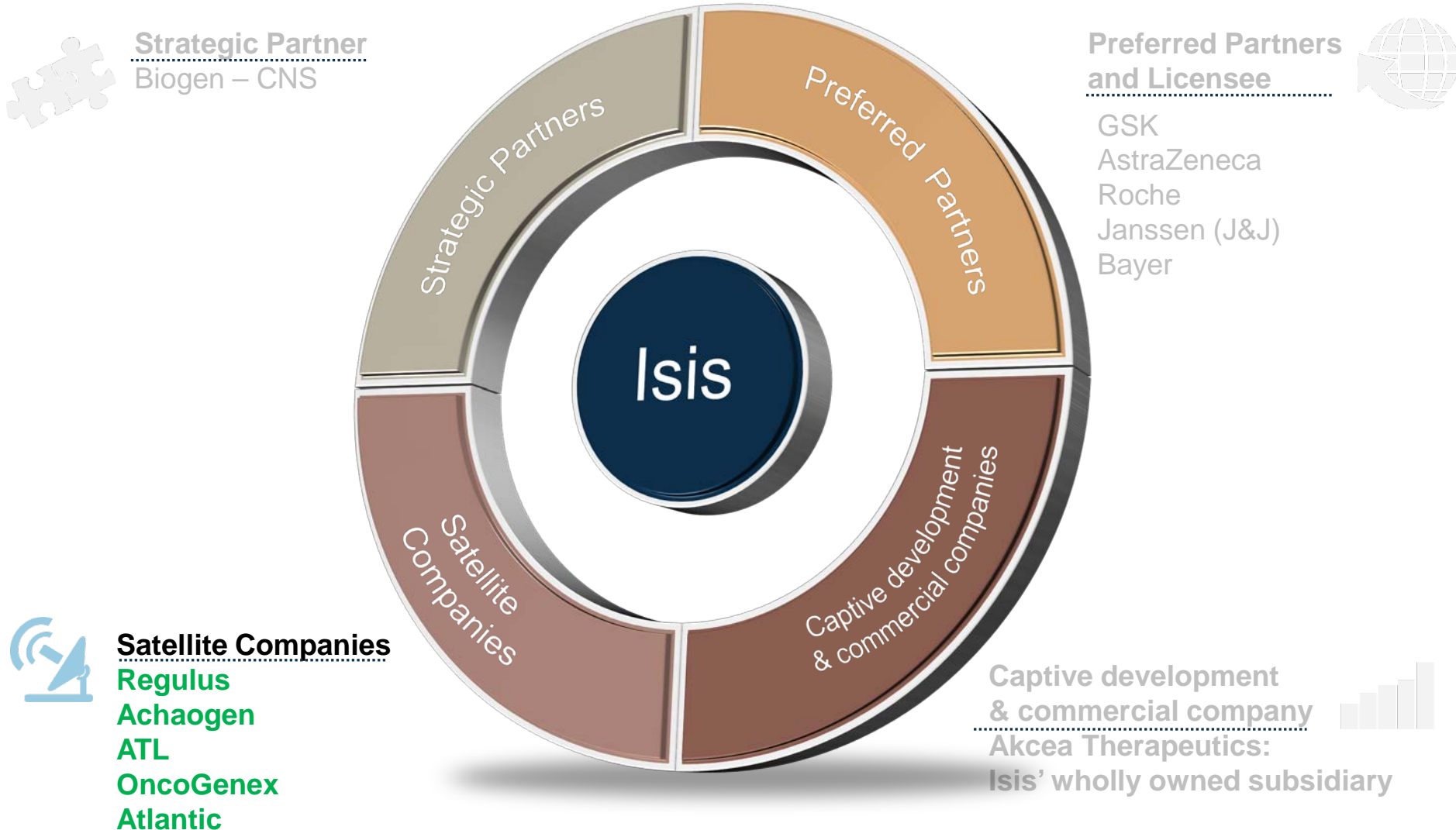
**Captive development
& commercial company**
Akcea Therapeutics:
Isis' wholly owned subsidiary



Isis' Business Model



Isis' Business Model



Broad Success and Enhanced Value

Success of Partnered Programs Support Strong Financial Position

Biogen

- Strategic Partner — CNS
- **>\$330M** received to date



ISIS-SMN _{Rx}	Spinal Muscular Atrophy (Infants)
ISIS-SMN _{Rx}	Spinal Muscular Atrophy (Children)
ISIS-DMPK-2.5 _{Rx}	Myotonic Dystrophy 1
ISIS-BIIB3 _{Rx}	Neurodegenerative Disease
ISIS-BIIB4 _{Rx}	Neurodegenerative Disease

Isis' Pipeline Continues to Grow and Expand

Commercialized		Phase 2 (cont)		Preclinical	
ACTH(1-24) ¹	Hormonal Receptor	IS-1000A ¹	Very high dose	IS-1000 ¹	Hormonal Receptor
Alvimop ¹	"Pharmacokinetic"	IS-1000B ¹	Getting Clinical	IS-1000B ¹	Neuroendocrine Disease
Alvimop ¹	DRB Binding	IS-1000C ¹	Diagnosis	IS-1000C ¹	Neuroendocrine Disease
* Normal Patient Safety					
Phase 3					
IS-1000A ¹	CRB Antagonist	IS-1000D ¹	Diagnosis	IS-1000D ¹	Neuroendocrine Disease
IS-1000B ¹	Spinal Muscular Atrophy	IS-1000E ¹	Diagnosis	IS-1000E ¹	Neuroendocrine Disease
IS-1000C ¹	Spinal Muscular Atrophy	IS-1000F ¹	Diagnosis	IS-1000F ¹	Neuroendocrine Disease
IS-1000D ¹	CRB Antagonist	IS-1000G ¹	Diagnosis	IS-1000G ¹	Neuroendocrine Disease
IS-1000E ¹	CRB Antagonist	IS-1000H ¹	Diagnosis	IS-1000H ¹	Neuroendocrine Disease
IS-1000F ¹	CRB Antagonist	IS-1000I ¹	Diagnosis	IS-1000I ¹	Neuroendocrine Disease
IS-1000G ¹	CRB Antagonist	IS-1000J ¹	Diagnosis	IS-1000J ¹	Neuroendocrine Disease
IS-1000H ¹	CRB Antagonist	IS-1000K ¹	Diagnosis	IS-1000K ¹	Neuroendocrine Disease
IS-1000I ¹	CRB Antagonist	IS-1000L ¹	Diagnosis	IS-1000L ¹	Neuroendocrine Disease
IS-1000J ¹	CRB Antagonist	IS-1000M ¹	Diagnosis	IS-1000M ¹	Neuroendocrine Disease
IS-1000K ¹	CRB Antagonist	IS-1000N ¹	Diagnosis	IS-1000N ¹	Neuroendocrine Disease
IS-1000L ¹	CRB Antagonist	IS-1000O ¹	Diagnosis	IS-1000O ¹	Neuroendocrine Disease
IS-1000M ¹	CRB Antagonist	IS-1000P ¹	Diagnosis	IS-1000P ¹	Neuroendocrine Disease
IS-1000N ¹	CRB Antagonist	IS-1000Q ¹	Diagnosis	IS-1000Q ¹	Neuroendocrine Disease
IS-1000O ¹	CRB Antagonist	IS-1000R ¹	Diagnosis	IS-1000R ¹	Neuroendocrine Disease
IS-1000P ¹	CRB Antagonist	IS-1000S ¹	Diagnosis	IS-1000S ¹	Neuroendocrine Disease
IS-1000Q ¹	CRB Antagonist	IS-1000T ¹	Diagnosis	IS-1000T ¹	Neuroendocrine Disease
IS-1000R ¹	CRB Antagonist	IS-1000U ¹	Diagnosis	IS-1000U ¹	Neuroendocrine Disease
IS-1000S ¹	CRB Antagonist	IS-1000V ¹	Diagnosis	IS-1000V ¹	Neuroendocrine Disease
IS-1000T ¹	CRB Antagonist	IS-1000W ¹	Diagnosis	IS-1000W ¹	Neuroendocrine Disease
IS-1000U ¹	CRB Antagonist	IS-1000X ¹	Diagnosis	IS-1000X ¹	Neuroendocrine Disease
IS-1000V ¹	CRB Antagonist	IS-1000Y ¹	Diagnosis	IS-1000Y ¹	Neuroendocrine Disease
IS-1000W ¹	CRB Antagonist	IS-1000Z ¹	Diagnosis	IS-1000Z ¹	Neuroendocrine Disease
IS-1000X ¹	CRB Antagonist	IS-1000AA ¹	Diagnosis	IS-1000AA ¹	Neuroendocrine Disease
IS-1000Y ¹	CRB Antagonist	IS-1000AB ¹	Diagnosis	IS-1000AB ¹	Neuroendocrine Disease
IS-1000Z ¹	CRB Antagonist	IS-1000AC ¹	Diagnosis	IS-1000AC ¹	Neuroendocrine Disease
IS-1000AA ¹	CRB Antagonist	IS-1000AD ¹	Diagnosis	IS-1000AD ¹	Neuroendocrine Disease
IS-1000AB ¹	CRB Antagonist	IS-1000AE ¹	Diagnosis	IS-1000AE ¹	Neuroendocrine Disease
IS-1000AC ¹	CRB Antagonist	IS-1000AF ¹	Diagnosis	IS-1000AF ¹	Neuroendocrine Disease
IS-1000AD ¹	CRB Antagonist	IS-1000AG ¹	Diagnosis	IS-1000AG ¹	Neuroendocrine Disease
IS-1000AE ¹	CRB Antagonist	IS-1000AH ¹	Diagnosis	IS-1000AH ¹	Neuroendocrine Disease
IS-1000AF ¹	CRB Antagonist	IS-1000AI ¹	Diagnosis	IS-1000AI ¹	Neuroendocrine Disease
IS-1000AG ¹	CRB Antagonist	IS-1000AJ ¹	Diagnosis	IS-1000AJ ¹	Neuroendocrine Disease
IS-1000AH ¹	CRB Antagonist	IS-1000AK ¹	Diagnosis	IS-1000AK ¹	Neuroendocrine Disease
IS-1000AI ¹	CRB Antagonist	IS-1000AL ¹	Diagnosis	IS-1000AL ¹	Neuroendocrine Disease
IS-1000AJ ¹	CRB Antagonist	IS-1000AM ¹	Diagnosis	IS-1000AM ¹	Neuroendocrine Disease
IS-1000AK ¹	CRB Antagonist	IS-1000AN ¹	Diagnosis	IS-1000AN ¹	Neuroendocrine Disease
IS-1000AL ¹	CRB Antagonist	IS-1000AO ¹	Diagnosis	IS-1000AO ¹	Neuroendocrine Disease
IS-1000AM ¹	CRB Antagonist	IS-1000AP ¹	Diagnosis	IS-1000AP ¹	Neuroendocrine Disease
IS-1000AN ¹	CRB Antagonist	IS-1000AQ ¹	Diagnosis	IS-1000AQ ¹	Neuroendocrine Disease
IS-1000AO ¹	CRB Antagonist	IS-1000AR ¹	Diagnosis	IS-1000AR ¹	Neuroendocrine Disease
IS-1000AP ¹	CRB Antagonist	IS-1000AS ¹	Diagnosis	IS-1000AS ¹	Neuroendocrine Disease
IS-1000AQ ¹	CRB Antagonist	IS-1000AT ¹	Diagnosis	IS-1000AT ¹	Neuroendocrine Disease
IS-1000AR ¹	CRB Antagonist	IS-1000AU ¹	Diagnosis	IS-1000AU ¹	Neuroendocrine Disease
IS-1000AS ¹	CRB Antagonist	IS-1000AV ¹	Diagnosis	IS-1000AV ¹	Neuroendocrine Disease
IS-1000AT ¹	CRB Antagonist	IS-1000AW ¹	Diagnosis	IS-1000AW ¹	Neuroendocrine Disease
IS-1000AU ¹	CRB Antagonist	IS-1000AX ¹	Diagnosis	IS-1000AX ¹	Neuroendocrine Disease
IS-1000AV ¹	CRB Antagonist	IS-1000AY ¹	Diagnosis	IS-1000AY ¹	Neuroendocrine Disease
IS-1000AW ¹	CRB Antagonist	IS-1000AZ ¹	Diagnosis	IS-1000AZ ¹	Neuroendocrine Disease
IS-1000AX ¹	CRB Antagonist	IS-1000BA ¹	Diagnosis	IS-1000BA ¹	Neuroendocrine Disease
IS-1000AY ¹	CRB Antagonist	IS-1000BB ¹	Diagnosis	IS-1000BB ¹	Neuroendocrine Disease
IS-1000AZ ¹	CRB Antagonist	IS-1000BC ¹	Diagnosis	IS-1000BC ¹	Neuroendocrine Disease
IS-1000BA ¹	CRB Antagonist	IS-1000BD ¹	Diagnosis	IS-1000BD ¹	Neuroendocrine Disease
IS-1000BB ¹	CRB Antagonist	IS-1000BE ¹	Diagnosis	IS-1000BE ¹	Neuroendocrine Disease
IS-1000BC ¹	CRB Antagonist	IS-1000BF ¹	Diagnosis	IS-1000BF ¹	Neuroendocrine Disease
IS-1000BD ¹	CRB Antagonist	IS-1000BG ¹	Diagnosis	IS-1000BG ¹	Neuroendocrine Disease
IS-1000BE ¹	CRB Antagonist	IS-1000BH ¹	Diagnosis	IS-1000BH ¹	Neuroendocrine Disease
IS-1000BF ¹	CRB Antagonist	IS-1000BI ¹	Diagnosis	IS-1000BI ¹	Neuroendocrine Disease
IS-1000BG ¹	CRB Antagonist	IS-1000BJ ¹	Diagnosis	IS-1000BJ ¹	Neuroendocrine Disease
IS-1000BH ¹	CRB Antagonist	IS-1000BK ¹	Diagnosis	IS-1000BK ¹	Neuroendocrine Disease
IS-1000BI ¹	CRB Antagonist	IS-1000BL ¹	Diagnosis	IS-1000BL ¹	Neuroendocrine Disease
IS-1000BJ ¹	CRB Antagonist	IS-1000BM ¹	Diagnosis	IS-1000BM ¹	Neuroendocrine Disease
IS-1000BK ¹	CRB Antagonist	IS-1000BN ¹	Diagnosis	IS-1000BN ¹	Neuroendocrine Disease
IS-1000BL ¹	CRB Antagonist	IS-1000BO ¹	Diagnosis	IS-1000BO ¹	Neuroendocrine Disease
IS-1000BM ¹	CRB Antagonist	IS-1000BP ¹	Diagnosis	IS-1000BP ¹	Neuroendocrine Disease
IS-1000BN ¹	CRB Antagonist	IS-1000BQ ¹	Diagnosis	IS-1000BQ ¹	Neuroendocrine Disease
IS-1000BO ¹	CRB Antagonist	IS-1000BR ¹	Diagnosis	IS-1000BR ¹	Neuroendocrine Disease
IS-1000BP ¹	CRB Antagonist	IS-1000BS ¹	Diagnosis	IS-1000BS ¹	Neuroendocrine Disease
IS-1000BQ ¹	CRB Antagonist	IS-1000BT ¹	Diagnosis	IS-1000BT ¹	Neuroendocrine Disease
IS-1000BR ¹	CRB Antagonist	IS-1000BU ¹	Diagnosis	IS-1000BU ¹	Neuroendocrine Disease
IS-1000BS ¹	CRB Antagonist	IS-1000BV ¹	Diagnosis	IS-1000BV ¹	Neuroendocrine Disease
IS-1000BT ¹	CRB Antagonist	IS-1000BW ¹	Diagnosis	IS-1000BW ¹	Neuroendocrine Disease
IS-1000BU ¹	CRB Antagonist	IS-1000BX ¹	Diagnosis	IS-1000BX ¹	Neuroendocrine Disease
IS-1000BV ¹	CRB Antagonist	IS-1000BY ¹	Diagnosis	IS-1000BY ¹	Neuroendocrine Disease
IS-1000BW ¹	CRB Antagonist	IS-1000BZ ¹	Diagnosis	IS-1000BZ ¹	Neuroendocrine Disease
IS-1000BX ¹	CRB Antagonist	IS-1000CA ¹	Diagnosis	IS-1000CA ¹	Neuroendocrine Disease
IS-1000BY ¹	CRB Antagonist	IS-1000CB ¹	Diagnosis	IS-1000CB ¹	Neuroendocrine Disease
IS-1000BZ ¹	CRB Antagonist	IS-1000CC ¹	Diagnosis	IS-1000CC ¹	Neuroendocrine Disease
IS-1000CA ¹	CRB Antagonist	IS-1000CD ¹	Diagnosis	IS-1000CD ¹	Neuroendocrine Disease
IS-1000CB ¹	CRB Antagonist	IS-1000CE ¹	Diagnosis	IS-1000CE ¹	Neuroendocrine Disease
IS-1000CC ¹	CRB Antagonist	IS-1000CF ¹	Diagnosis	IS-1000CF ¹	Neuroendocrine Disease
IS-1000CD ¹	CRB Antagonist	IS-1000CG ¹	Diagnosis	IS-1000CG ¹	Neuroendocrine Disease
IS-1000CE ¹	CRB Antagonist	IS-1000CH ¹	Diagnosis	IS-1000CH ¹	Neuroendocrine Disease
IS-1000CF ¹	CRB Antagonist	IS-1000CI ¹	Diagnosis	IS-1000CI ¹	Neuroendocrine Disease
IS-1000CG ¹	CRB Antagonist	IS-1000CJ ¹	Diagnosis	IS-1000CJ ¹	Neuroendocrine Disease
IS-1000CH ¹	CRB Antagonist	IS-1000CK ¹	Diagnosis	IS-1000CK ¹	Neuroendocrine Disease
IS-1000CI ¹	CRB Antagonist	IS-1000CL ¹	Diagnosis	IS-1000CL ¹	Neuroendocrine Disease
IS-1000CJ ¹	CRB Antagonist	IS-1000CM ¹	Diagnosis	IS-1000CM ¹	Neuroendocrine Disease
IS-1000CK ¹	CRB Antagonist	IS-1000CN ¹	Diagnosis	IS-1000CN ¹	Neuroendocrine Disease
IS-1000CL ¹	CRB Antagonist	IS-1000CO ¹	Diagnosis	IS-1000CO ¹	Neuroendocrine Disease
IS-1000CM ¹	CRB Antagonist	IS-1000CP ¹	Diagnosis	IS-1000CP ¹	Neuroendocrine Disease
IS-1000CN ¹	CRB Antagonist	IS-1000CQ ¹	Diagnosis	IS-1000CQ ¹	Neuroendocrine Disease
IS-1000CO ¹	CRB Antagonist	IS-1000CR ¹	Diagnosis	IS-1000CR ¹	Neuroendocrine Disease
IS-1000CP ¹	CRB Antagonist	IS-1000CS ¹	Diagnosis	IS-1000CS ¹	Neuroendocrine Disease
IS-1000CQ ¹	CRB Antagonist	IS-1000CT ¹	Diagnosis	IS-1000CT ¹	Neuroendocrine Disease
IS-1000CR ¹	CRB Antagonist	IS-1000CU ¹	Diagnosis	IS-1000CU ¹	Neuroendocrine Disease
IS-1000CS ¹	CRB Antagonist	IS-1000CV ¹	Diagnosis	IS-1000CV ¹	Neuroendocrine Disease
IS-1000CT ¹	CRB Antagonist	IS-1000CW ¹	Diagnosis	IS-1000CW ¹	Neuroendocrine Disease
IS-1000CU ¹	CRB Antagonist	IS-1000CX ¹	Diagnosis	IS-1000CX ¹	Neuroendocrine Disease
IS-1000CV ¹	CRB Antagonist	IS-1000CY ¹	Diagnosis	IS-1000CY ¹	Neuroendocrine Disease
IS-1000CW ¹	CRB Antagonist	IS-1000CZ ¹	Diagnosis	IS-1000CZ ¹	Neuroendocrine Disease
IS-1000CX ¹	CRB Antagonist	IS-1000DA ¹	Diagnosis	IS-1000DA ¹	Neuroendocrine Disease
IS-1000CY ¹	CRB Antagonist	IS-1000DB ¹	Diagnosis	IS-1000DB ¹	Neuroendocrine Disease
IS-1000CZ ¹	CRB Antagonist	IS-1000DC ¹	Diagnosis	IS-1000DC ¹	Neuroendocrine Disease
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IS-1000DB ¹	CRB Antagonist	IS-1000DE ¹	Diagnosis	IS-1000DE ¹	Neuroendocrine Disease
IS-1000DC ¹	CRB Antagonist	IS-1000DF ¹	Diagnosis	IS-1000DF ¹	Neuroendocrine Disease
IS-1000DD ¹	CRB Antagonist	IS-1000DG ¹	Diagnosis	IS-1000DG ¹	Neuroendocrine Disease
IS-1000DE ¹	CRB Antagonist	IS-1000DH ¹	Diagnosis	IS-1000DH ¹	Neuroendocrine Disease
IS-1000DF ¹	CRB Antagonist	IS-1000DI ¹	Diagnosis	IS-1000DI ¹	Neuroendocrine Disease
IS-1000DG ¹	CRB Antagonist	IS-1000DJ ¹	Diagnosis	IS-1000DJ ¹	Neuroendocrine Disease
IS-1000DH ¹	CRB Antagonist	IS-1000DK ¹	Diagnosis	IS-1000DK ¹	Neuroendocrine Disease
IS-1000DI ¹	CRB Antagonist	IS-1000DL ¹	Diagnosis	IS-1000DL ¹	Neuroendocrine Disease
IS-1000DJ ¹	CRB Antagonist	IS-1000DM ¹	Diagnosis	IS-1000DM ¹	Neuroendocrine Disease
IS-1000DK ¹	CRB Antagonist	IS-1000DN ¹	Diagnosis	IS-1000DN ¹	Neuroendocrine Disease
IS-1000DL ¹	CRB Antagonist	IS-1000DO ¹	Diagnosis	IS-1000DO ¹	Neuroendocrine Disease
IS-1000DM ¹	CRB Antagonist	IS-1000DP ¹	Diagnosis	IS-1000DP ¹	Neuroendocrine Disease
IS-1000DN ¹	CRB Antagonist	IS-1000DQ ¹	Diagnosis	IS-1000DQ ¹	Neuroendocrine Disease
IS-1000DO ¹	CRB Antagonist	IS-1000DR ¹	Diagnosis	IS-1000DR ¹	Neuroendocrine Disease
IS-1000DP ¹	CRB Antagonist	IS-1000DS ¹	Diagnosis	IS-1000DS ¹	Neuroendocrine Disease
IS-1000DQ ¹	CRB Antagonist	IS-1000DT ¹	Diagnosis	IS-1000DT ¹	Neuroendocrine Disease
IS-1000DR ¹	CRB Antagonist	IS-1000DU ¹	Diagnosis	IS-1000DU ¹	Neuroendocrine Disease
IS-1000DS ¹	CRB Antagonist	IS-1000DV ¹	Diagnosis	IS-1000DV ¹	Neuroendocrine Disease
IS-1000DT ¹	CRB Antagonist	IS-1000DW ¹	Diagnosis	IS-1000DW ¹	Neuroendocrine Disease
IS-1000DU ¹	CRB Antagonist	IS-1000DX ¹	Diagnosis	IS-1000DX ¹	Neuroendocrine Disease
IS-1000DV ¹	CRB Antagonist	IS-1000DY ¹	Diagnosis	IS-1000DY ¹	Neuroendocrine Disease
IS-1000DW ¹	CRB Antagonist	IS-1000DZ ¹	Diagnosis	IS-1000DZ ¹	Neuroendocrine Disease
IS-1000DX ¹	CRB Antagonist	IS-1000EA ¹	Diagnosis	IS-1000EA ¹	Neuroendocrine Disease
IS-1000DY ¹	CRB Antagonist	IS-1000EB ¹	Diagnosis	IS-1000EB ¹	Neuroendocrine Disease
IS-1000DZ ¹	CRB Antagonist	IS-1000EC ¹	Diagnosis	IS-1000EC ¹	Neuroendocrine Disease
IS-1000EA ¹	CRB Antagonist	IS-1000ED ¹	Diagnosis	IS-1000ED ¹	Neuroendocrine Disease
IS-1000EB ¹	CRB Antagonist	IS-1000EE ¹	Diagnosis	IS-1000EE ¹	Neuroendocrine Disease
IS-1000EC ¹	CRB Antagonist	IS-1000EF ¹	Diagnosis	IS-1000EF ¹	Neuroendocrine Disease
IS-1000ED ¹	CRB Antagonist	IS-1000EG ¹	Diagnosis	IS-1000EG ¹	Neuroendocrine Disease
IS-1000EE ¹	CRB Antagonist	IS-1000EH ¹	Diagnosis	IS-1000EH ¹	Neuroendocrine Disease
IS-1000EF ¹	CRB Antagonist	IS-1000EI ¹	Diagnosis	IS-1000EI ¹	Neuroendocrine Disease
IS-1000EG ¹	CRB Antagonist	IS-1000EJ ¹	Diagnosis	IS-1000EJ ¹	Neuroendocrine Disease
IS-1000EH ¹	CRB Antagonist	IS-1000EK ¹	Diagnosis	IS-1000EK ¹	Neuroendocrine Disease
IS-1000EI ¹	CRB Antagonist	IS-1000EL ¹	Diagnosis	IS-1000EL ¹	Neuroendocrine Disease
IS-1000EJ ¹	CRB Antagonist	IS-1000EM ¹	Diagnosis	IS-1000EM ¹	Neuroendocrine Disease
IS-1000EK ¹	CRB Antagonist	IS-1000EN ¹	Diagnosis	IS-1000EN ¹	Neuroendocrine Disease
IS-1000EL ¹	CRB Antagonist	IS-1000EO ¹	Diagnosis	IS-10	

