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.

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

ISIS PHARMACEUTICALS

The Year In Review

AKCEA THERAPEUTICS

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)

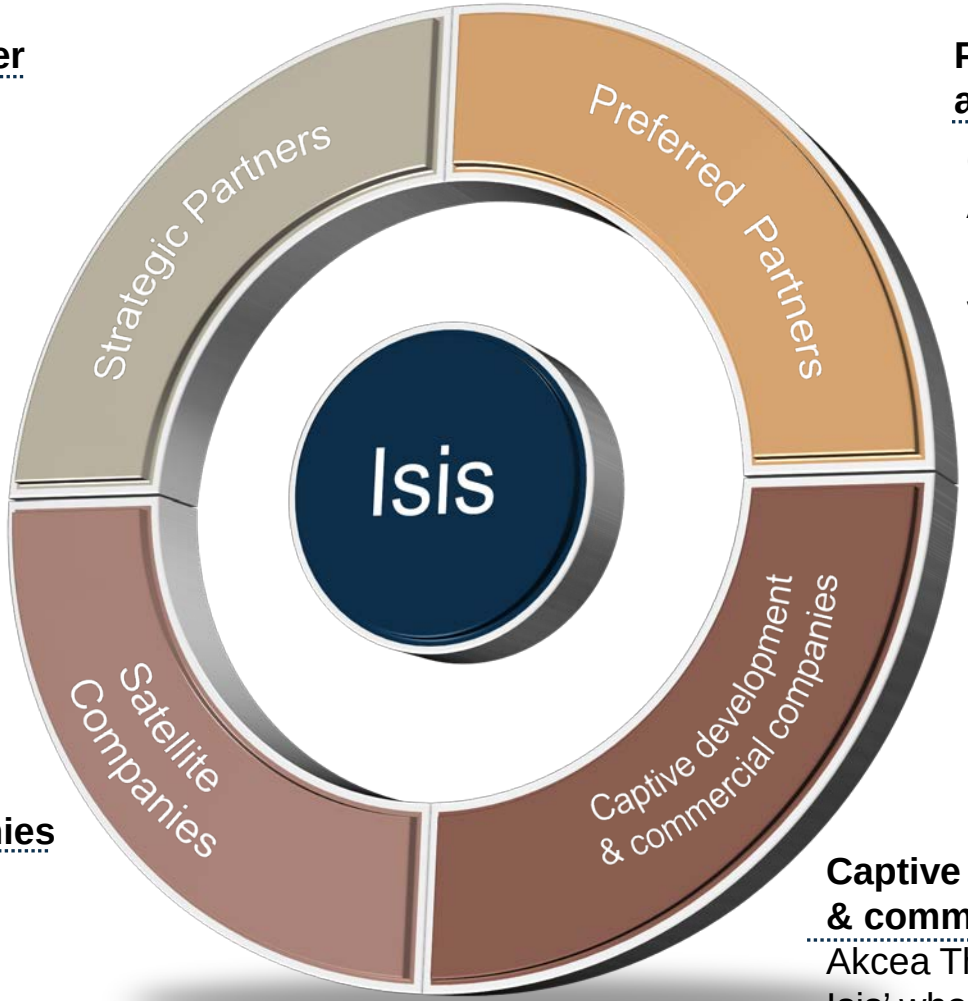
Drug	Indication	Phase
ISIS-TTR$_{Rx}$	Familial Amyloid Polyneuropathy	OLE
ISIS-SMN$_{Rx}$	Spinal Muscular Atrophy (infants) update	2
ISIS-SMN$_{Rx}$	Spinal Muscular Atrophy (children) update	2
ISIS-PTP1B$_{Rx}$	Type 2 Diabetes	2
ISIS-STAT3-2.5$_{Rx}$	Lymphoma	2
ISIS-PKK$_{Rx}$	Healthy Volunteers	1
ISIS-ANGPTL3$_{Rx}$	Healthy Volunteers	1

Positive study

Negative study

Isis' Business Model

Strategic Partner
Biogen – CNS



Preferred Partners and Licensee

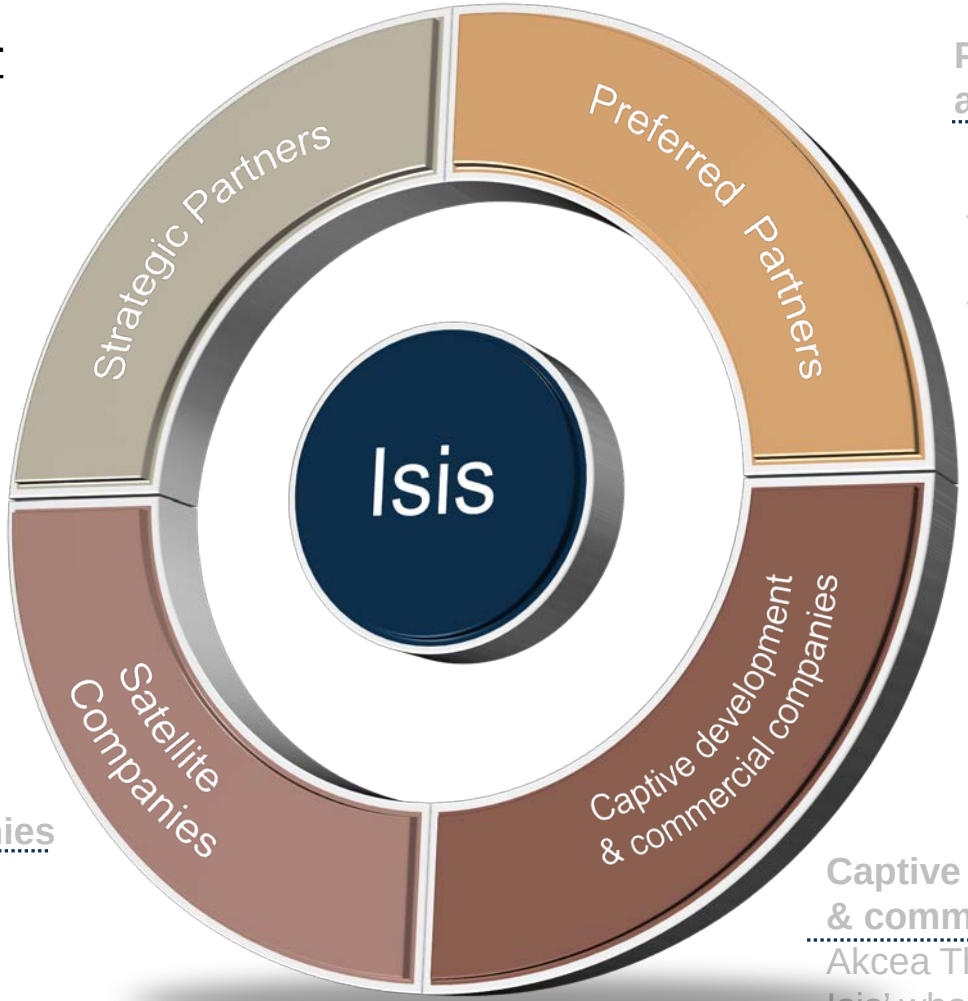
GSK
AstraZeneca
Roche
Janssen (J&J)
Bayer

Satellite Companies
Regulus
Achaogen
ATL
OncoGenex
Atlantic

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

Isis' Business Model

Strategic Partner
Biogen – CNS



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Isis' Business Model

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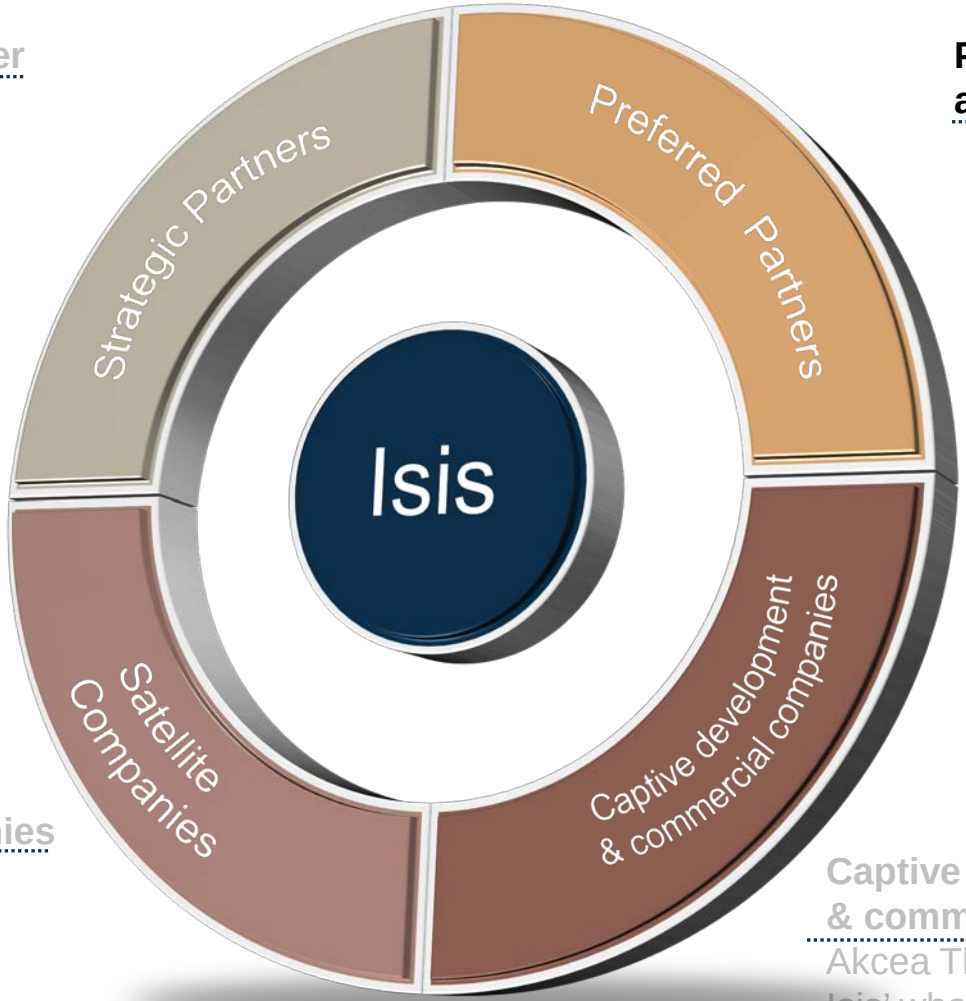
Biogen – CNS