Broad Success and Enhanced Value

Success of Partnered Programs Support Strong Financial Position

GlaxoSmithKline

- Preferred Partner — Rare, infectious and ocular diseases
- **>\$135M** received to date



ISIS-TTR _{Rx}	TTR Amyloidosis
ISIS-HBV _{Rx}	HBV
ISIS-RHO-2.5 _{Rx}	Autosomal Dominant Retinitis Pigmentosa
ISIS-GSK4-L _{Rx}	Ocular Disease
ISIS-GSK6-L _{Rx}	Antiviral

Isis' Pipeline Continues to Grow and Expand

Commercialized	Phase 2 (cont.)	Preclinical
Commercialized SYMBIOSE Allogene Viquan® * Novel Patient Supply	Phase 2 (cont.) ISIS-AP001 _L Very High Lipid ISIS-F1 _L Cystic Disease ISIS-OC01 _L Diabetes ISIS-OC02 _L Diabetes ISIS-PT01 _L Cancer Autotem ISIS-AT01 _L Cancer ISIS-STAT02 _L Cancer ISIS-AR-2 _L Cancer ISIS-021 (P042371) Scurvy ATL1102 Multiple Sclerosis RD-101 HCL	Preclinical ISIS-TTR _L Huntington's Disease ISIS-018 _L Neurodegenerative Disease ISIS-018 _L Neurodegenerative Disease ISIS-RHO-2.5 _L Autosomal Dominant Retinitis Pigmentosa ISIS-GSK4 _L Ocular Disease ISIS-AT01 _L Treatment-Resistant Hypertension ISIS-ANGPT2 _L Hypertension ISIS-AP001 _L Severely High Trig ISIS-TUP001 _L 2-Thalassemia ISIS-00AT _L NASH ISIS-GSK4 _L Ocular Disease ISIS-GSK6 _L Antiviral
Phase 3	Phase 1	
Phase 3 ISIS-TTR _L TTR Amyloidosis ISIS-BAN _L Spinal Muscular Atrophy ISIS-BAN _L Spinal Muscular Atrophy Volanesoren PCP Volanesoren Fanconi Renal Transplantation KYNAREO® Prostate / Lung Cancer Culexan (GSK011) Severe Bacterial Infection Plapociclovir	Phase 1 ISIS-OC01 _L Cystic Fibrosis ISIS-012 Hepatitis Angioma ISIS-ANGPT2 _L NASH Syndrome ISIS-ANGPT2 _L Hypertension ISIS-AP001 _L Very High Lipid ISIS-F1 _L Cystic Fibrosis ISIS-HBV _L HBV	
Phase 2		
Phase 2 ATL1102 Acromegaly ISIS-OMP02 _L Myotonic Dystrophy 1		

Broad Success and Enhanced Value

Success of Partnered Programs Support Strong Financial Position

AstraZeneca

- Preferred Partner — Cancer
- **>\$70M** received to date



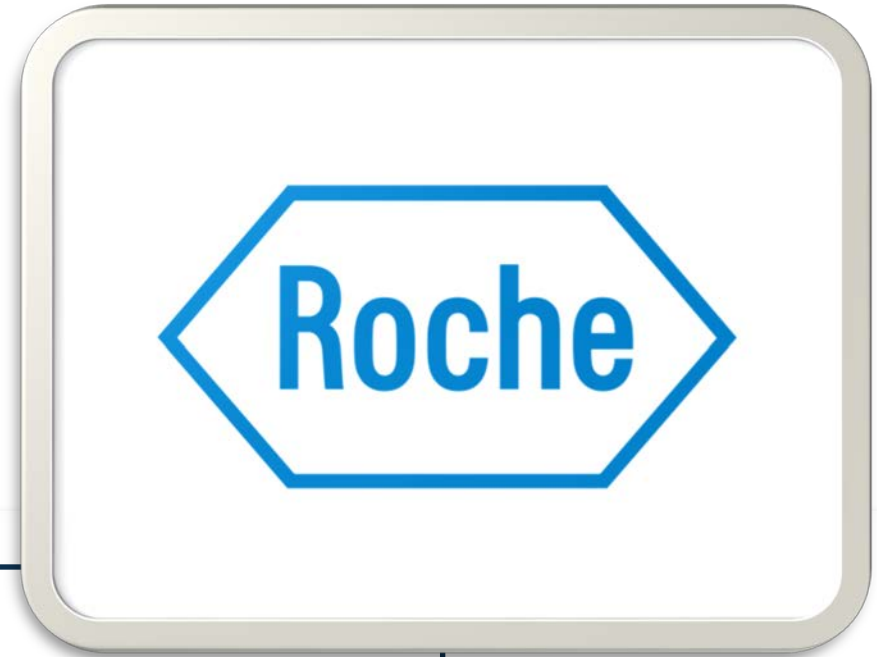
ISIS-STAT3-2.5 _{Rx} (AZD9150)	Cancer
ISIS-AR-2.5 _{Rx} (AZD5312)	Cancer

Isis' Pipeline Continues to Grow and Expand

Commercialized	Phase 2 (cont.)	Preclinical
KYNARON Indication: *Pneumonia Volanesoren <small>* Serum Patient Supply</small>	ISIS-APOLN ₁ ISIS-ATN ₁ ISIS-OCOL ₁ ISIS-OCOL ₂ ISIS-PTPIS ₁ Atalapha ISIS-AR ₁	ISIS-HTT ₁ ISIS-BIS ₁ ISIS-BIS ₂ ISIS-PHO ₁ ISIS-PHO ₂ ISIS-ADT ₁ ISIS-ADT ₂ ISIS-ANGPT1 ₁ ISIS-ANGPT1 ₂ ISIS-ANGPT1 ₃ ISIS-ANGPT1 ₄ ISIS-ANGPT1 ₅ ISIS-ANGPT1 ₆ ISIS-ANGPT1 ₇ ISIS-ANGPT1 ₈ ISIS-ANGPT1 ₉ ISIS-ANGPT1 ₁₀ ISIS-ANGPT1 ₁₁ ISIS-ANGPT1 ₁₂ ISIS-ANGPT1 ₁₃ ISIS-ANGPT1 ₁₄ ISIS-ANGPT1 ₁₅ ISIS-ANGPT1 ₁₆ ISIS-ANGPT1 ₁₇ ISIS-ANGPT1 ₁₈ ISIS-ANGPT1 ₁₉ ISIS-ANGPT1 ₂₀ ISIS-ANGPT1 ₂₁ ISIS-ANGPT1 ₂₂ ISIS-ANGPT1 ₂₃ ISIS-ANGPT1 ₂₄ ISIS-ANGPT1 ₂₅ ISIS-ANGPT1 ₂₆ ISIS-ANGPT1 ₂₇ ISIS-ANGPT1 ₂₈ ISIS-ANGPT1 ₂₉ ISIS-ANGPT1 ₃₀ ISIS-ANGPT1 ₃₁ ISIS-ANGPT1 ₃₂ ISIS-ANGPT1 ₃₃ ISIS-ANGPT1 ₃₄ ISIS-ANGPT1 ₃₅ ISIS-ANGPT1 ₃₆ ISIS-ANGPT1 ₃₇ ISIS-ANGPT1 ₃₈ ISIS-ANGPT1 ₃₉ ISIS-ANGPT1 ₄₀ ISIS-ANGPT1 ₄₁ ISIS-ANGPT1 ₄₂ ISIS-ANGPT1 ₄₃ ISIS-ANGPT1 ₄₄ ISIS-ANGPT1 ₄₅ ISIS-ANGPT1 ₄₆ ISIS-ANGPT1 ₄₇ ISIS-ANGPT1 ₄₈ ISIS-ANGPT1 ₄₉ ISIS-ANGPT1 ₅₀ ISIS-ANGPT1 ₅₁ ISIS-ANGPT1 ₅₂ ISIS-ANGPT1 ₅₃ ISIS-ANGPT1 ₅₄ ISIS-ANGPT1 ₅₅ ISIS-ANGPT1 ₅₆ ISIS-ANGPT1 ₅₇ ISIS-ANGPT1 ₅₈ ISIS-ANGPT1 ₅₉ ISIS-ANGPT1 ₆₀ ISIS-ANGPT1 ₆₁ ISIS-ANGPT1 ₆₂ ISIS-ANGPT1 ₆₃ ISIS-ANGPT1 ₆₄ ISIS-ANGPT1 ₆₅ ISIS-ANGPT1 ₆₆ ISIS-ANGPT1 ₆₇ ISIS-ANGPT1 ₆₈ ISIS-ANGPT1 ₆₉ ISIS-ANGPT1 ₇₀ ISIS-ANGPT1 ₇₁ ISIS-ANGPT1 ₇₂ ISIS-ANGPT1 ₇₃ ISIS-ANGPT1 ₇₄ ISIS-ANGPT1 ₇₅ ISIS-ANGPT1 ₇₆ ISIS-ANGPT1 ₇₇ ISIS-ANGPT1 ₇₈ ISIS-ANGPT1 ₇₉ ISIS-ANGPT1 ₈₀ ISIS-ANGPT1 ₈₁ ISIS-ANGPT1 ₈₂ ISIS-ANGPT1 ₈₃ ISIS-ANGPT1 ₈₄ ISIS-ANGPT1 ₈₅ ISIS-ANGPT1 ₈₆ ISIS-ANGPT1 ₈₇ ISIS-ANGPT1 ₈₈ ISIS-ANGPT1 ₈₉ ISIS-ANGPT1 ₉₀ ISIS-ANGPT1 ₉₁ ISIS-ANGPT1 ₉₂ ISIS-ANGPT1 ₉₃ ISIS-ANGPT1 ₉₄ ISIS-ANGPT1 ₉₅ ISIS-ANGPT1 ₉₆ ISIS-ANGPT1 ₉₇ ISIS-ANGPT1 ₉₈ ISIS-ANGPT1 ₉₉ ISIS-ANGPT1 ₁₀₀
Phase 3 ISIS-TTN ₁ ISIS-BIS ₁ ISIS-BIS ₂ ISIS-BIS ₃ ISIS-BIS ₄ ISIS-BIS ₅ ISIS-BIS ₆ ISIS-BIS ₇ ISIS-BIS ₈ ISIS-BIS ₉ ISIS-BIS ₁₀ ISIS-BIS ₁₁ ISIS-BIS ₁₂ ISIS-BIS ₁₃ ISIS-BIS ₁₄ ISIS-BIS ₁₅ ISIS-BIS ₁₆ ISIS-BIS ₁₇ ISIS-BIS ₁₈ ISIS-BIS ₁₉ ISIS-BIS ₂₀ ISIS-BIS ₂₁ ISIS-BIS ₂₂ ISIS-BIS ₂₃ ISIS-BIS ₂₄ ISIS-BIS ₂₅ ISIS-BIS ₂₆ ISIS-BIS ₂₇ ISIS-BIS ₂₈ ISIS-BIS ₂₉ ISIS-BIS ₃₀ ISIS-BIS ₃₁ ISIS-BIS ₃₂ ISIS-BIS ₃₃ ISIS-BIS ₃₄ ISIS-BIS ₃₅ ISIS-BIS ₃₆ ISIS-BIS ₃₇ ISIS-BIS ₃₈ ISIS-BIS ₃₉ ISIS-BIS ₄₀ ISIS-BIS ₄₁ ISIS-BIS ₄₂ ISIS-BIS ₄₃ ISIS-BIS ₄₄ ISIS-BIS ₄₅ ISIS-BIS ₄₆ ISIS-BIS ₄₇ ISIS-BIS ₄₈ ISIS-BIS ₄₉ ISIS-BIS ₅₀ ISIS-BIS ₅₁ ISIS-BIS ₅₂ ISIS-BIS ₅₃ ISIS-BIS ₅₄ ISIS-BIS ₅₅ ISIS-BIS ₅₆ ISIS-BIS ₅₇ ISIS-BIS ₅₈ ISIS-BIS ₅₉ ISIS-BIS ₆₀ ISIS-BIS ₆₁ ISIS-BIS ₆₂ ISIS-BIS ₆₃ ISIS-BIS ₆₄ ISIS-BIS ₆₅ ISIS-BIS ₆₆ ISIS-BIS ₆₇ ISIS-BIS ₆₈ ISIS-BIS ₆₉ ISIS-BIS ₇₀ ISIS-BIS ₇₁ ISIS-BIS ₇₂ ISIS-BIS ₇₃ ISIS-BIS ₇₄ ISIS-BIS ₇₅ ISIS-BIS ₇₆ ISIS-BIS ₇₇ ISIS-BIS ₇₈ ISIS-BIS ₇₉ ISIS-BIS ₈₀ ISIS-BIS ₈₁ ISIS-BIS ₈₂ ISIS-BIS ₈₃ ISIS-BIS ₈₄ ISIS-BIS ₈₅ ISIS-BIS ₈₆ ISIS-BIS ₈₇ ISIS-BIS ₈₈ ISIS-BIS ₈₉ ISIS-BIS ₉₀ ISIS-BIS ₉₁ ISIS-BIS ₉₂ ISIS-BIS ₉₃ ISIS-BIS ₉₄ ISIS-BIS ₉₅ ISIS-BIS ₉₆ ISIS-BIS ₉₇ ISIS-BIS ₉₈ ISIS-BIS ₉₉ ISIS-BIS ₁₀₀	Phase 1 ISIS-OCOL ₁ ISIS-OCOL ₂ ISIS-OCOL ₃ ISIS-OCOL ₄ ISIS-OCOL ₅ ISIS-OCOL ₆ ISIS-OCOL ₇ ISIS-OCOL ₈ ISIS-OCOL ₉ ISIS-OCOL ₁₀ ISIS-OCOL ₁₁ ISIS-OCOL ₁₂ ISIS-OCOL ₁₃ ISIS-OCOL ₁₄ ISIS-OCOL ₁₅ ISIS-OCOL ₁₆ ISIS-OCOL ₁₇ ISIS-OCOL ₁₈ ISIS-OCOL ₁₉ ISIS-OCOL ₂₀ ISIS-OCOL ₂₁ ISIS-OCOL ₂₂ ISIS-OCOL ₂₃ ISIS-OCOL ₂₄ ISIS-OCOL ₂₅ ISIS-OCOL ₂₆ ISIS-OCOL ₂₇ ISIS-OCOL ₂₈ ISIS-OCOL ₂₉ ISIS-OCOL ₃₀ ISIS-OCOL ₃₁ ISIS-OCOL ₃₂ ISIS-OCOL ₃₃ ISIS-OCOL ₃₄ ISIS-OCOL ₃₅ ISIS-OCOL ₃₆ ISIS-OCOL ₃₇ ISIS-OCOL ₃₈ ISIS-OCOL ₃₉ ISIS-OCOL ₄₀ ISIS-OCOL ₄₁ ISIS-OCOL ₄₂ ISIS-OCOL ₄₃ ISIS-OCOL ₄₄ ISIS-OCOL ₄₅ ISIS-OCOL ₄₆ ISIS-OCOL ₄₇ ISIS-OCOL ₄₈ ISIS-OCOL ₄₉ ISIS-OCOL ₅₀ ISIS-OCOL ₅₁ ISIS-OCOL ₅₂ ISIS-OCOL ₅₃ ISIS-OCOL ₅₄ ISIS-OCOL ₅₅ ISIS-OCOL ₅₆ ISIS-OCOL ₅₇ ISIS-OCOL ₅₈ ISIS-OCOL ₅₉ ISIS-OCOL ₆₀ ISIS-OCOL ₆₁ ISIS-OCOL ₆₂ ISIS-OCOL ₆₃ ISIS-OCOL ₆₄ ISIS-OCOL ₆₅ ISIS-OCOL ₆₆ ISIS-OCOL ₆₇ ISIS-OCOL ₆₈ ISIS-OCOL ₆₉ ISIS-OCOL ₇₀ ISIS-OCOL ₇₁ ISIS-OCOL ₇₂ ISIS-OCOL ₇₃ ISIS-OCOL ₇₄ ISIS-OCOL ₇₅ ISIS-OCOL ₇₆ ISIS-OCOL ₇₇ ISIS-OCOL ₇₈ ISIS-OCOL ₇₉ ISIS-OCOL ₈₀ ISIS-OCOL ₈₁ ISIS-OCOL ₈₂ ISIS-OCOL ₈₃ ISIS-OCOL ₈₄ ISIS-OCOL ₈₅ ISIS-OCOL ₈₆ ISIS-OCOL ₈₇ ISIS-OCOL ₈₈ ISIS-OCOL ₈₉ ISIS-OCOL ₉₀ ISIS-OCOL ₉₁ ISIS-OCOL ₉₂ ISIS-OCOL ₉₃ ISIS-OCOL ₉₄ ISIS-OCOL ₉₅ ISIS-OCOL ₉₆ ISIS-OCOL ₉₇ ISIS-OCOL ₉₈ ISIS-OCOL ₉₉ ISIS-OCOL ₁₀₀	Phase 2 AT1103 ISIS-ANGPT1 ₁ ISIS-ANGPT1 ₂ ISIS-ANGPT1 ₃ ISIS-ANGPT1 ₄ ISIS-ANGPT1 ₅ ISIS-ANGPT1 ₆ ISIS-ANGPT1 ₇ ISIS-ANGPT1 ₈ ISIS-ANGPT1 ₉ ISIS-ANGPT1 ₁₀ ISIS-ANGPT1 ₁₁ ISIS-ANGPT1 ₁₂ ISIS-ANGPT1 ₁₃ ISIS-ANGPT1 ₁₄ ISIS-ANGPT1 ₁₅ ISIS-ANGPT1 ₁₆ ISIS-ANGPT1 ₁₇ ISIS-ANGPT1 ₁₈ ISIS-ANGPT1 ₁₉ ISIS-ANGPT1 ₂₀ ISIS-ANGPT1 ₂₁ ISIS-ANGPT1 ₂₂ ISIS-ANGPT1 ₂₃ ISIS-ANGPT1 ₂₄ ISIS-ANGPT1 ₂₅ ISIS-ANGPT1 ₂₆ ISIS-ANGPT1 ₂₇ ISIS-ANGPT1 ₂₈ ISIS-ANGPT1 ₂₉ ISIS-ANGPT1 ₃₀ ISIS-ANGPT1 ₃₁ ISIS-ANGPT1 ₃₂ ISIS-ANGPT1 ₃₃ ISIS-ANGPT1 ₃₄ ISIS-ANGPT1 ₃₅ ISIS-ANGPT1 ₃₆ ISIS-ANGPT1 ₃₇ ISIS-ANGPT1 ₃₈ ISIS-ANGPT1 ₃₉ ISIS-ANGPT1 ₄₀ ISIS-ANGPT1 ₄₁ ISIS-ANGPT1 ₄₂ ISIS-ANGPT1 ₄₃ ISIS-ANGPT1 ₄₄ ISIS-ANGPT1 ₄₅ ISIS-ANGPT1 ₄₆ ISIS-ANGPT1 ₄₇ ISIS-ANGPT1 ₄₈ ISIS-ANGPT1 ₄₉ ISIS-ANGPT1 ₅₀ ISIS-ANGPT1 ₅₁ ISIS-ANGPT1 ₅₂ ISIS-ANGPT1 ₅₃ ISIS-ANGPT1 ₅₄ ISIS-ANGPT1 ₅₅ ISIS-ANGPT1 ₅₆ ISIS-ANGPT1 ₅₇ ISIS-ANGPT1 ₅₈ ISIS-ANGPT1 ₅₉ ISIS-ANGPT1 ₆₀ ISIS-ANGPT1 ₆₁ ISIS-ANGPT1 ₆₂ ISIS-ANGPT1 ₆₃ ISIS-ANGPT1 ₆₄ ISIS-ANGPT1 ₆₅ ISIS-ANGPT1 ₆₆ ISIS-ANGPT1 ₆₇ ISIS-ANGPT1 ₆₈ ISIS-ANGPT1 ₆₉ ISIS-ANGPT1 ₇₀ ISIS-ANGPT1 ₇₁ ISIS-ANGPT1 ₇₂ ISIS-ANGPT1 ₇₃ ISIS-ANGPT1 ₇₄ ISIS-ANGPT1 ₇₅ ISIS-ANGPT1 ₇₆ ISIS-ANGPT1 ₇₇ ISIS-ANGPT1 ₇₈ ISIS-ANGPT1 ₇₉ ISIS-ANGPT1 ₈₀ ISIS-ANGPT1 ₈₁ ISIS-ANGPT1 ₈₂ ISIS-ANGPT1 ₈₃ ISIS-ANGPT1 ₈₄ ISIS-ANGPT1 ₈₅ ISIS-ANGPT1 ₈₆ ISIS-ANGPT1 ₈₇ ISIS-ANGPT1 ₈₈ ISIS-ANGPT1 ₈₉ ISIS-ANGPT1 ₉₀ ISIS-ANGPT1 ₉₁ ISIS-ANGPT1 ₉₂ ISIS-ANGPT1 ₉₃ ISIS-ANGPT1 ₉₄ ISIS-ANGPT1 ₉₅ ISIS-ANGPT1 ₉₆ ISIS-ANGPT1 ₉₇ ISIS-ANGPT1 ₉₈ ISIS-ANGPT1 ₉₉ ISIS-ANGPT1 ₁₀₀

Success of Partnered Programs Support Strong Financial Position

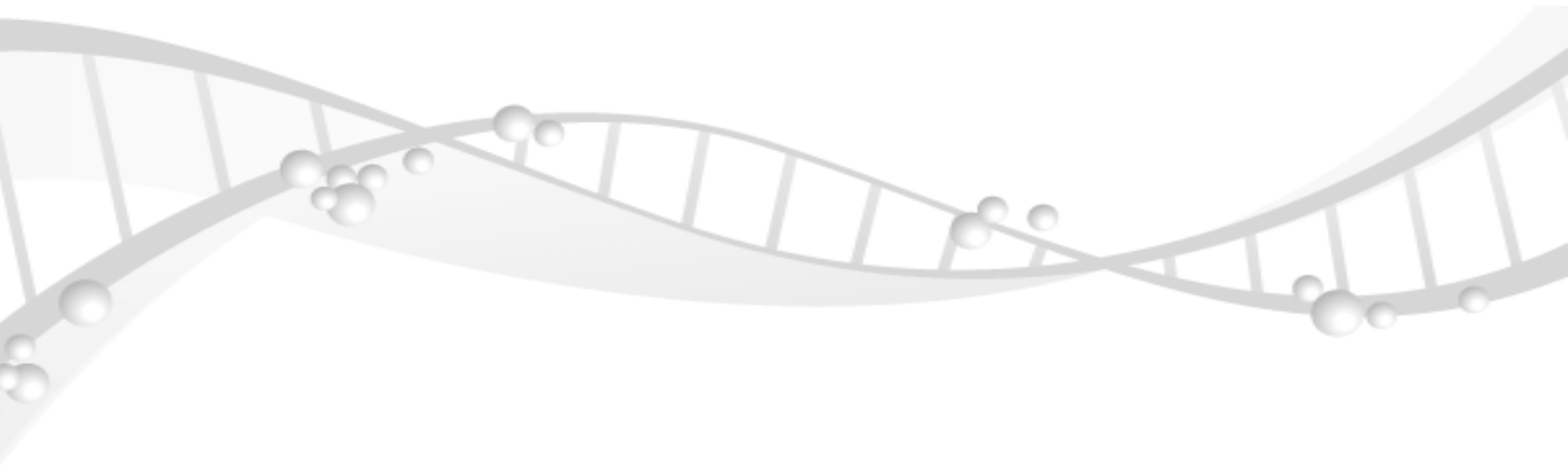
- Preferred Partner — Huntington's Disease
- **>\$31M** received to date



Huntington's Disease

Commercialized	Phase 2 (cont.)	Preclinical	
KYNAROR Alcogel Vagisil [®]	homologous Rx "Pseudo" DMV Reagents	HBV Huntington's Disease Hemophilia Diabetes Neurodegeneration Diabetes Alzheimer's Disease Atherosclerosis Retinitis Pigmentosa	
* Normal Patient Supply			
Phase 3			
ISS-TAT ₁ ISS-SIN ₁ ISS-SIN ₂	ISS-APOL ₁ ISS-OCOL ₁ ISS-OCOL ₂ ISS-PTPL ₁ Korinex (D00427) ISS-STAT2 ₁ ISS-WI ₁ ISS-01 PP-0473871	ISS-TAT ₂ ISS-RHO ₁ ISS-RHO ₂ ISS-ORL ₁ ISS-AGT ₁ ISS-ANG1 ₁ ISS-APOL ₂ ISS-THERP ₁ ISS-00AT ₁ ISS-00K ₁ ISS-00K ₂	HBV Hemophilia Diabetes Neurodegeneration Diabetes Alzheimer's Disease Atherosclerosis Retinitis Pigmentosa Acromegaly Tremor/Spastic Hypertension Hypertension Severely High TGs 2-Thromboses NASH Ocular Disease Actin
Vagisil [®] KYNAROR Cylactin (D00411) Pleomin [®]	PCB Painful, Rapid Lipidolysis Severe Infection Prostate / Lung Cancer Bleed: Severe Bleed: Severe	Multiple Sclerosis MDV	
Phase 1			
ISS-OCOL ₁ ISS-RHO ₁ RHO1 ₁ ISS-ANGPT ₁ ISS-APOL ₁ ISS-OPRA ₁ ISS-SIN ₁	Coating & Implants Hereditary Angiodys Acanthosis Hypertension Very High Lox Coast HBV		
Phase 2			
ATL1103 ISS-OPPR ₁ ISS-OPPR ₂ ISS-SIN ₁	Acromegaly Myotonic Dystrophy 1		

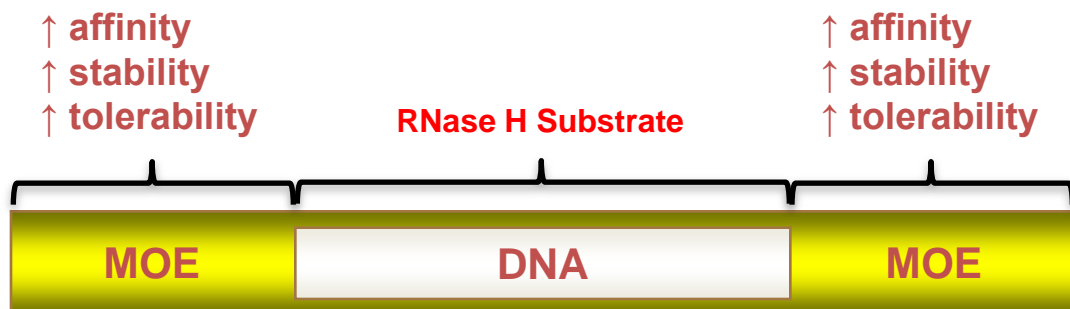
Antisense Technology: Current Status and Future



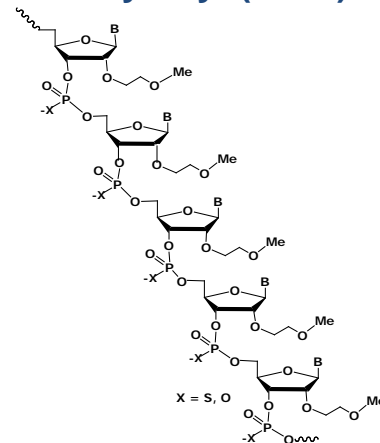
RNase H1 Antisense Mechanism

The Most Advanced Antisense Mechanism

Chimeric RNase H Antisense Drug Design



2'-O-methoxyethyl (MOE)



Compared to first generation antisense drugs, second generation antisense drugs:

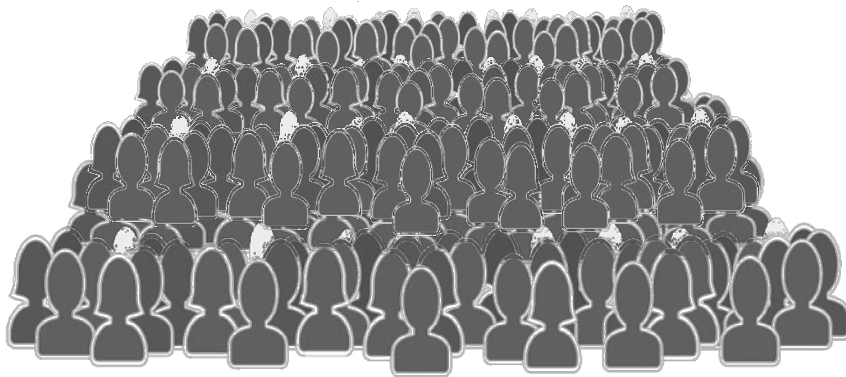
- Increase potency >100 fold
- Increase duration of action 10-20 fold (50-100 fold less drug)
- Decrease unwanted side effects

Clinical Experience:

- >6,000 subjects dosed; >3,000 in Isis database
- >60 clinical studies
- Multiple therapeutic indications
- >100 patients dosed for >1 year
- Some patients dosed for >4 years
- Doses as high as 1,200 mg tolerated

Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- **Efficient – 1 drug per 11 Isis employees**



Traditional Pharma
1 drug / ~1,000 employees

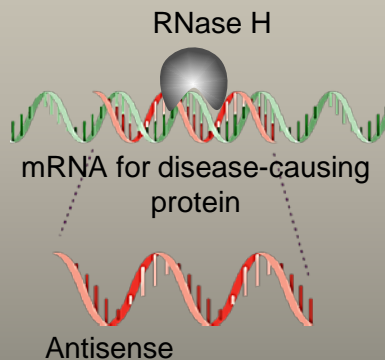


ISIS
1 drug / 11 employees

Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

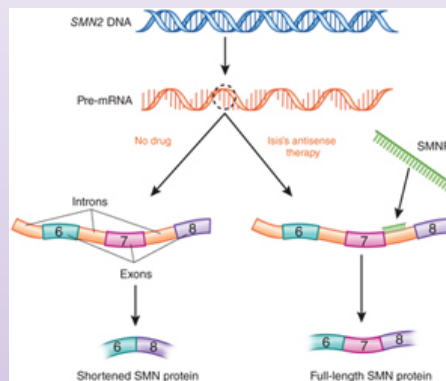
- *Efficient – 1 drug / 11 Isis employee*
- **Robust – multiple mechanisms**
 - Ability to increase or decrease protein production
 - Single-stranded antisense drugs can effectively target RNAs in cytoplasm AND nucleus of the cell