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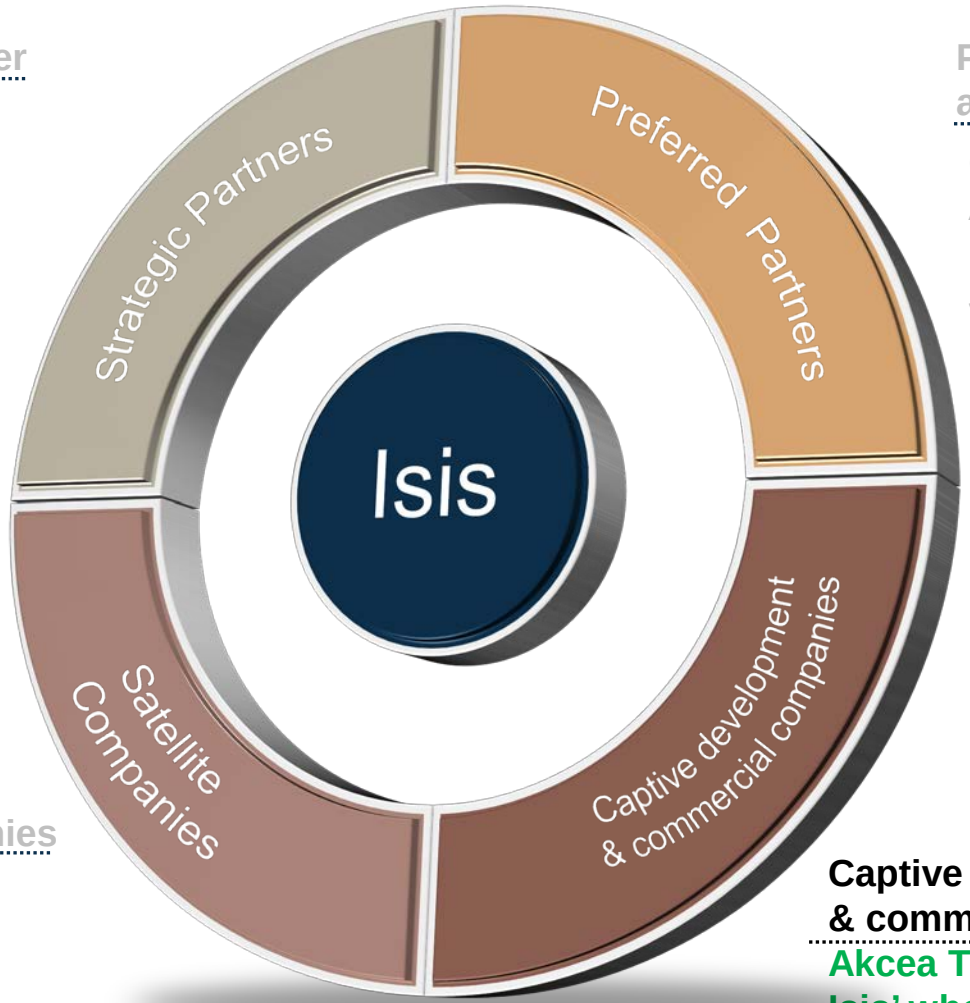

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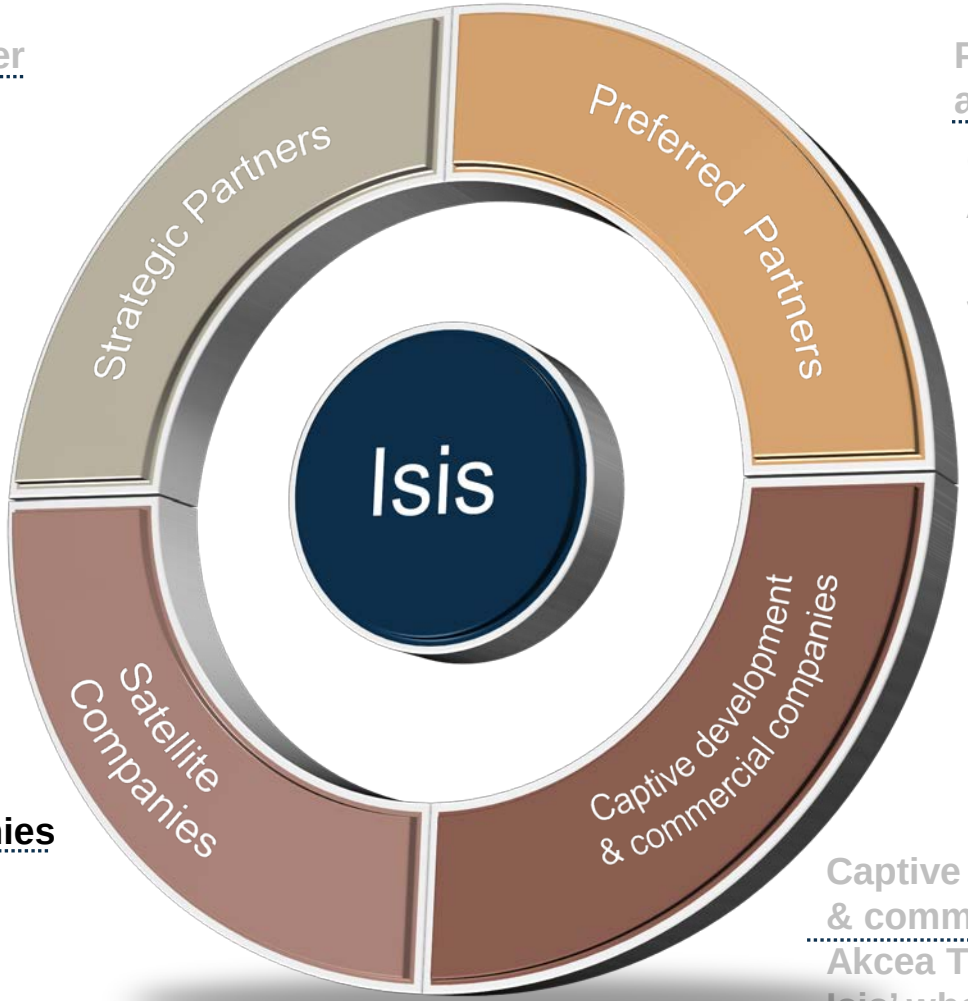
Isis' Business Model