Reduces target RNA & prevents production of protein



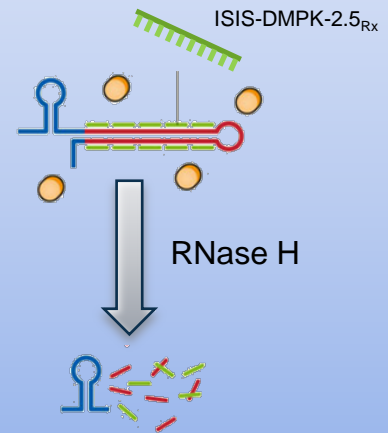
Example: Volanesorsen

Increases production of therapeutic protein



Example: ISIS-SMN_{Rx}

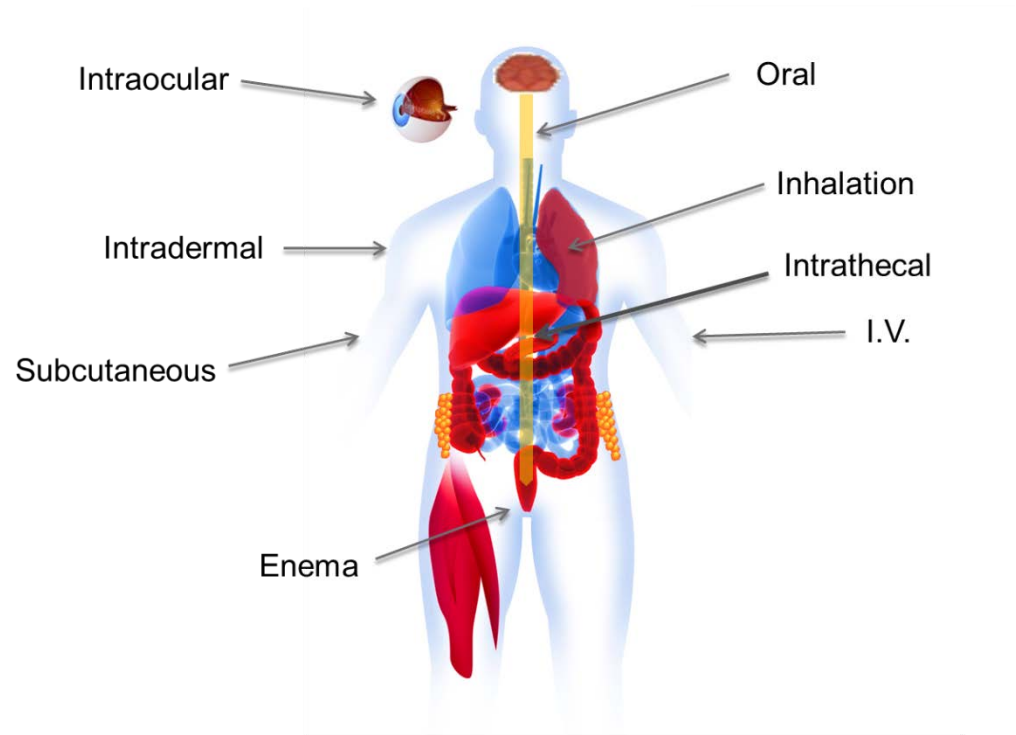
Removes toxic RNA



Example: ISIS-DMPK-2.5_{Rx}

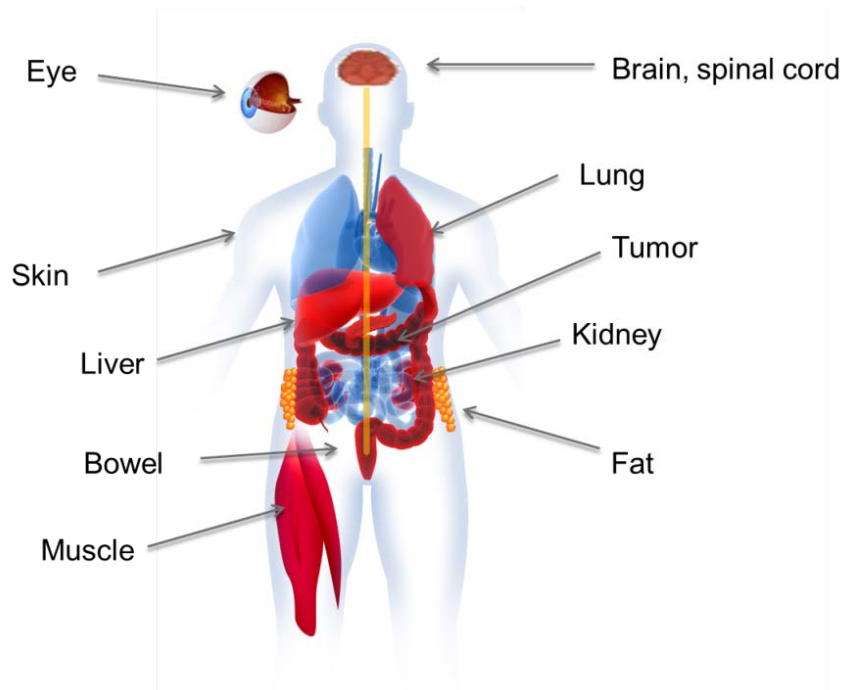
Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- *Efficient – 1 drug / 11 Isis employee*
- *Robust – multiple mechanisms*
- **Robust – multiple routes of delivery**



Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- *Efficient – 1 drug / 11 Isis employee*
- *Robust – multiple mechanisms*
- *Robust – multiple routes of delivery*
- **Robust – broad clinical activity in multiple tissues**



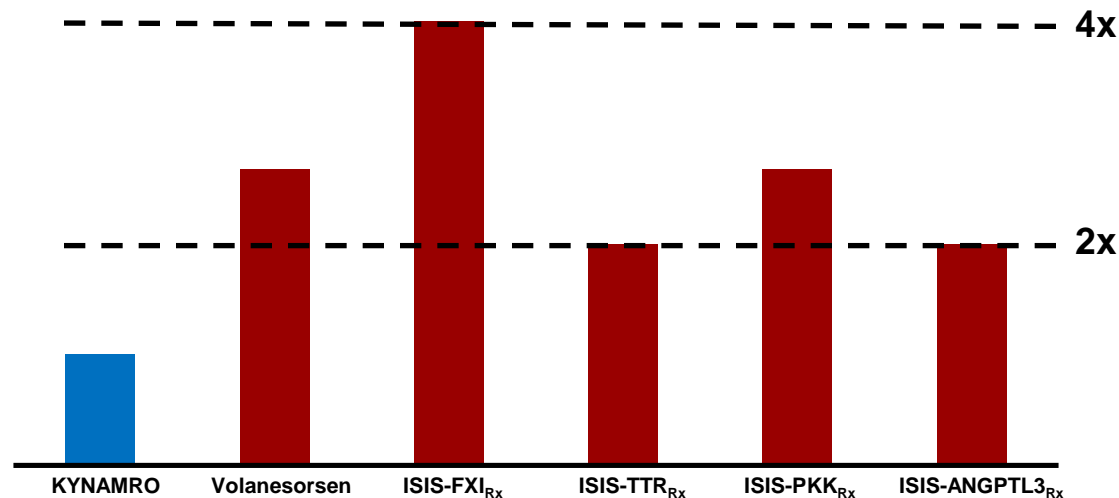
Gen 2.0 Antisense Drugs

Activity of Multiple Drugs in Multiple Tissues and Multiple Diseases by Multiple Routes

Drug	Target	Indications	Primary Organs	Endpoints
Kynamro®	ApoB-100	Hyperlipidemia	Liver	ApoB, LDL-C, & Others
Volanesorsen	ApoC-III	High TGs	Liver	ApoC-III levels & TGs
ISIS-SMN _{Rx}	SMN2	SMA	Brain & spinal cord	SMN RNA, SMN Protein
Custirsen	Clusterin	Prostate Cancer	Prostate, Lymph nodes	Target reduction, Apoptosis, Survival
ISIS-TTR _{Rx}	TTR	TTR Amyloidosis	Liver	TTR levels
ISIS-FXI _{Rx}	Factor XI	Clotting Disorders	Liver	Factor XI levels & decreased clotting
EXC 001	CTGF	Scarring	Skin	Scarring endpoints, CTGF in skin
ISIS-113715 _{Rx}	PTP1B	Diabetes	Liver, Fat cells	Glucose, LDL-C
ISIS-PTP1B _{Rx}	PTP1B	Diabetes	Liver, Fat cells	Glucose, LDL-C
ISIS-APO(a) _{Rx}	Apo(a)	Lipid Disorders	Liver	Lp(a) levels
ISIS-CRP _{Rx}	CRP	CV Disease Inflammation	Liver	CRP in plasma
ATL1102	VLA4	MS	Bone marrow Lymph nodes	MRS Measurements of CNS lesions
ISIS-GCGR _{Rx}	GCGR	Diabetes	Liver	Glucose & glycogen in plasma
ATL1103	GHr	Acromegaly	Liver	IGF1 levels
ISIS-104838	TNF α	RA	Joints, Lymph nodes	ACR 20 & Target reduction
ISIS-STAT3-2.5 _{Rx}	STAT3	Cancer	Tumors / tumor stromal cells	STAT3 RNA and protein
ISIS-ANPTL3 _{Rx}	ANPTL3	Lipid Disorders	Liver	ANPTL3, TGs in plasma
ISIS-SGLT2 _{Rx}	SGLT2	Diabetes	Kidney	Increase glucose in urine
ISIS-PKK _{Rx}	PKK	HAE	Liver	PKK in plasma

Advances in Antisense Technology Broaden Utility and Value: Improved Screening

Gen 2.0+ Antisense Drugs are More Potent* Than KYNAMRO



*Potency derived from ED₅₀ after 4 weeks of treatment; compared to KYNAMRO Phase 1 studies

Improvement in Side Effects Observed in Newer Gen 2.0 Antisense Drugs Compared to KYNAMRO in Phase 1 Studies

Parameter	Volanesorsen	ISIS-FXI _{Rx}	ISIS-TTR _{Rx}	ISIS-PKK _{Rx}	ISIS-ANGPTL3 _{Rx}
Injection-site Reactions (% SC Injections)	89% fewer ISRs	64% fewer ISRs	65% fewer ISRs	50% fewer ISRs	65% fewer ISRs
Flu-like Symptoms	None	None	Very low incidence	None	None

Advances in Antisense Technology Broaden Utility and Value

■ Generation 2.5 drugs:

- Enhance affinity for target sequence
- Up to 10-fold increase in potency
- Enhance target engagement in new tissues
 - Activity in cancer and stromal cells
 - ISIS-DMPK-2.5_{Rx} program to evaluate activity in muscle cells
- Good safety profile observed with Generation 2.5 chemistry to date
- Four Generation 2.5 drugs in pipeline:
 - ISIS-STAT3-2.5_{Rx} (AZD9150)
 - ISIS-AR-2.5_{Rx} (AZD5312)
 - ISIS-DMPK-2.5_{Rx}
 - ISIS-RHO-2.5_{Rx}

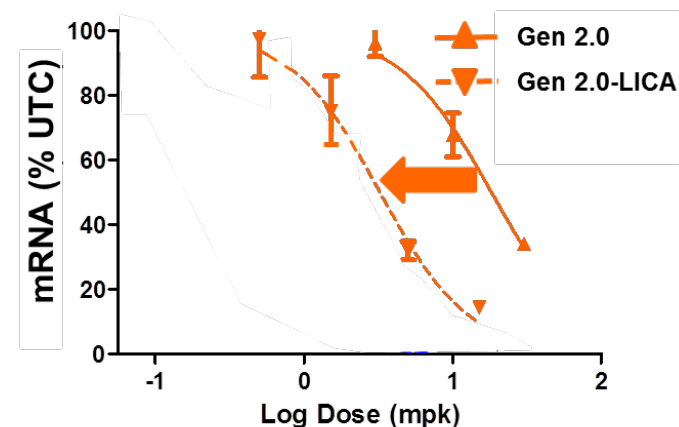
Antisense Compound	ID ₅₀ in Humans (mg/wk)
Gen 2.0	< 150
Gen 2.5	< 15

Advances in Antisense Technology Broaden Utility and Value

LICA Conjugation

- LICA conjugation technology
 - Enhance effective distribution for liver targets
 - Up to 10-fold increase in potency
 - First LICA drug in clinical development
 - Additional drugs with LICA conjugation nearing clinical stage for liver targets
 - Optimal for use in broader indications, lower dosing and less frequent dosing
 - Eight LICA drugs in pipeline

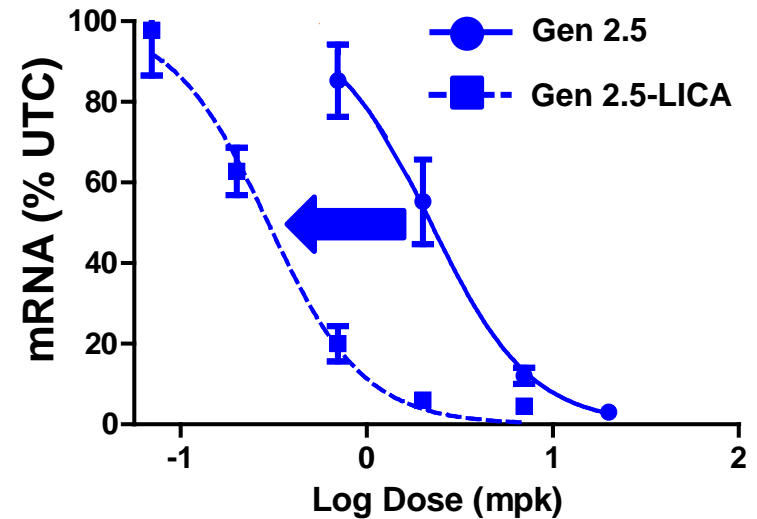
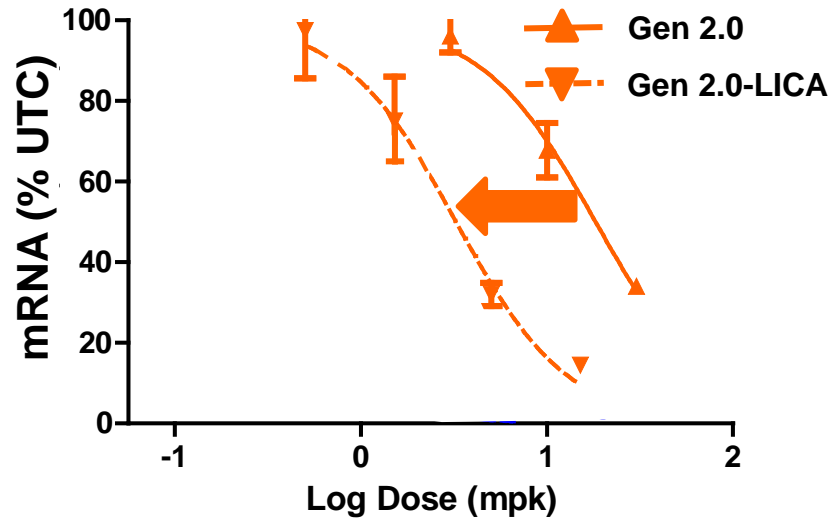
Antisense Compound	ID ₅₀ in Humans (mg/wk)
Gen 2.0	<150
Gen 2.0-LICA	<15



LICA Improves Potency of Gen 2.0 and Gen 2.5 Antisense Compounds

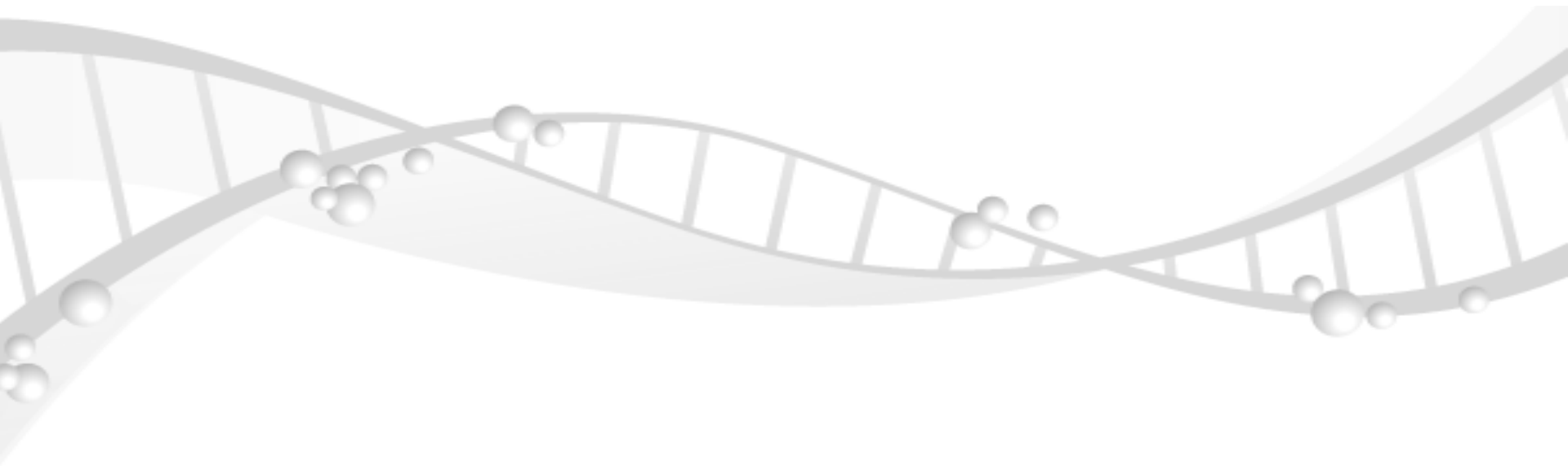
Continue to Advance Antisense Technology

Enhanced affinity and enhanced distribution



Antisense Compound	Projected Dose in Humans (mg/wk)
Gen 2.0	100 – 300
Gen 2.0-LICA	10 – 30
Gen 2.5	10 – 30
Gen 2.5-LICA	1.0 – 3.0

Partnership Strategy and Execution



Isis' Flexible Development and Partnership Strategy

Maximizes Value, Minimizes Risk and Decreases Time to Market

Partner Early

- Significant technical or target risk
- Complex, difficult, expensive Phase 2 program
- Challenging endpoints
- Expertise from partner could provide increased likelihood of success

License After POC

- Complex, expensive Phase 3 development
- Straightforward, effective Phase 2 program with definitive endpoints
- Multiple indications
- Large patient population
- Large marketing and sales effort

Keep Longer

- Clear Phase 2, Phase 3 development path
- Low to moderate total development costs
- Potential for initial rare disease opportunity
- Consistent with Isis intellectual franchises

Examples:

ISIS-SMN_{Rx}
ISIS-DMPK-2.5_{Rx}
ISIS-STAT3-2.5_{Rx}
 (AZD9150)
ISIS-AR-2.5_{Rx}
 (AZD5312)

Biogen

AstraZeneca

Janssen (J&J)

ISIS-FXI_{Rx} (Bayer)

Volanesorsen
 ISIS-APO(a)_{Rx}
 ISIS-ANGPTL3-L_{Rx}
 + follow-on drugs

AKCEA
THERAPEUTICS

Isis - Janssen Collaboration

RNA-targeted Therapies for Autoimmune Diseases in GI Tract

- Collaboration provides several advantages
 - Combines Isis' RNA-targeted technology with Janssen's expertise in autoimmune disorders and therapeutic formulation
 - Provides Isis with a low-risk, low-cost opportunity to expand our technology into oral local delivery for GI and autoimmune diseases
- \$35 million in upfront payments
- ~\$800 million in development, regulatory, sales milestones and license fees
- Average royalties on sales in the double-digits

Isis — Bayer License Agreement

\$155M in Near-term Payments; Bayer to Develop ISIS-FXI_{Rx} for the Prevention of Thrombosis

- Bayer is a leader in the treatment of thrombotic diseases with the global reach to support robust development program
- Bayer plans to invest substantially in a broad development plan designed to take advantage of the profile of ISIS-FXI_{Rx} and maximize its value
 - Initially, plans to evaluate the therapeutic profile of ISIS-FXI_{Rx} in patients for whom currently available anticoagulants may not be used
 - Additional plans to develop ISIS-FXI_{Rx} for patients who are underserved by current antithrombotics
- Tiered royalties in the low to high 20 percent range on gross margins of ISIS-FXI_{Rx}
- \$155 million in near-term payments
 - \$100 million up-front payment
 - \$55 million payment upon advancement of the program following the Phase 2 study in patients with compromised kidney function
- In total, Isis has the opportunity to earn up to \$375 million in payments, plus royalties

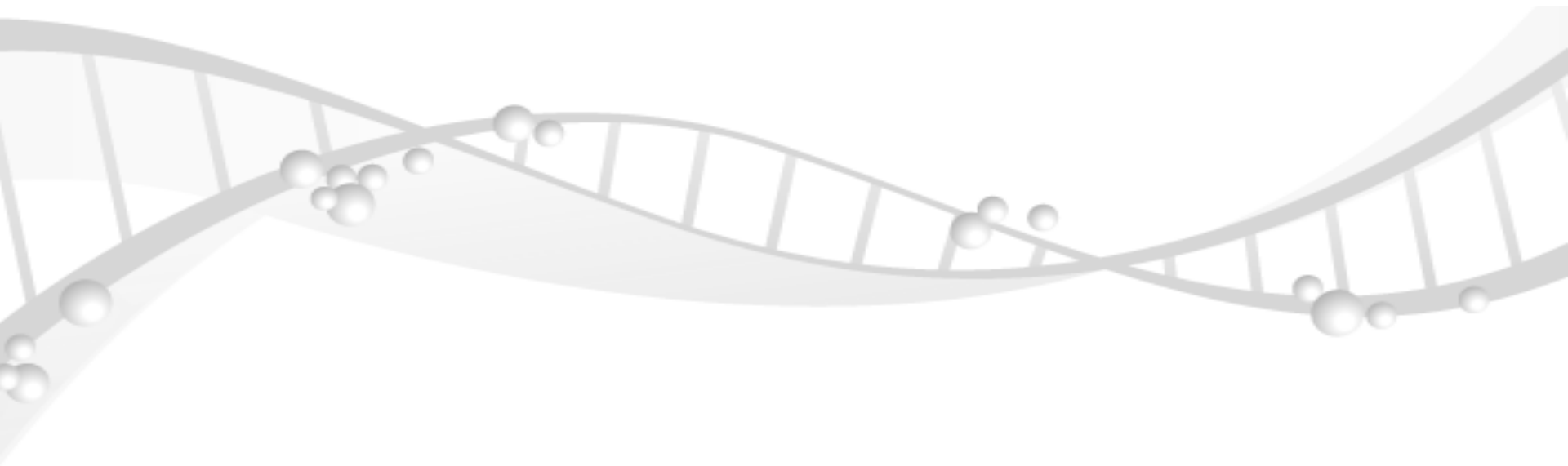
Partnership Strategy Continues to be Highly Productive

- In 2015, we have generated more than \$195 million in payments from partners, including the following:
 - \$100 million from Bayer
 - \$42 million from Biogen
 - \$35 million from Janssen (J&J)
 - \$19 million from GSK
-

Total: \$196M

KYNAMRO

Position Strengthening



KYNAMRO: Position Strengthening

- KYNAMRO is marketed and approved in the U.S. and additional countries
- Genzyme continues to invest significantly in KYNAMRO
- Increased sales growth in 2014
- Projected increase in sales for 2015



Who is the patient for KYNAMRO® (mipomersen sodium) Injection 200 mg/mL?

Clinical Profiles Consistent with Homozygous Familial Hypercholesterolemia (HoFH)

KYNAMRO is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

LIMITATIONS OF USE

- The safety and effectiveness of KYNAMRO have not been established in patients with hypercholesterolemia who do not have HoFH
- The effect of KYNAMRO on cardiovascular morbidity and mortality has not been determined
- The safety and effectiveness of KYNAMRO as an adjunct to LDL apheresis have not been established; therefore, the use of KYNAMRO as an adjunct to LDL apheresis is not recommended

Please see enclosed full Prescribing Information and Medication Guide, including Boxed Warning.

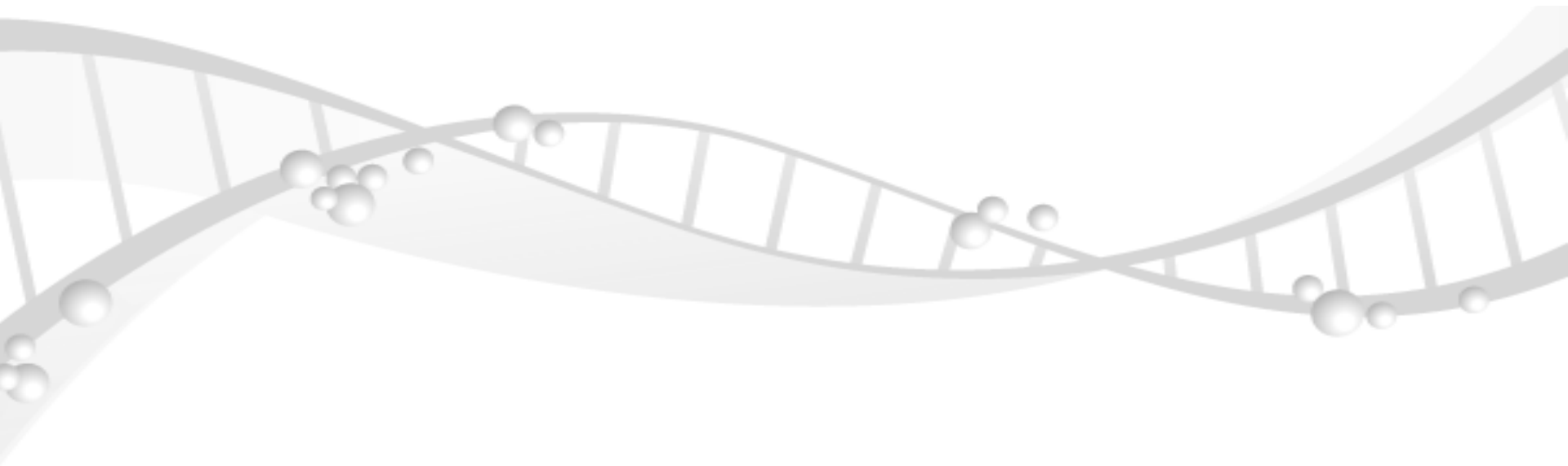
KYNAMRO: Position Strengthening

- Results from a retrospective analysis reported at the 2014 American Heart Association annual meeting showed that, in HoFH and HeFH patients, **the rate of major adverse cardiovascular events decreased seven-fold after two years of KYNAMRO treatment** vs. the two years prior to treatment (3.6 vs. 25.7; per 1000 patient-months)
- Study of 7 patients who had liver biopsies published in *Journal of Clinical Lipidology**. Findings suggest that in these patients during treatment with KYNAMRO measured liver fat is benign, simple steatosis without significant inflammation or fibrosis and therefore different and distinct from nonalcoholic steatohepatitis.
- Continuing advancement with FOCUS FH, a Phase 3 study in patients with Severe HeFH
 - Enrollment completed
 - FOCUS FH data planned mid 2015

* Hashemi, N. et al. (2014) *J Clin Lipidol.* 8, 606-611.

ISIS-SMN_{Rx}

For Patients with Spinal Muscular Atrophy



ISIS-SMN_{Rx} for Spinal Muscular Atrophy (SMA)

Severe Genetic Neuromuscular Disease Affecting Infants and Children

- SMA is a rare disease that affects approximately 30-35K children in United States, Europe and Japan
 - Number one genetic cause of death in infants
 - Caused by genetic defects in the SMN1 gene that result in a lack of functional SMN protein
 - Characterized by progressive muscle atrophy and loss of motor function
- Over half of all SMA patients are born with the most severe form of SMA (Type I)
 - Very short life expectancy
 - Unable to sit or stand
- No currently approved therapies for SMA



Type I Spinal Muscular Atrophy

Type I

- Median time to death or permanent ventilation: 6.1* to 10.5** months
- Steady decline in muscle function over time
 - Mean rate of decline in CHOP INTEND is 1.27/yr**

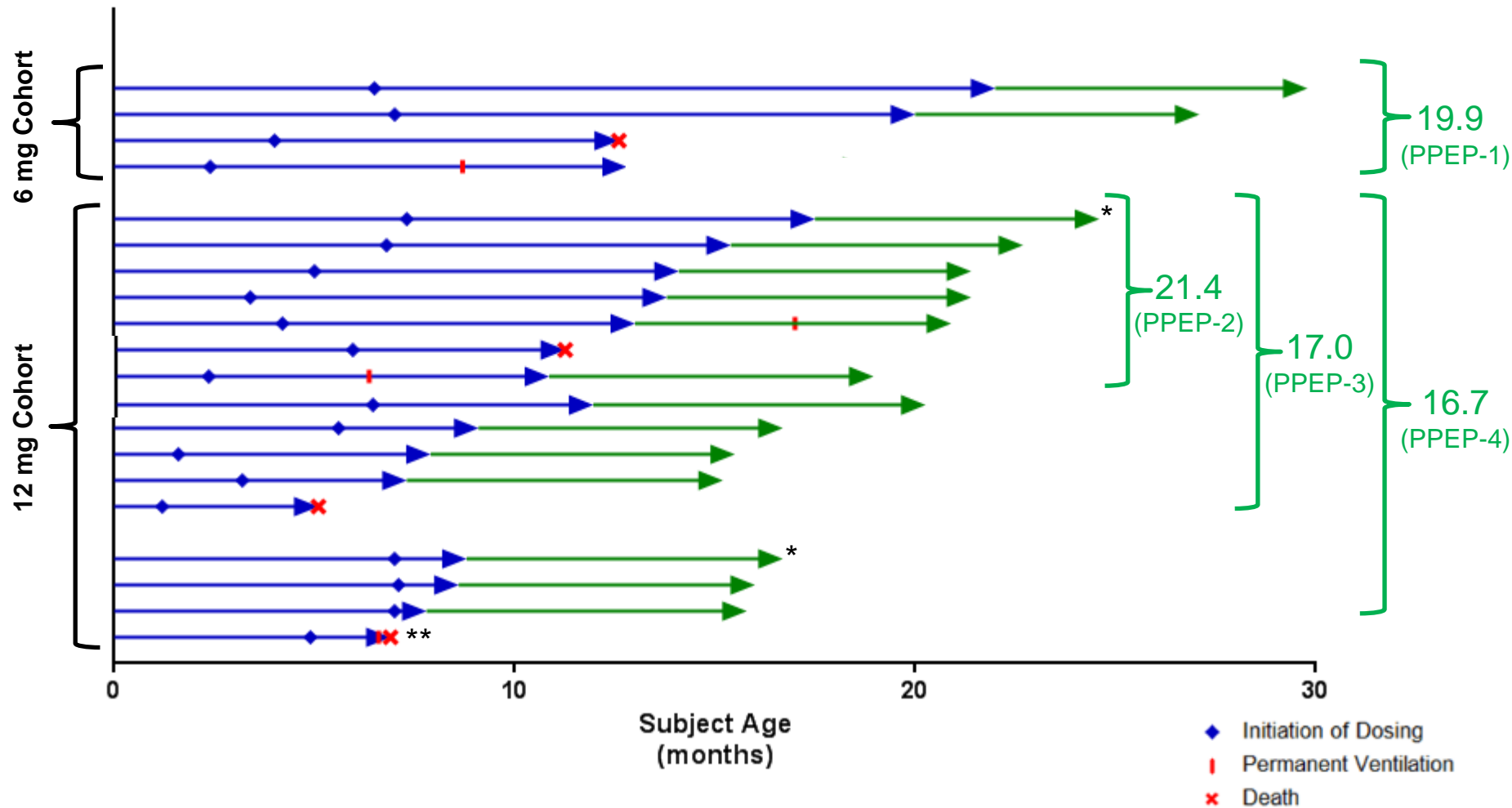
* Rudnik-Schöneborn et al. *Clin Genet*. 2009 Aug;76(2):168-78

** Finkel et al. *Neurology*. 2014 Aug 26;83(9):810-7.



Median Event-free Age Continues to Increase in Type I SMA Infants Treated with ISIS-SMN_{RX}

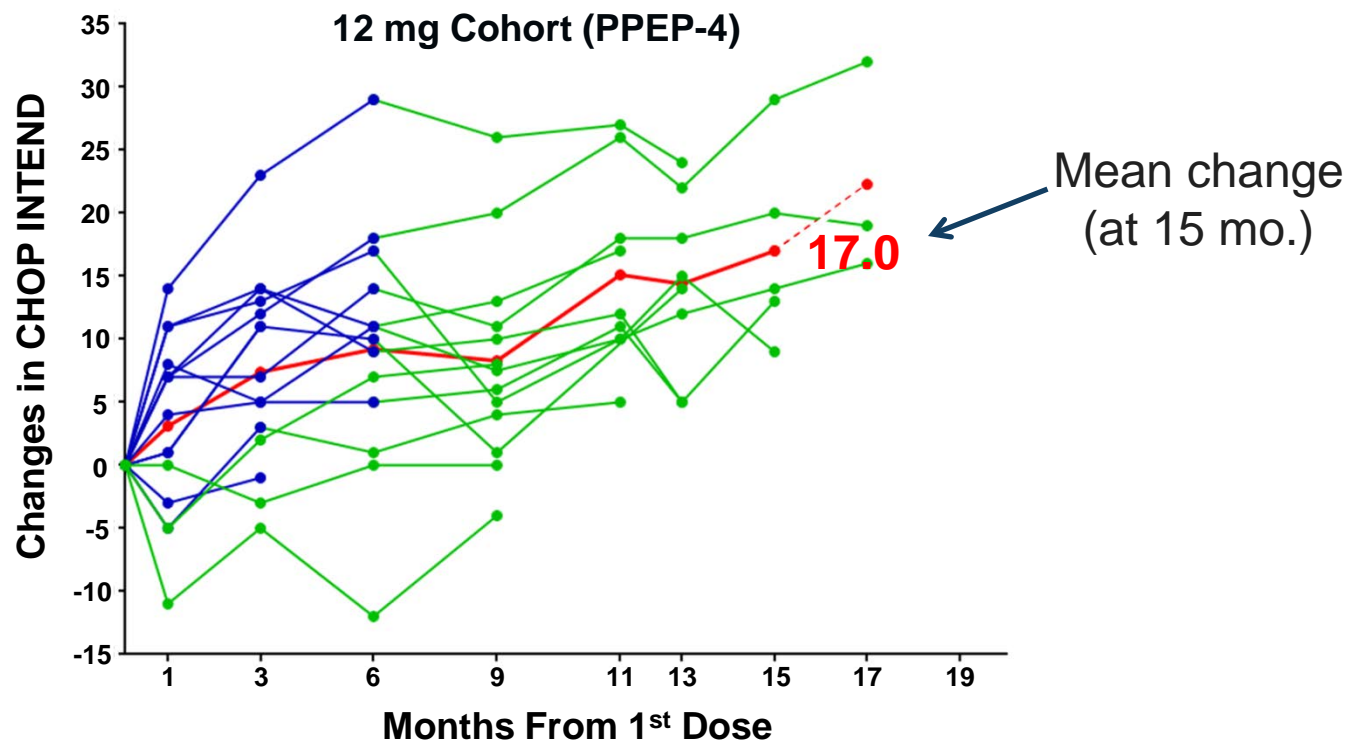
Phase 2 Open-label Study **as of Sept 2, 2014** and **as of April 17, 2015**



*SMN2 copy number of 3; **SMN2 copy number not known; all other infants have SMN2 copy number of 2

Increased Muscle Function (CHOP INTEND) Scores Observed in SMA Infants Treated with ISIS-SMN_{Rx}

Phase 2 Open-label Study as of Sept 2, 2014 and as of April 17, 2015



- In the 12 mg cohort, 12 of 15 infants achieved increases in CHOP INTEND scores
- A substantial number of SMA Infants (53%) achieved a CHOP INTEND Score of 40 or greater
 - Median baseline score* = 26.0
- “A score of 40 on the CHOP INTEND is at the lower end of the range of normal for healthy infants 3 to 12 months of age, whereas it is very uncommon for an infant with Type I SMA to ever score above 40 points.” –Dr. Richard Finkel

*CHOP INTEND scores can range on a scale from 0 to 64

Summary of ISIS-SMN_{Rx} Phase 2 Study in Infants with SMA

As of April 17, 2015

- Safety profile of ISIS-SMN_{Rx} in infants with SMA supports continued development
- Totality and consistency of clinical data gives us encouragement about the performance of ISIS-SMN_{Rx}
- The median event-free age in infants treated with ISIS-SMN_{Rx} continues to increase
 - In the 12 mg cohort, 73% of the infants (11 of 15) remain event-free and all of these infants are older than 15 months
 - In the 6 mg cohort, 50% of the infants (2 of 4) are event free and both infants are older than 27 months
- ISIS-SMN_{Rx}-treated SMA infants continue to demonstrate increases in motor function scores
 - CHOP INTEND: mean increase in the 12 mg cohort of 17 points at 15 months; 53% achieved score of 40 or greater
 - Motor milestones: nearly all ISIS-SMN_{Rx}-treated SMA infants achieved new motor milestones; five now sitting
- Clinical data are consistent with the mechanism by which ISIS-SMN_{Rx} was designed to work

Type II / Type III Spinal Muscular Atrophy

Type II / Type III Natural History

- Prospective studies show continued decline in motor function scores (HFMSE) in children with Type II / Type III SMA, mean change in HFMSE score at:
 - Year 1 = 0.15*
 - Year 2 = - 0.54**
 - Year 3 = - 1.71**



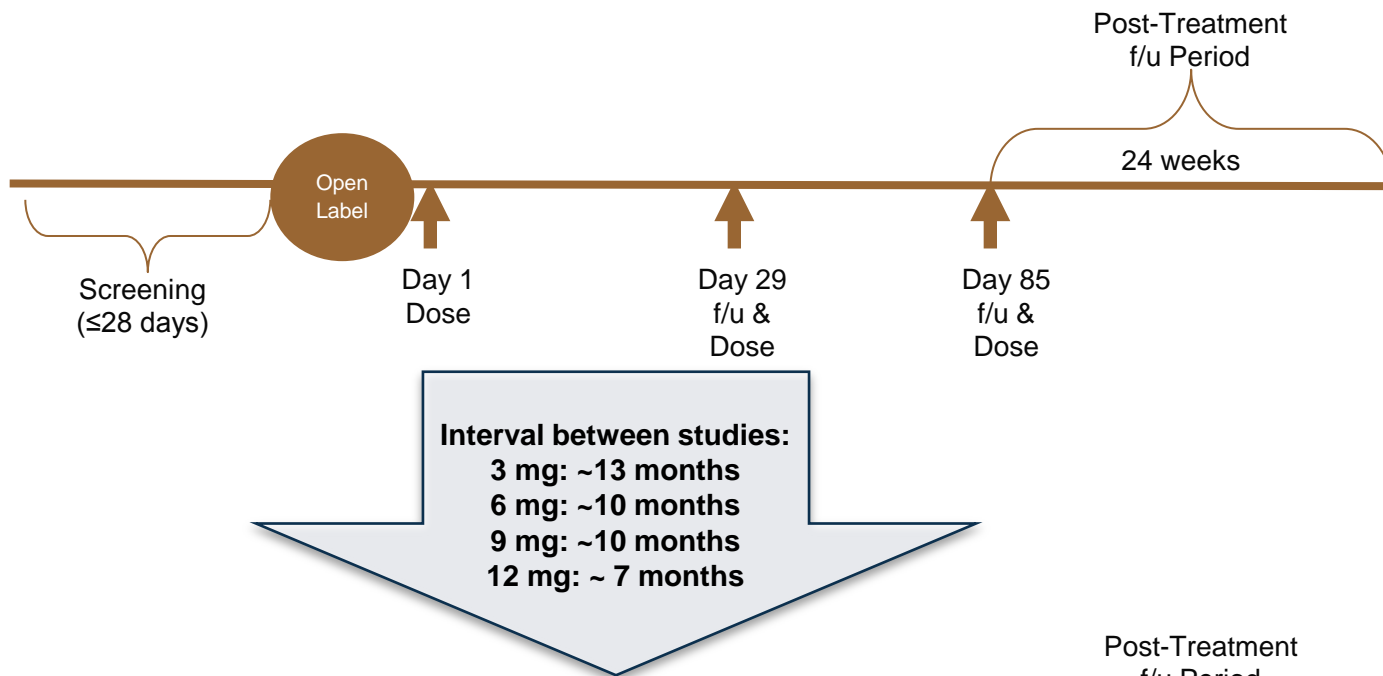
* Kaufmann et al. *Arch Neurol.* 2011 June; 68(6): 779-786