Strategic Partner
Biogen – CNS



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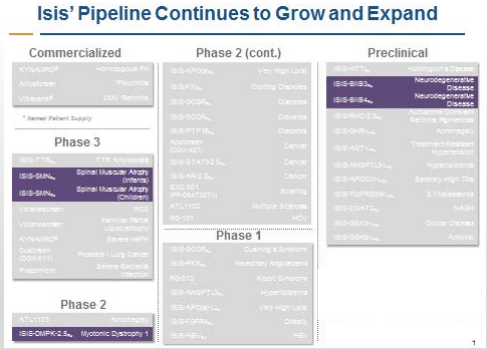
Broad Success and Enhanced Value

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



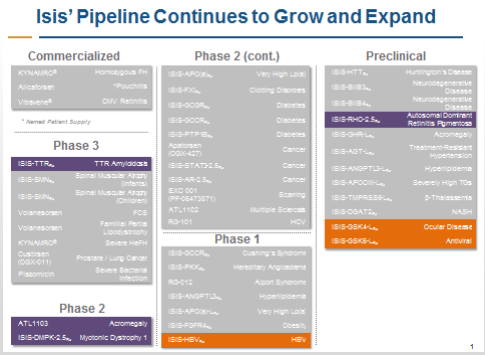
Broad Success and Enhanced Value

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



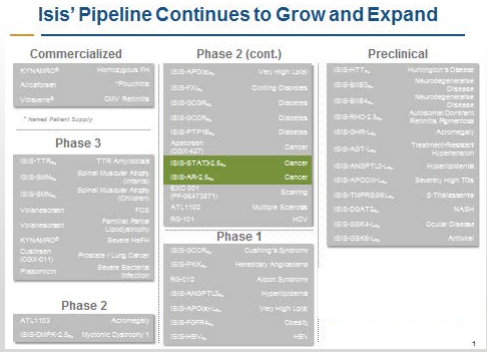
Broad Success and Enhanced Value

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



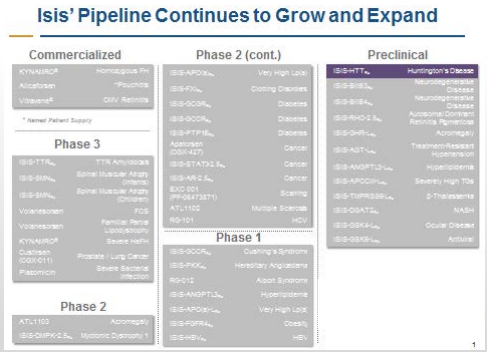
Broad Success and Enhanced Value

Success of Partnered Programs Support Strong Financial Position

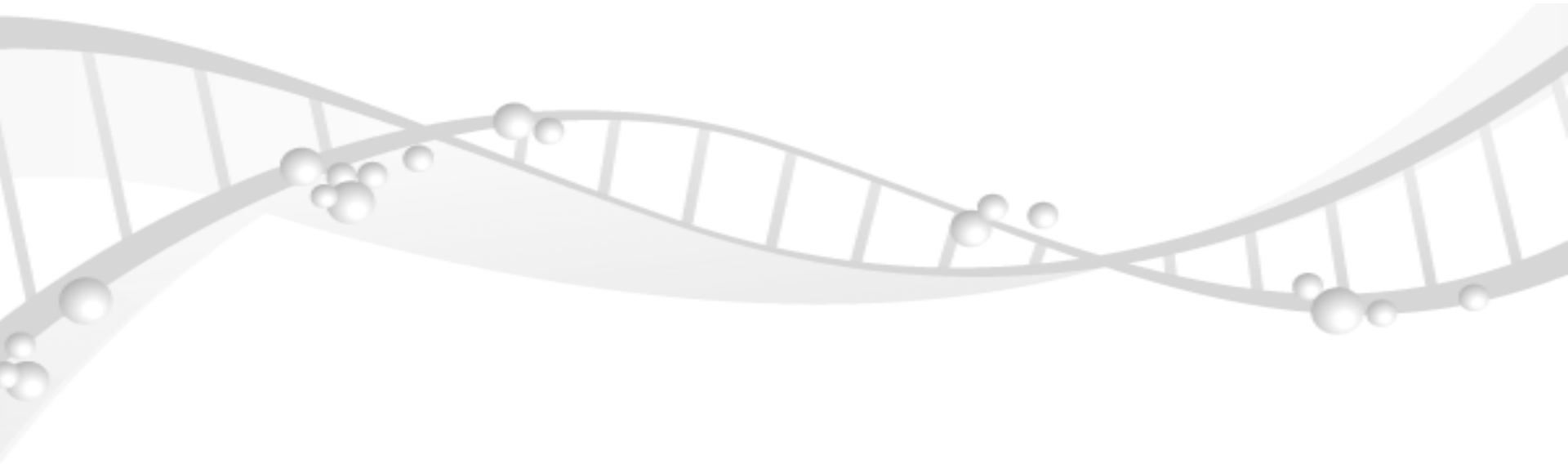
Roche

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

ISIS-HTT$_{Rx}$ — Huntington's Disease



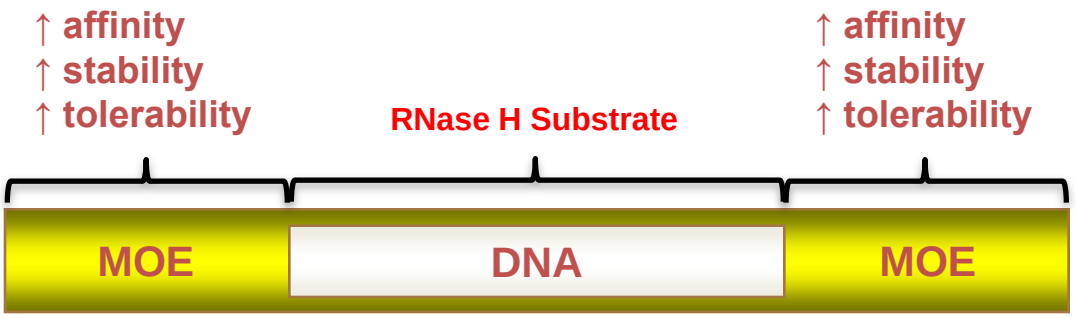