**Kaufmann et al. *Neurology.* 2012 October; 79(18) 1889-1897

Study Design for ISIS-SMN_{Rx} Phase 2 and OLE Studies in Children with SMA

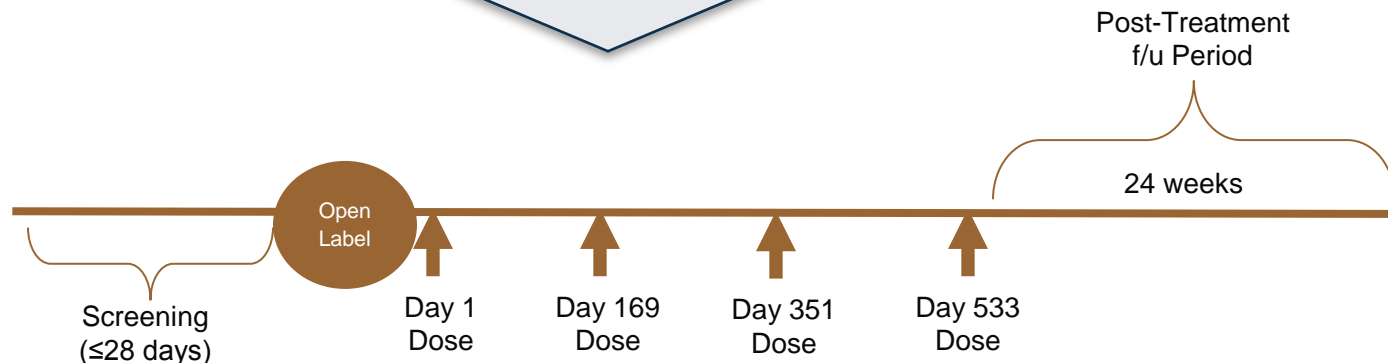
Phase 2 Study

Cohort	Total Dose	n
3 mg	9 mg	8
6 mg	18 mg	8
9 mg	18 mg	9
12 mg	36 mg	9



OLE Study

Cohort	Total Dose	n
12 mg	36 mg	9



Summary of ISIS-SMN_{Rx} Phase 2/OLE Study in Children with SMA

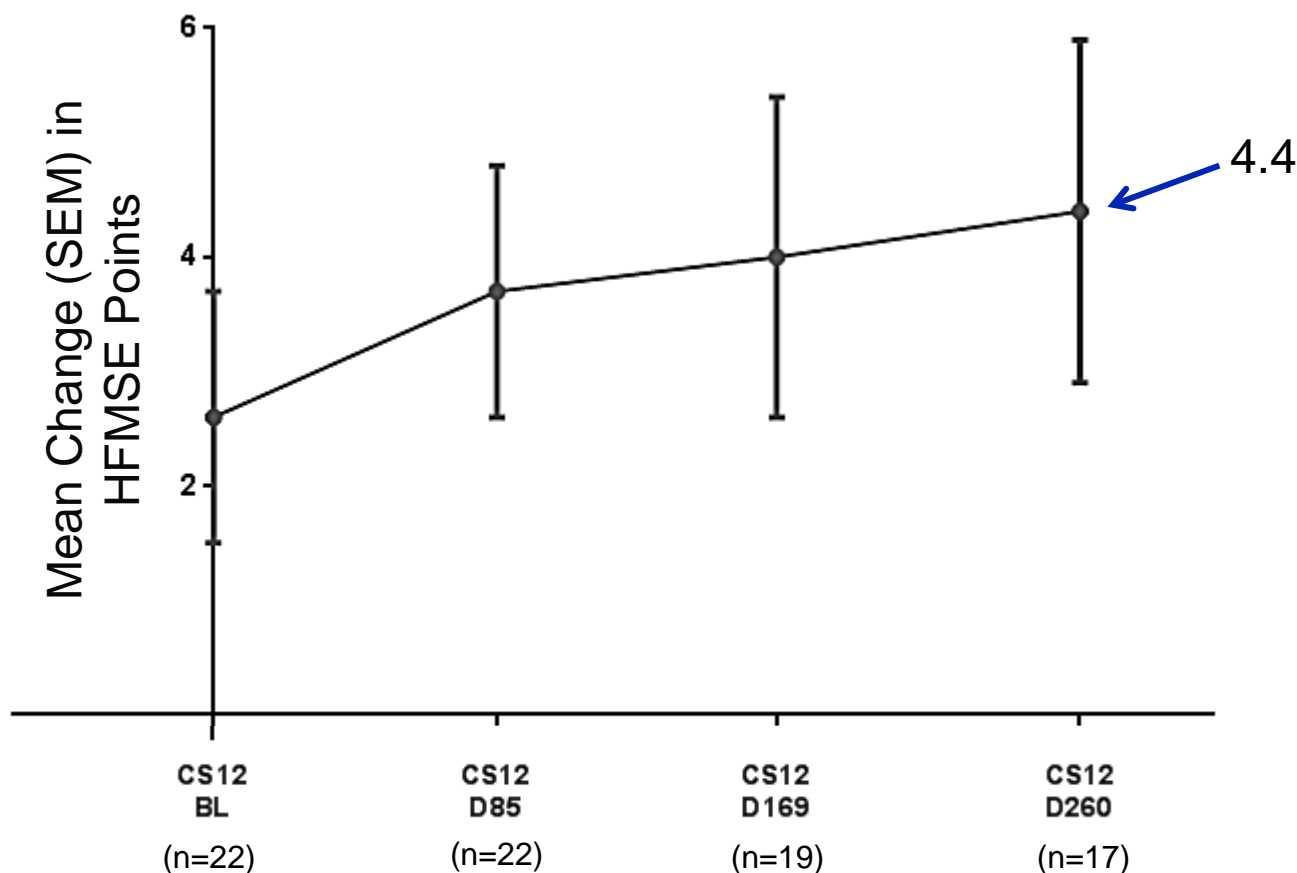
As of May 15, 2015

- Safety profile of ISIS-SMN_{Rx} in children with SMA supports continued development
- Continued and durable increases in measures of muscle function with 57% of children achieving a 3 point or greater change in HFMSE scores
- Increases in multiple measures of muscle function at Day 260
 - Mean increase of 3.8 points in HFMSE score (n=22)
 - In a subgroup analysis of children who had incoming HFMSE scores that met the inclusion criteria for the ongoing Phase 3 CHERISH study (≥ 10 and ≤ 54 ; n=17) mean increase in HFMSE score was 4.4 points
 - Mean 6MWT scores increased by 55 meters (n=11)
 - Mean ULM scores increased by 2.0 points (n=12)

Durable and Consistent Increases in Motor Function Scores (HFMSE) in Children with SMA

Open-label Extension Study After Nine Months Dosing with ISIS-SMN_{Rx}

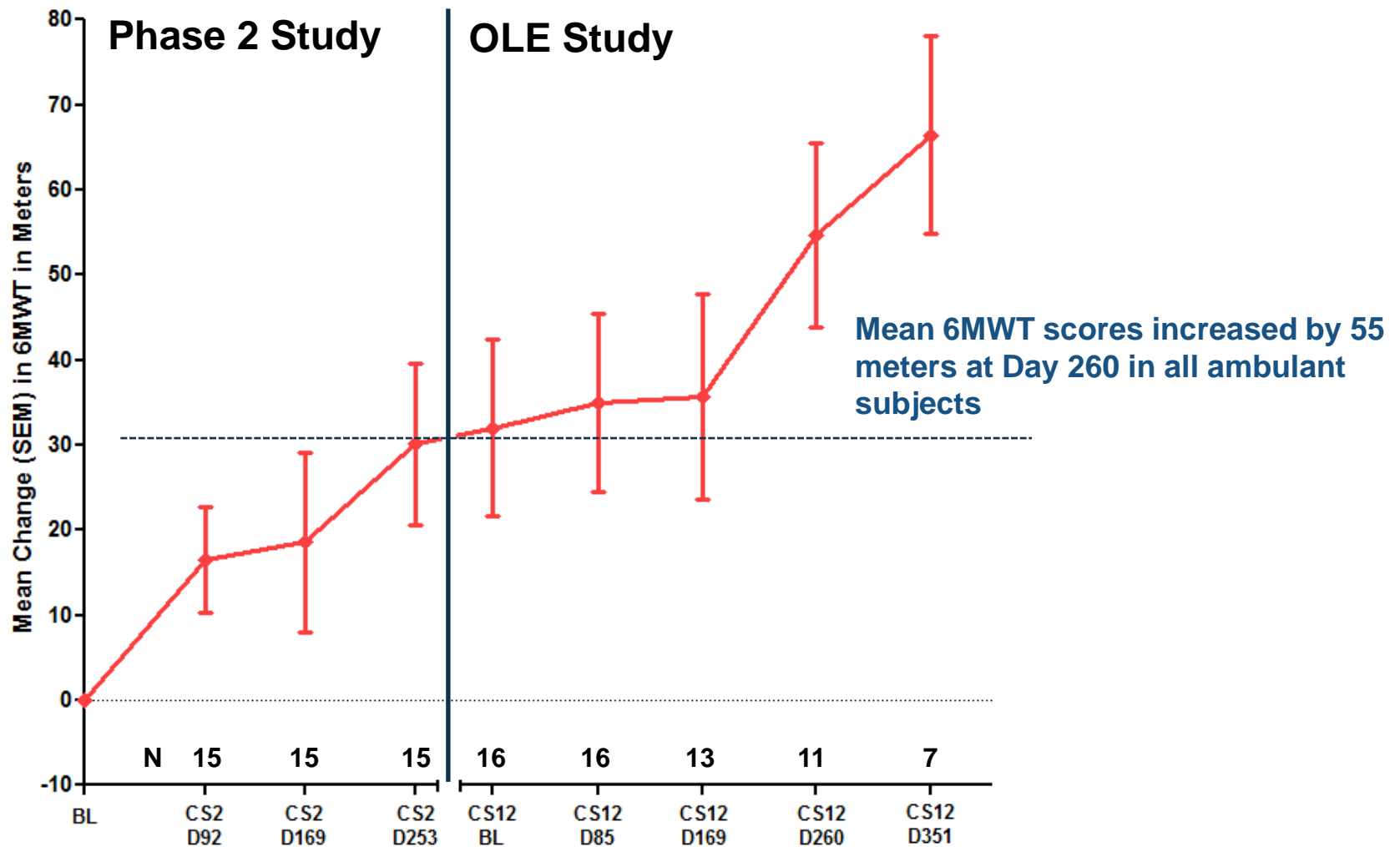
As of May 15, 2015



Subgroup analysis of children with SMA with Phase 2 baseline score ≥ 10 and ≤ 54 (CHERISH Phase 3 study criteria)

Substantial Increases in Motor Function Score (6-Minute Walk Test) in Children with SMA

As of May 15, 2015



ISIS-SMN_{Rx} Phase 3 Program



- ENDEAR (Isis study): Infant Onset SMA Registration Trial
 - First patient dosed in August 2014
 - Eligible patients may continue in open label extension
 - Data planned 2016/2017



- CHERISH (Isis study): Childhood Onset SMA Registration Trial
 - First patient dosed in November 2014
 - Eligible patients may continue in open label extension study
 - Data planned 2016/2017



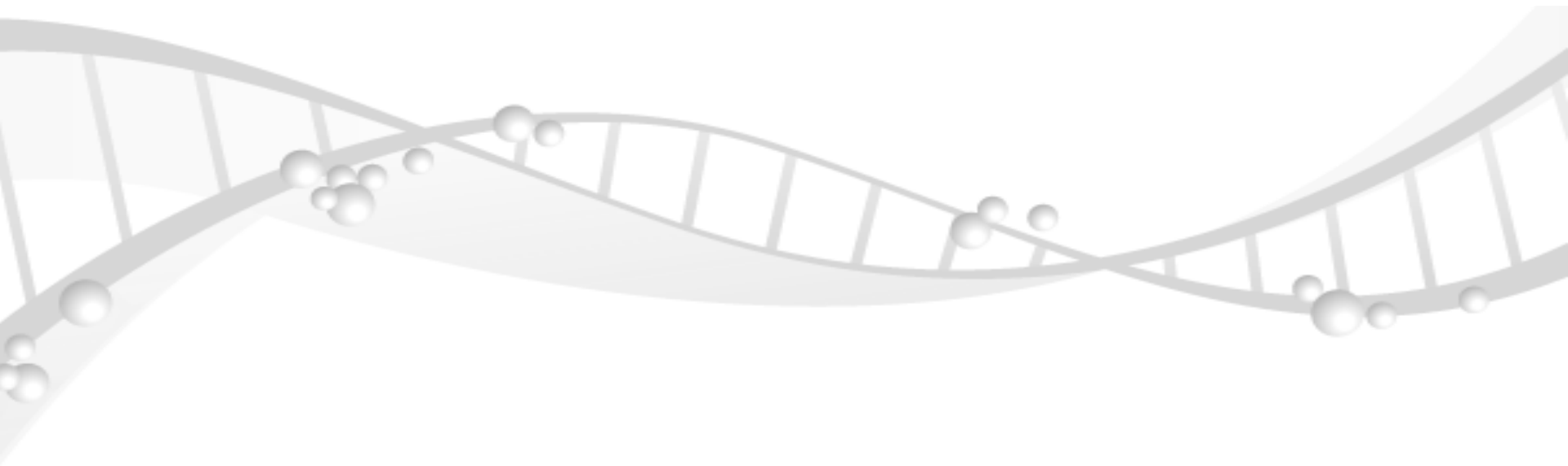
- NURTURE (Biogen study) : Phase 2 study in pre-symptomatic newborns that are genetically predisposed to the disease
 - Study is designed to enhance our understanding of early diagnosis and treatment



- EMBRACE (Biogen study): Phase 2 study in patients with infantile or childhood-onset SMA
 - Study is designed to bridge the gap in a small subset of patients that do not meet the age and inclusion criteria of ENDEAR and CHERISH studies

ISIS-TTR_{Rx}

**For Patients with
Transthyretin (TTR) Amyloidosis**



A Potential Treatment for TTR Amyloidosis

Unmet Medical Need

Mutant TTR forms amyloid deposits in nerves, heart and other organs, resulting in poor quality of life and eventually death

Patient Population (World Wide)

- Familial Amyloid Polyneuropathy ~ 10,000 (FAP)
- Familial Amyloid Cardiomyopathy ~ 40,000 (FAC)

Current Treatment Options

- Treatments limited
- No treatments halt or reverse disease
- Liver transplant for early stage FAP (not FAC)

ISIS-TTR_{Rx}: Phase 3 Program Well Underway

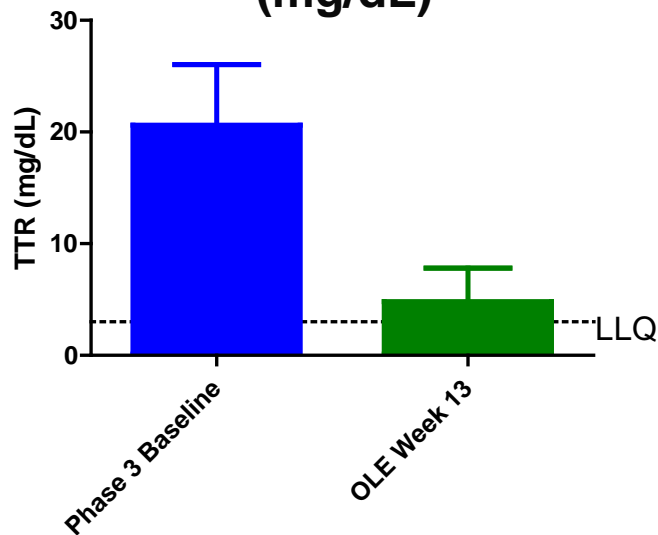
Potentially First-In-Class & Best-In-Class

- Most advanced TTR RNA targeted therapeutic drug in development
 - First patient dosed early 2013
 - Open-label extension study initiated
- Once-weekly SC injections
 - Self administered at home
 - Low volume single injection
- Safety and tolerability profile continues to support Phase 3 development

Robust TTR Reductions in ISIS-TTR_{Rx} Open-Label Extension Study

Analysis From First 13 Patients to Reach Three Months of Treatment*

Median Absolute TTR Levels
(mg/dL)



**TTR % Reduction
ISIS-TTR_{Rx} 300 mg
(N=13)**

**Median = 78%
Up to = 92%**

8 Different TTR Mutations

- Val30Met
- Asp38Ala
- Thr49Ala
- Thr60Ala
- Gly67Arg
- Lys70Asn
- Ser77Phe
- Ile84Ser

- >90% participation in the Open Label Extension Study
- Blinded safety analysis of the ongoing Phase 3 study showed that ISRs occurred in ~1% of all injections

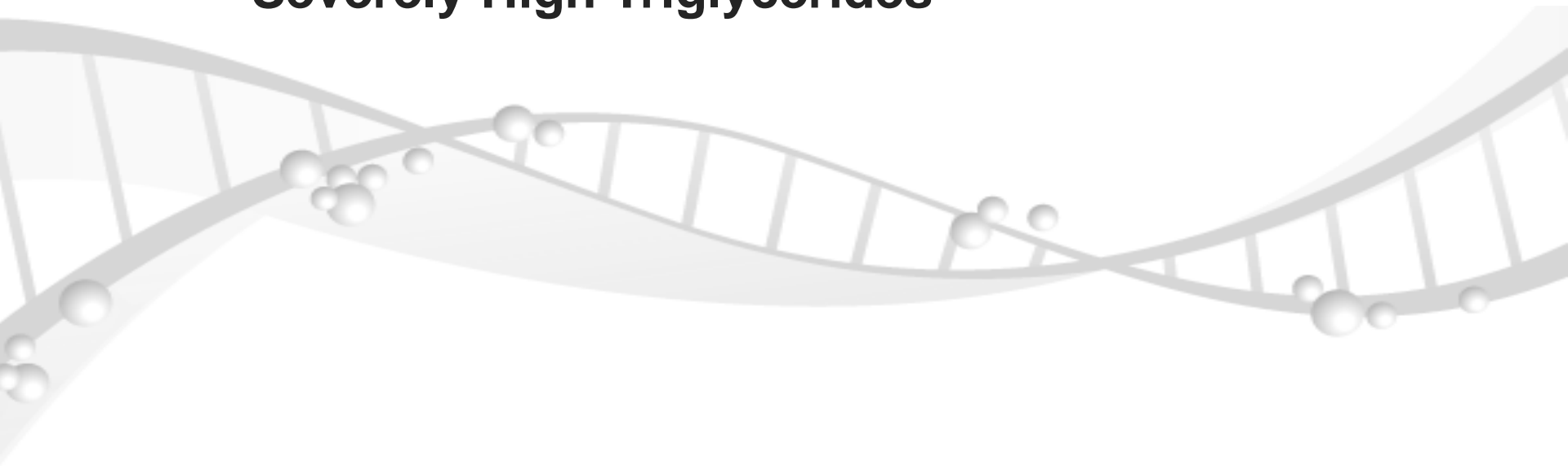
* Data presented at the American Academy of Neurology Annual Meeting, April 23, 2015

ISIS-TTR_{Rx} Program

- In Progress
 - Phase 3 FAP study – Data planned 1H 2017
 - Open-label extension for FAP
 - Investigator-initiated open-label study in patients with familial cardiomyopathy and senile systemic amyloidosis
 - Conducted by Dr. Merrill Benson, University of Indiana
- Additional Studies
 - GSK initiating a Phase 3 study in patients with TTR-related cardiomyopathy
 - GSK initiating a Phase 3 study in Japan in patients with FAP

Volanesorsen and ISIS-APOCIII-L_{Rx}

**For Patients with Familial
Chylomicronemia Syndrome (FCS),
Familial Partial Lipodystrophy (FPL) and
Severely High Triglycerides**



Familial Chylomicronemia Syndrome (FCS):

Ultra-Orphan Disease Caused by Lipoprotein Lipase (LPL) Deficiency

- FCS is a rare lipid disorder (~3-5K patients world wide) associated with extremely high levels of triglycerides, often >2,000 mg/dL
- FCS is caused by genetic defects in genes known to modulate LPL activity, including LPL, apoCII, GPIHBP1, ApoA5 and LMF1
- Patients with FCS are at extreme risk for acute pancreatitis events and other serious conditions
- Limited treatment options for patients with FCS
 - Glybera® – approved in EU for patients with LPL deficiency

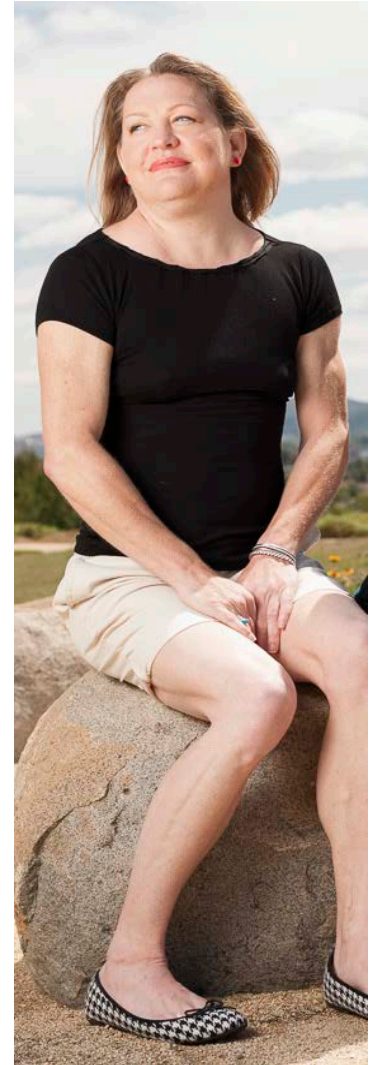


-Lindsey

Familial Partial Lipodystrophy (FPL)

A Second Ultra-orphan Indication for Volanesorsen

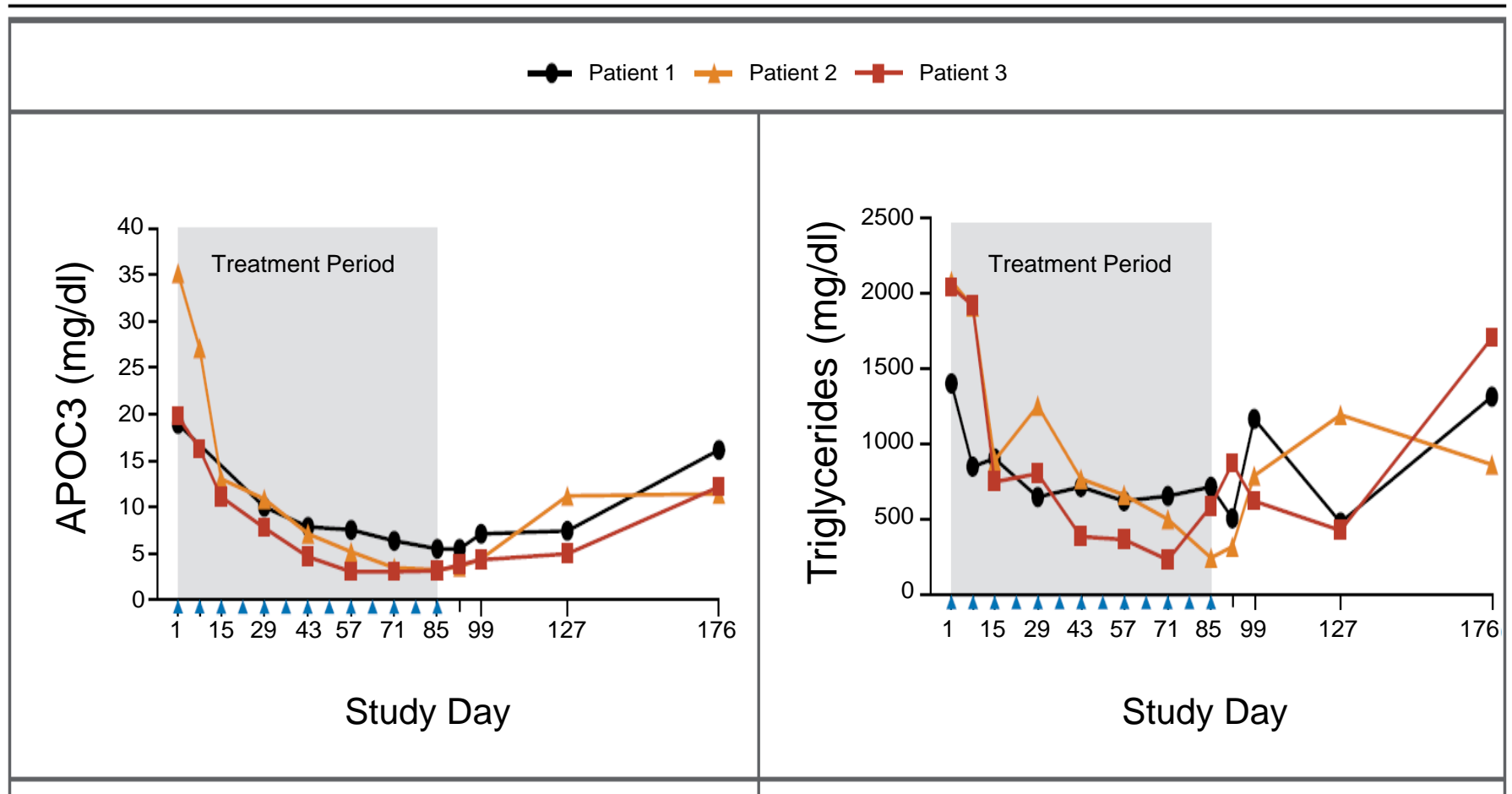
- FPL is a rare lipid disorder (~3-5K patients) characterized by elevated levels of ApoC-III and triglycerides
 - FPL is distinct from generalized lipodystrophy, which is a disease primarily driven by inadequate leptin activity
- Patients with FPL exhibit:
 - Loss of fat from extremities, trunk and gluteal region with excess fat deposits around neck and face
 - Extremely high levels of serum triglycerides and ApoC-III
 - Increased risk for pancreatitis and early atherosclerosis
 - Severe insulin resistance/diabetes
 - Accumulation of fat in liver can cause scarring and cirrhosis, and eventually, liver dysfunction
 - Early cardiovascular events & other co-morbidities
- No approved treatments for patients with FPL
 - Conventional drugs to reduce triglycerides and control glucose do not work well in FPL patients





Targeting APOC3 in the Familial Chylomicronemia Syndrome

Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., and Joseph L. Witztum, M.D.



Volanesorsen Phase 2 Program

Robust TG Lowering in Multiple Patient Populations,
As Monotherapy and in Combination with Fibrates

Triglyceride Reductions

Mean % Decrease from Baseline

MONOTHERAPY



-71%

ADD-ON TO FIBRATE



-64%

HIGH TG WITH T2D



-69%

FCS

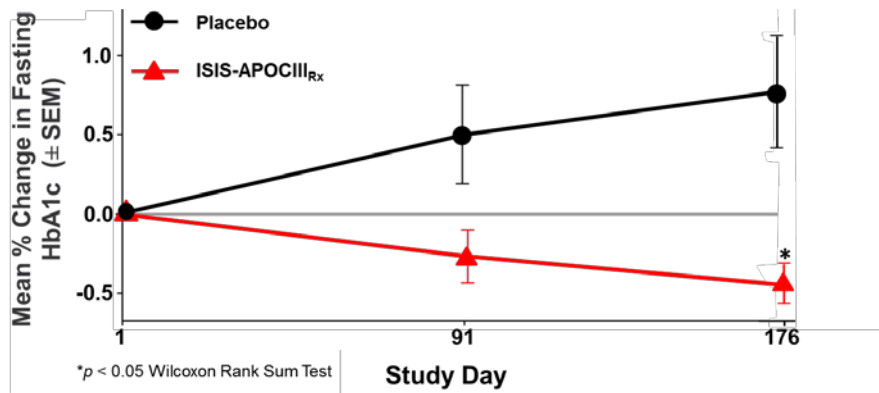


-69%

Volanesorsen: Potential for Additional Profile Benefits

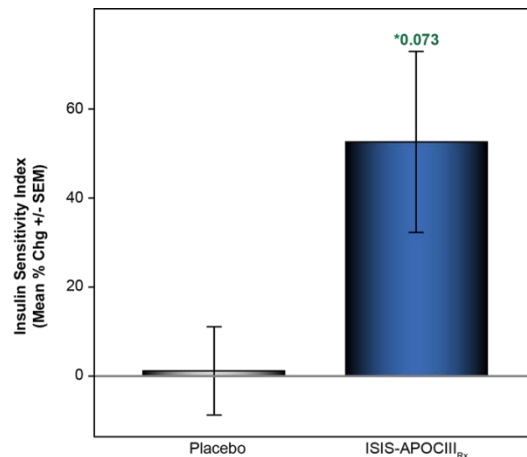
Improved Glucose Control By Multiple Measures

HbA1c Analysis in Diabetic Patients



Euglycemic Clamp

A Measure of Tissue Insulin Sensitivity



*Wilcoxon Rank Sum Test p-value

Important Added Benefit

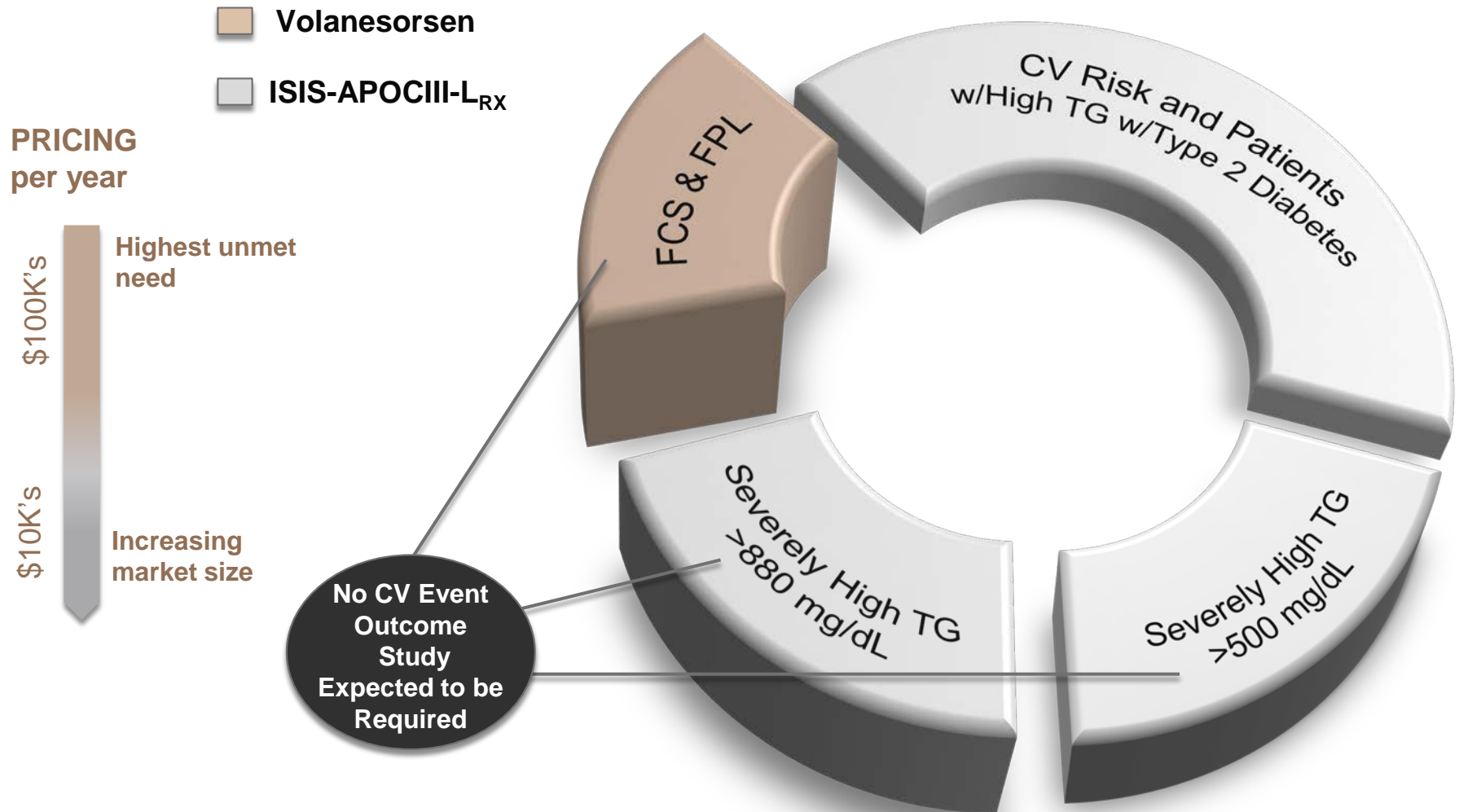
Reduced ApoC-III Improved Glucose Control

- **Decreased HbA1c**
 - ▣ 1.22 percentage-point decrease (Pbo-adjusted)
- **Improved Insulin Sensitivity**
- **Decreased:**
 - ▣ Glycated Albumin
 - ▣ Fasting Fructosamine

ISIS-APOCIII-L_{Rx}: Follow-on to Volanesorsen

- ISIS-APOCIII-L_{Rx} incorporates our LICA technology
 - Up to 10-fold increase in potency
 - Possibility for monthly dosing – enhance patient convenience
- Enhanced profile for broader utility in patients with severely high triglycerides and patients with high triglycerides and type 2 diabetes
- Extends ApoC-III product life cycle
- Phase 1 study initiation planned 1H 2016

Staged Development Plan for Volanesorsen & LICA Follow-on Maximizes Short, Mid, Long Term Value Creation



Volanesorsen: Phase 3 Program

FCS

approach
STUDY

:Phase 3 Study in Patients with FCS

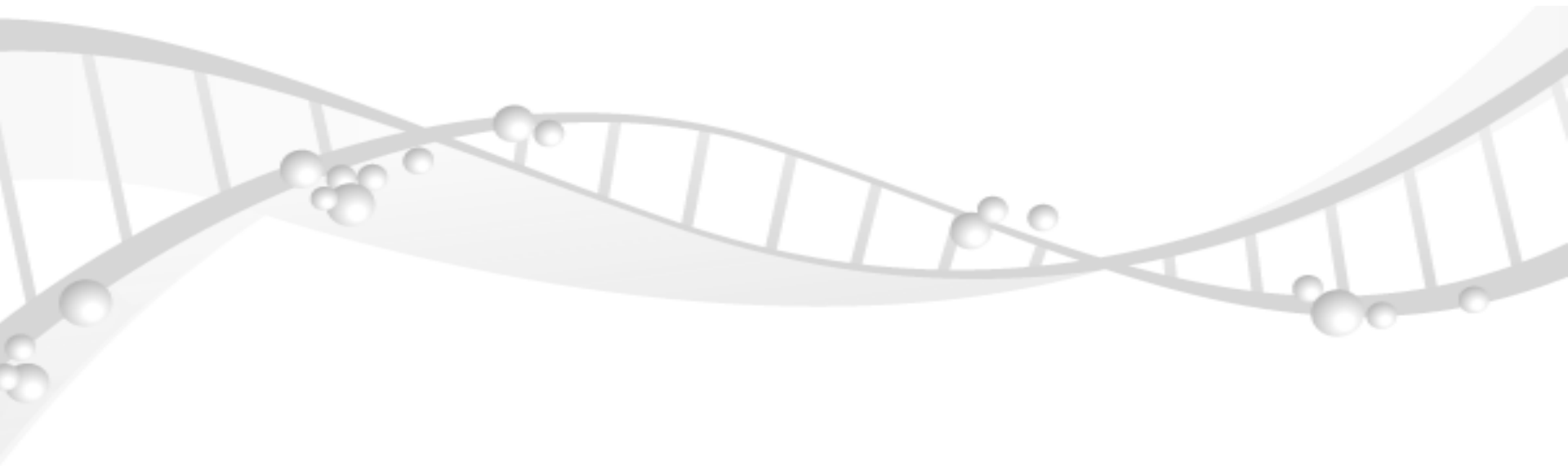
- Initiated August 2014
- 52-week study designed to evaluate the efficacy and safety of 300 mg volanesorsen in patients diagnosed with FCS
- Data planned late 2016/early 2017

FPL

- Phase 3 study initiation planned mid-2015
- Data planned late 2016/early 2017

ISIS-FXI_{Rx}

**Toward a More Effective, Safer Antithrombotic
for Patients at High Risk for Thrombosis**





The NEW ENGLAND
JOURNAL of MEDICINE

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D., David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D., Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D.,
for the FXI-ASO TKA Investigators

- Seven-fold lower incidence of VTE in patients treated with 300 mg ISIS-FXI_{Rx} compared with enoxaparin-treated patients (4% vs. 30%)
- Demonstrates for the first time a clear dissociation between thrombosis and bleeding