Antisense Technology: Current Status and Future



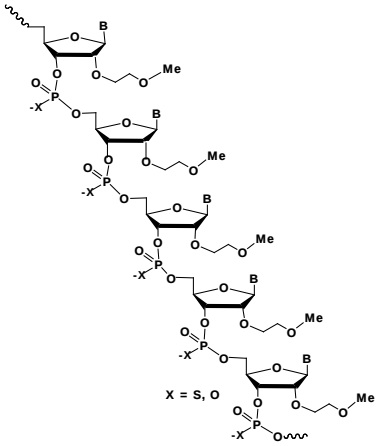
RNase H1 Antisense Mechanism

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:

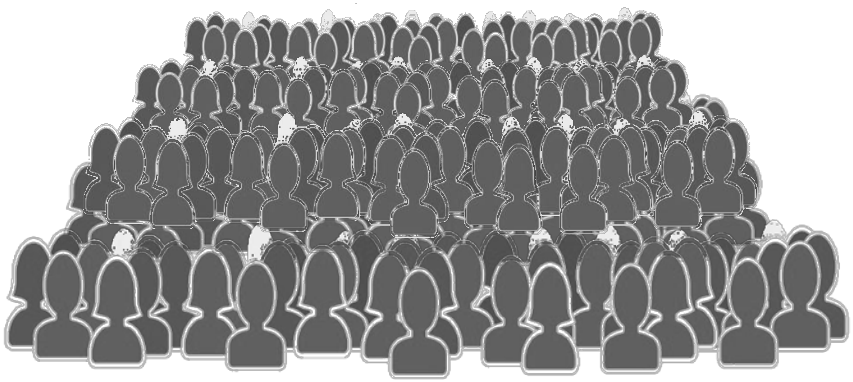
- Increase potency >100 fold
- Increase duration of action 10-20 fold (50-100 fold less drug)
- Decrease unwanted side effects

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**



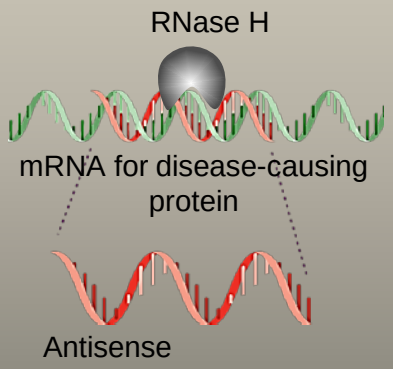
Traditional Pharma
1 drug / ~1,000 employees

ISIS
1 drug / 11 employees

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

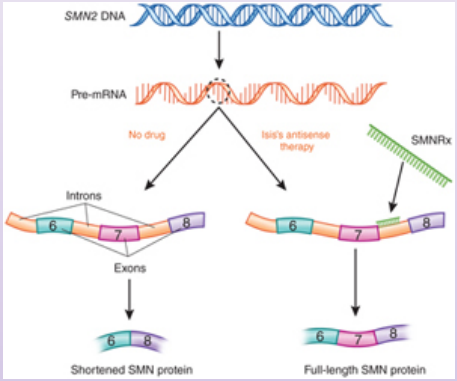
- *Efficient – 1 drug / 11 Isis employee*
- **Robust – multiple mechanisms**
  - **Ability to increase or decrease protein production**
  - **Single-stranded antisense drugs can effectively target RNAs in cytoplasm AND nucleus of the cell**

Reduces target RNA & prevents production of protein



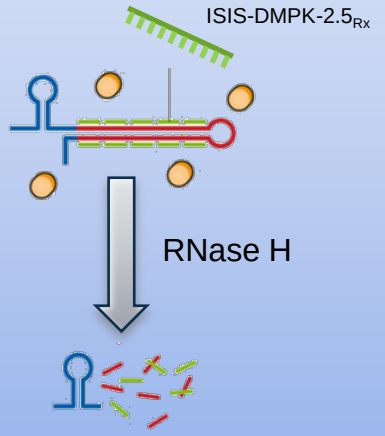
Example: Volanesorsen

Increases production of therapeutic protein



Example: ISIS-SMN$_{Rx}$

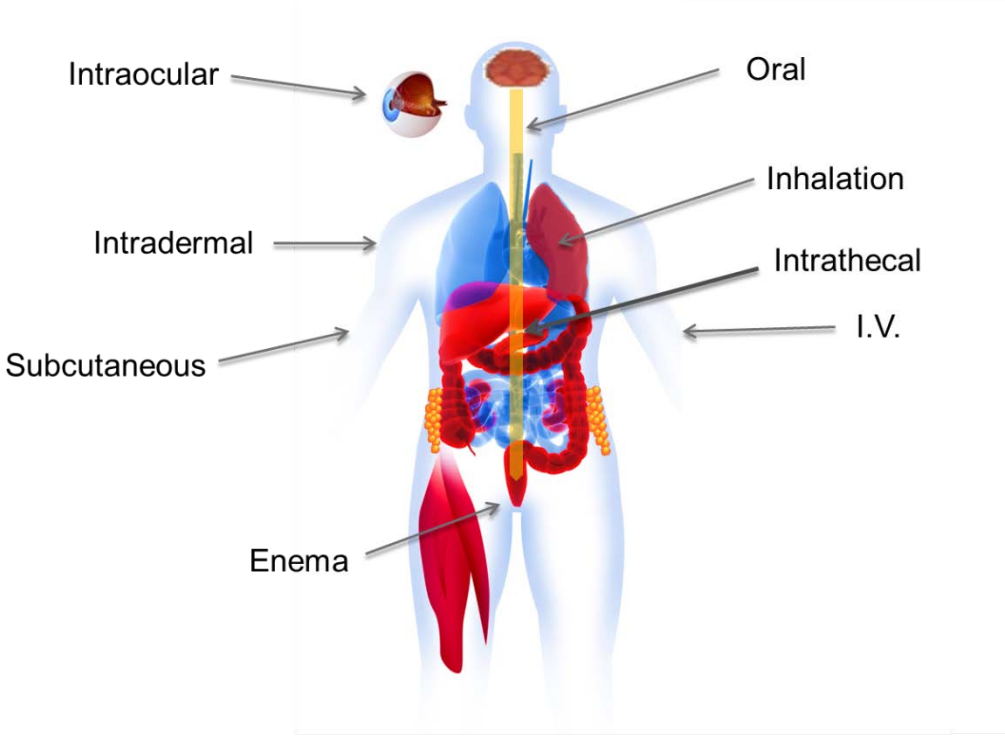
Removes toxic RNA



Example: ISIS-DMPK-2.5$_{Rx}$

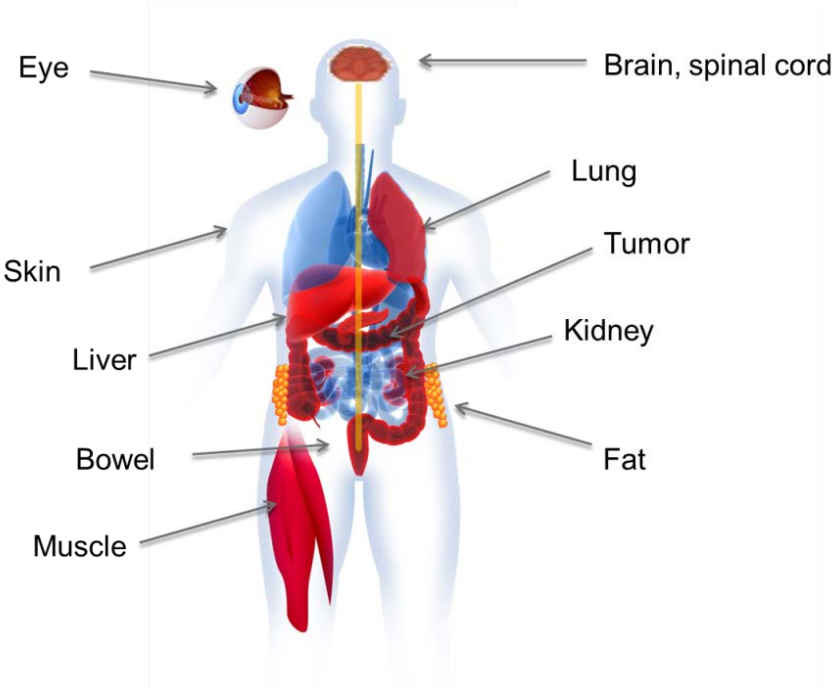
Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- *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**