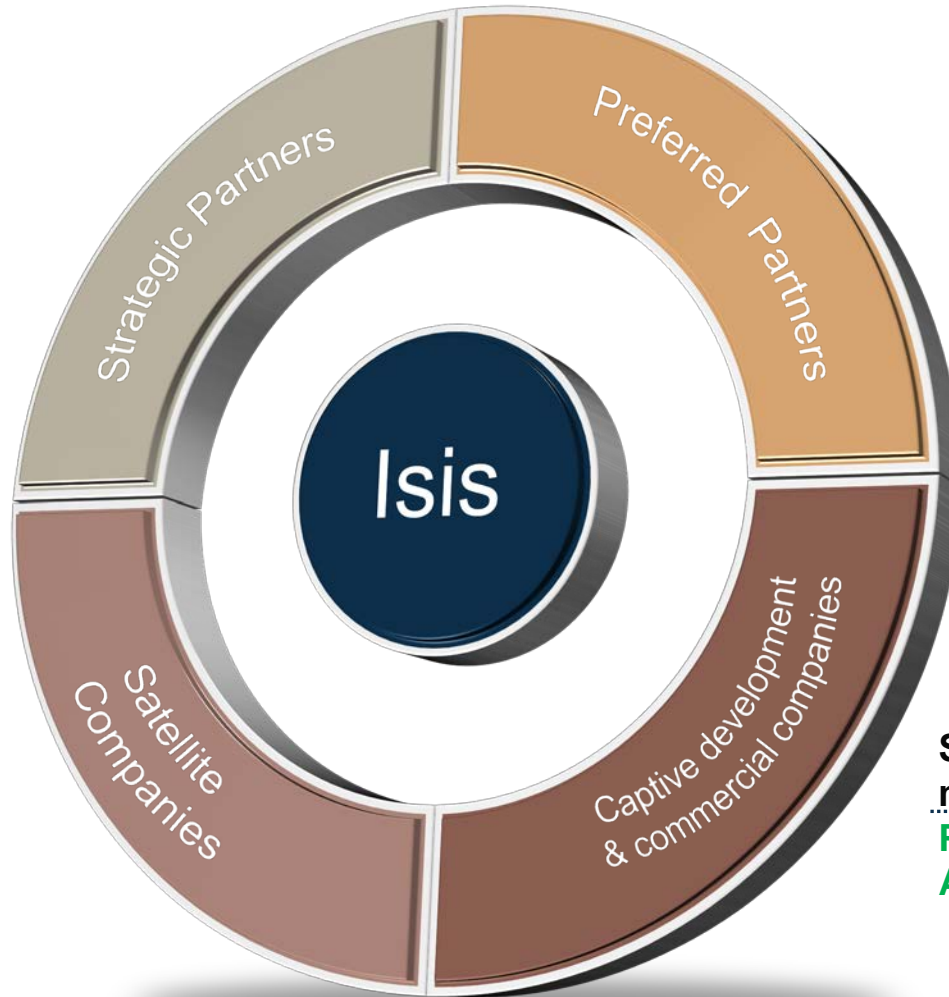
Results From ISIS-FXI_{Rx} Phase 2 Study – Lowest Reported VTE Incidence and 7-fold Reduction vs. Enoxaparin

Drug	ISIS-FXI _{Rx} (Phase 2)	enoxaparin*
Dosing	300mg sub-q weekly	40mg sub-q daily
Rates of VTE and all cause death	4.2%	30.4%
Fold reduction in rates of all VTE and all cause death vs. enoxaparin	7.0	N/A
Rates of Major/CRNM bleeding	2.6% [‡]	8.3% [‡]
Fold reduction in Major/CRNM bleeding vs. enoxaparin	2.7 [‡]	N/A

[‡]Safety set for time period from first study drug administration to end of study

***Enoxaparin results in ISIS-FXI_{Rx} Phase 2 study were consistent with previously published data for enoxaparin in this population**

Strengthening Isis Leadership



**Strengthening
management**
.....
Sarah Boyce, CBO Isis

**Strengthening
management**
.....
**Paula Soteropoulos, CEO
Akcea Therapeutics**

Sarah Boyce – Isis Chief Business Officer

Adds Strategic Business and Commercial Expertise to Isis

- Senior business leader who led global commercialization activities
 - Novartis
 - Alexion
 - Forest Laboratories
- As a member of Isis' senior management team, provides strategic leadership to all business activities
 - Lead Isis' corporate development and patient advocacy groups
 - Oversee Isis' broad alliance activities
 - Provide valuable commercial expertise to Isis' research and development activities



Akcea Therapeutics

Transformative Medicines for Cardiometabolic Lipid Disorders

A development and commercialization company

Focused on delivering transformative medicines for patients with serious cardiometabolic lipid disorders

Near term global commercial opportunity with volanesorsen

Akcea's Pipeline

Advancing Medicines for Cardiometabolic Lipid Disorders

Target Franchise (Genetically Validated Targets)	Lipid Disorders	
	Rare Diseases	Broader Cardiometabolic Diseases
APOCIII <i>Triglycerides</i>	Familial Chylomicronemia Syndrome – Phase 3	Severe High Triglycerides (SHTG)
	Familial Partial Lipodystrophy – Phase 3	High Triglycerides with Type 2 Diabetes
APO(a) <i>Lp(a)</i>	Recurrent CVD with High Lp(a) – Phase 2	Aortic Stenosis with High Lp(a)
		CVD with High Lp(a)
ANGPTL3	Mixed Dyslipidemias	

Building an Experienced Leadership Team

Rare Disease, Lipid and Cardiovascular Focus



Paula Soteropoulos, President & CEO

- 25+ years in Biotech/Pharma/Life Sciences
- Moderna SVP, Rare Diseases, Cardiometabolic and Strategic Alliances; Genzyme GM, Cardiovascular
- Led global development, commercialization, manufacturing ops, strategic alliances, business dvpt
- Rare disease, cardiovascular, oncology, infectious disease, renal



Jeff Goldberg, COO

- 20+ years in Biotech/Pharma/Life Sciences
- Proteostasis, Sanofi, Genzyme
- Led program management, brand leadership, business development & business operations, product launch & commercialization
- Rare disease, neurology, oncology, renal



Molly Harper, VP, Commercial Development

- 15+ years in Biotech/Pharma/Life Sciences
- Genzyme, Merck, UBS Warburg
- Led global marketing, sales; US Commercial Endocrine business
- Rare disease, lipids, atherosclerosis, CV, endocrine



***Andres DiGenio, MD, PhD
VP, Clinical Development***

- Board certified physician/extensive clinical practice
- 15 years in Biotech/Pharma Industry
- Isis, Sanofi, Pfizer, Vanderbilt Cardiovascular Dept
- Clinical development, medical affairs, IND to filing
- Cardiovascular, metabolic/endocrine, rare disease



Alan Gilstrap, Patient Advocacy & Policy

- 24 years in Biotech/Pharma/Life Sciences
- Genzyme, Abbott, Glaxo, Syntex
- Led Patient Advocacy, Sales & marketing, Field sales leadership, Sales training
- Rare disease, lipids and cardiovascular, endocrine

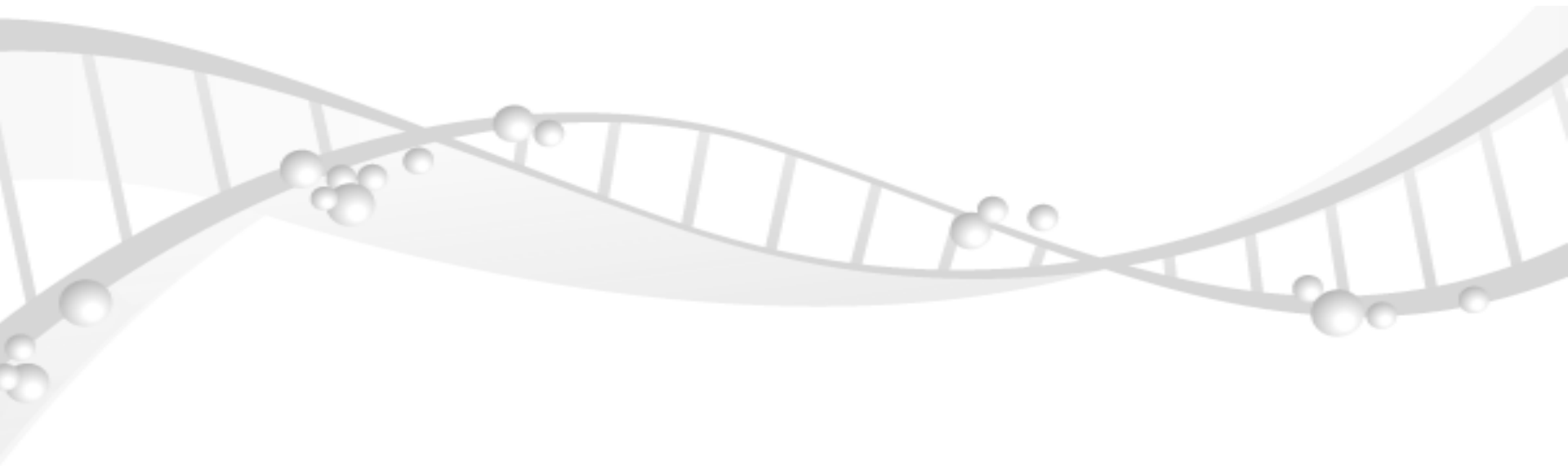


Jonathan Guerriero, Clinical Operations

- 15+ years in Biotech/Pharma/Life Sciences
- Synageva, Radius Health, EMD Serono,
- Program & Operations Leader from Early Stage (Pre-IND) to Late stage (Phase 3, BLA filing)
- Rare disease, neurology, women's health, osteoporosis

Antisense Technology: The Future

Continue to Advance the Technology

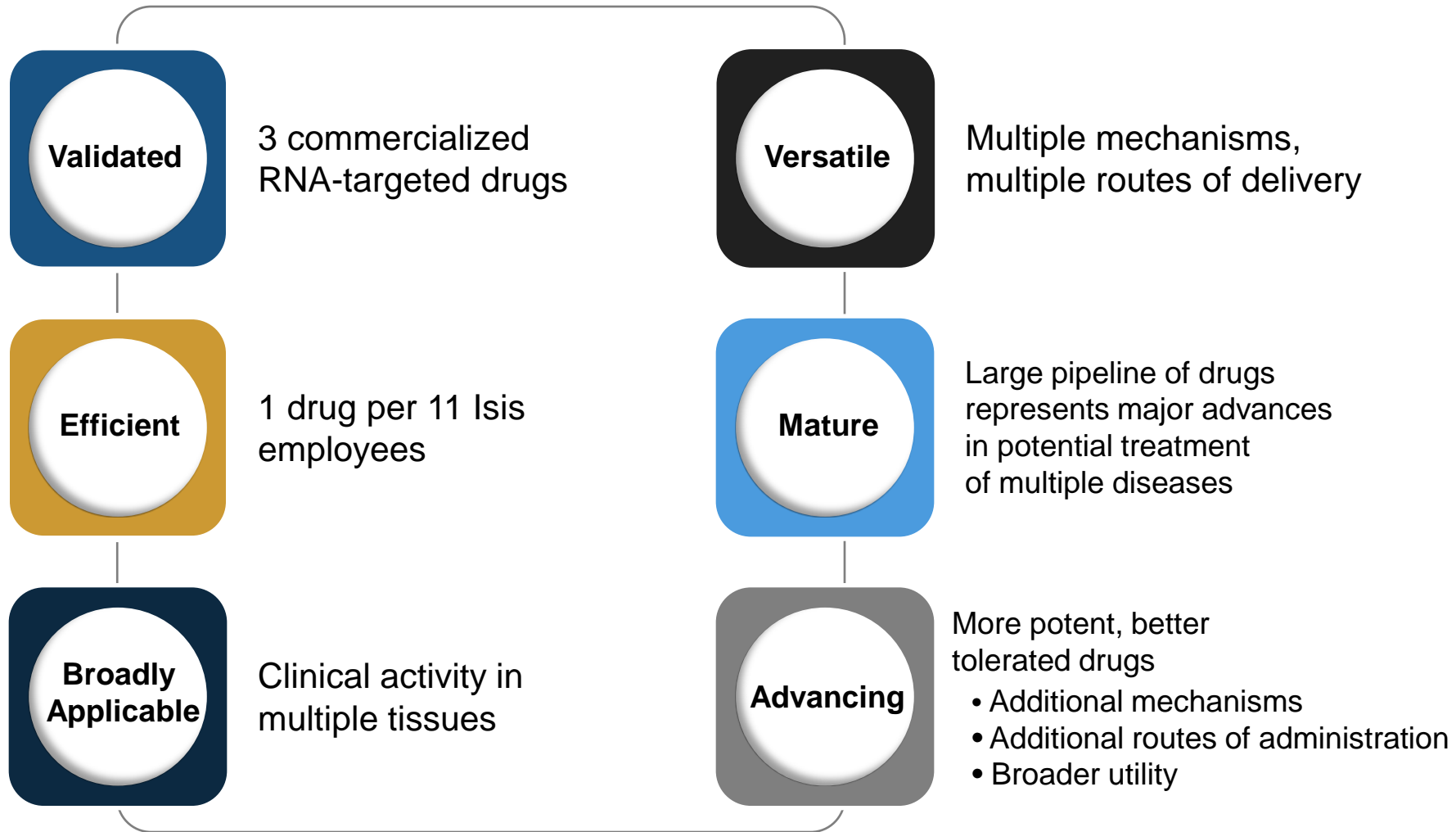


New Mechanisms to Increase Protein Synthesis

- Recent Progress Suggests:
 - Many, if not most, mRNAs regulate their own translation
 - Sequence and structural motifs throughout mRNAs appear to play key roles in regulating translation
- Several new mechanisms identified to enhance protein production
- More than 80% of cellular proteins may be increased specifically using these mechanisms
- Preliminary SAR (structure activity relationship) defined

Isis Antisense Drug Technology

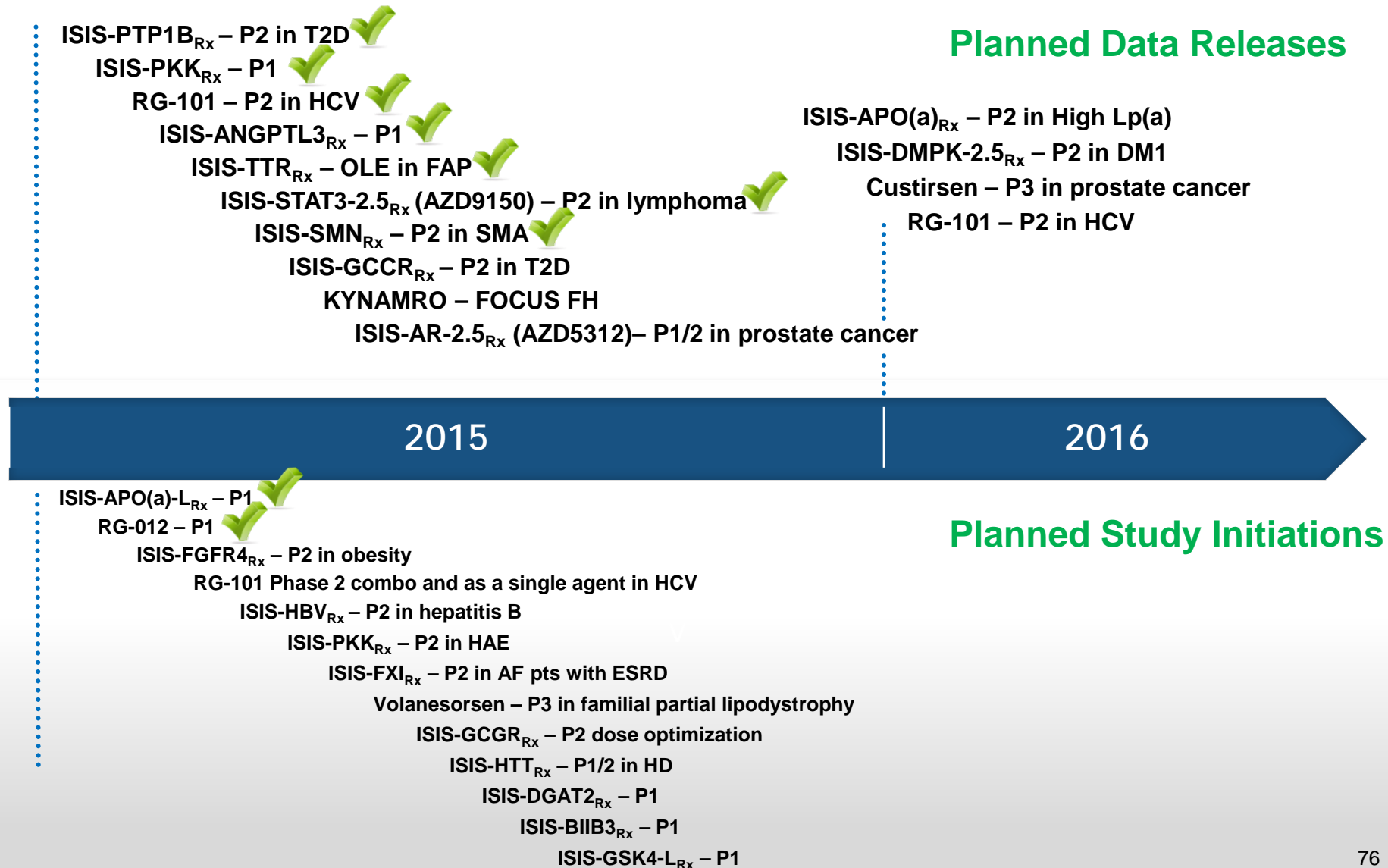
A Proven Drug Discovery Platform



2015 Objectives – On Track

- Continue to successfully execute business strategy to generate revenue and cash
- Advance the pipeline
- Broaden pipeline by adding new drugs in both partnered and unpartnered programs
- Advance the technology

Isis' Broad and Deep Pipeline Creates a Continuous Stream of News



Isis 2015 Guidance

On Track to Improve Upon 2015 Guidance

- Pro Forma NOL: Mid \$50M range
- Cash: Year-end cash of >\$630M
- We are on track to significantly improve upon 2015 guidance

**UPDATE 2015 FINANCIAL GUIDANCE
MID-YEAR**

Isis Pharmaceuticals: The Leader in RNA-targeted Drug Discovery and Development



COMMERCIAL OPPORTUNITIES

Potential for multiple near-term commercial opportunities in lipid and severe and rare diseases



EXPANDING PIPELINE

Broad, mature pipeline of 38 potential first-in-class or best-in-class drugs that will continue to grow



UNIQUE BUSINESS STRATEGY MAXIMIZES VALUE

Broad successes in partnered programs, newly formed development and commercial subsidiary (Akcea), and satellite companies



ADVANCING TECHNOLOGY

Advances in antisense technology improve performance and breadth of utility of our drugs: more potent, better tolerated, enhanced distribution, multiple mechanisms of action



FINANCIAL GROWTH

Unique business strategy coupled to efficiencies of antisense technology enables potential for long-term financial success