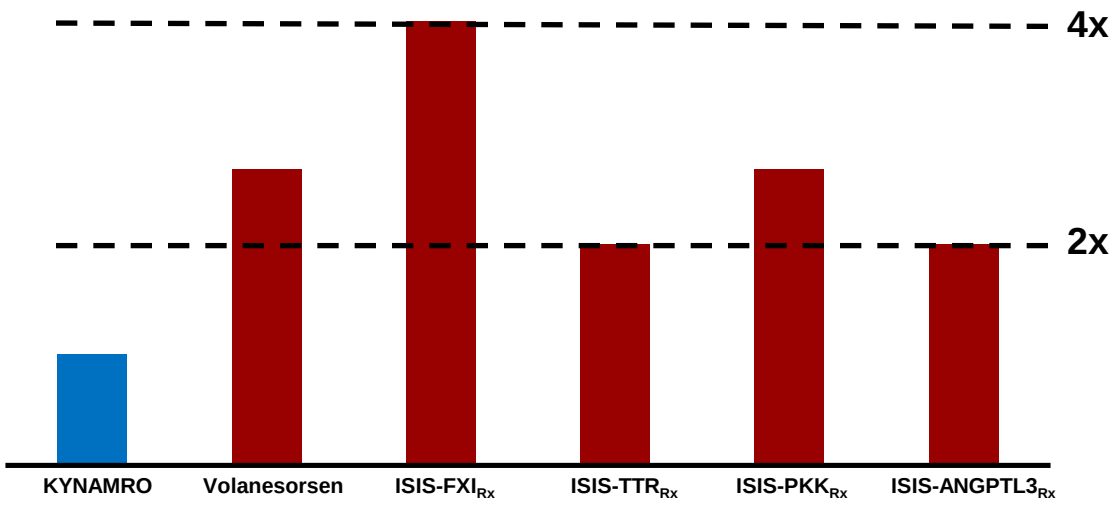
Gen 2.0 Antisense Drugs

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	TNFα	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 ED_{50} 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$_{Rx}$

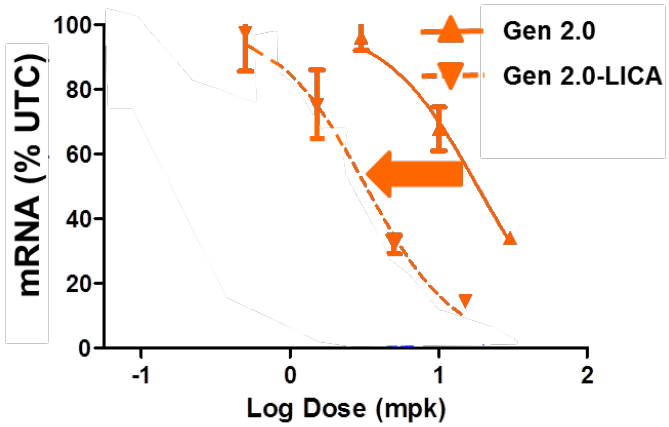
Antisense Compound	ID_{50} in Humans (mg/wk)
Gen 2.0	< 150
Gen 2.5	< 15

Advances in Antisense Technology Broaden Utility and Value

LICA Conjugation

- LICA conjugation technology
  - Enhance effective distribution for liver targets
  - Up to10-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

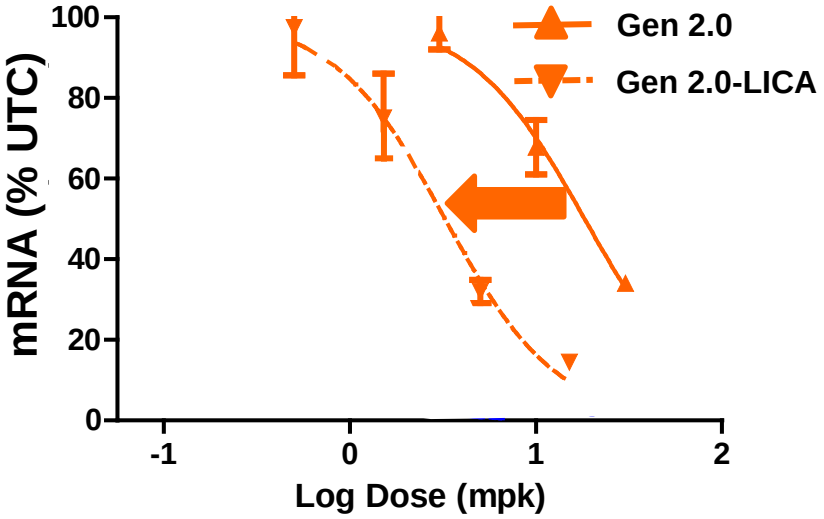
Antisense Compound	ID_{50} in Humans (mg/wk)
Gen 2.0	<150
Gen 2.0-LICA	<15

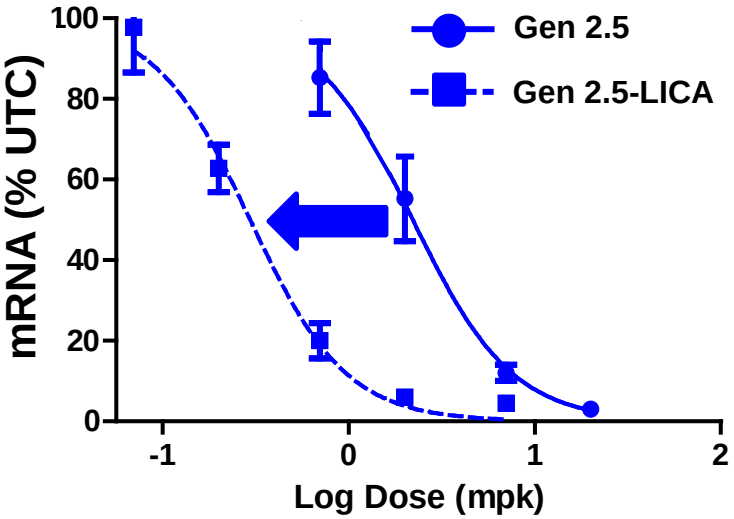


LICA Improves Potency of Gen 2.0 and Gen 2.5 Antisense Compounds

Continue to Advance Antisense Technology

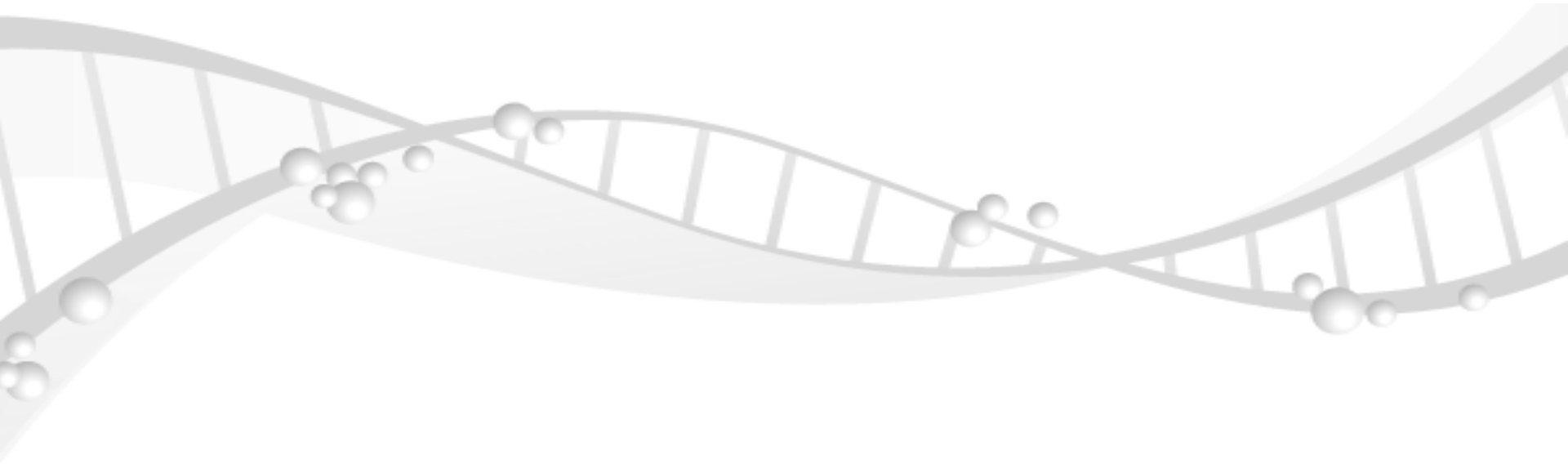
Enhanced affinity and enhanced distribution





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	License After POC	Keep Longer
■ Significant technical or target risk	■ Complex, expensive Phase 3 development	■ Clear Phase 2, Phase 3 development path
■ Complex, difficult, expensive Phase 2 program	■ Straightforward, effective Phase 2 program with definitive endpoints	■ Low to moderate total development costs
■ Challenging endpoints	■ Multiple indications	■ Potential for initial rare disease opportunity
■ Expertise from partner could provide increased likelihood of success	■ Large patient population	■ Consistent with Isis intellectual franchises
	■ Large marketing and sales effort	

Examples:

ISIS-SMN$_{Rx}$ — Biogen

ISIS-DMPK-2.5$_{Rx}$

ISIS-STAT3-2.5$_{Rx}$ (AZD9150) — AstraZeneca

ISIS-AR-2.5$_{Rx}$ (AZD5312)

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

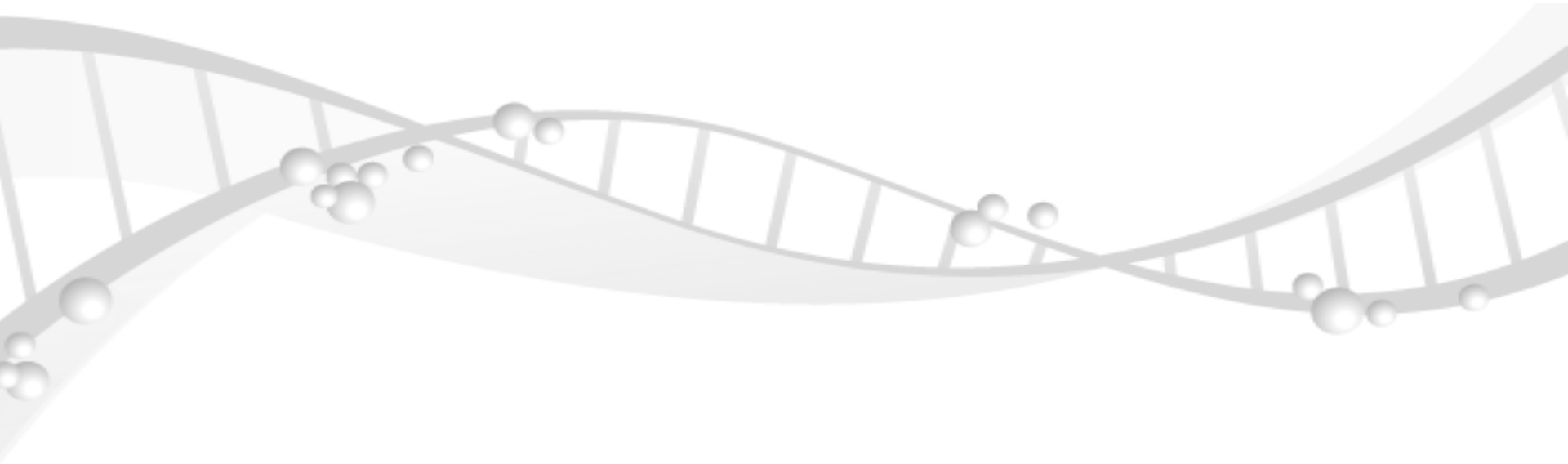
KYNAMRO: Position Strengthening

- 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

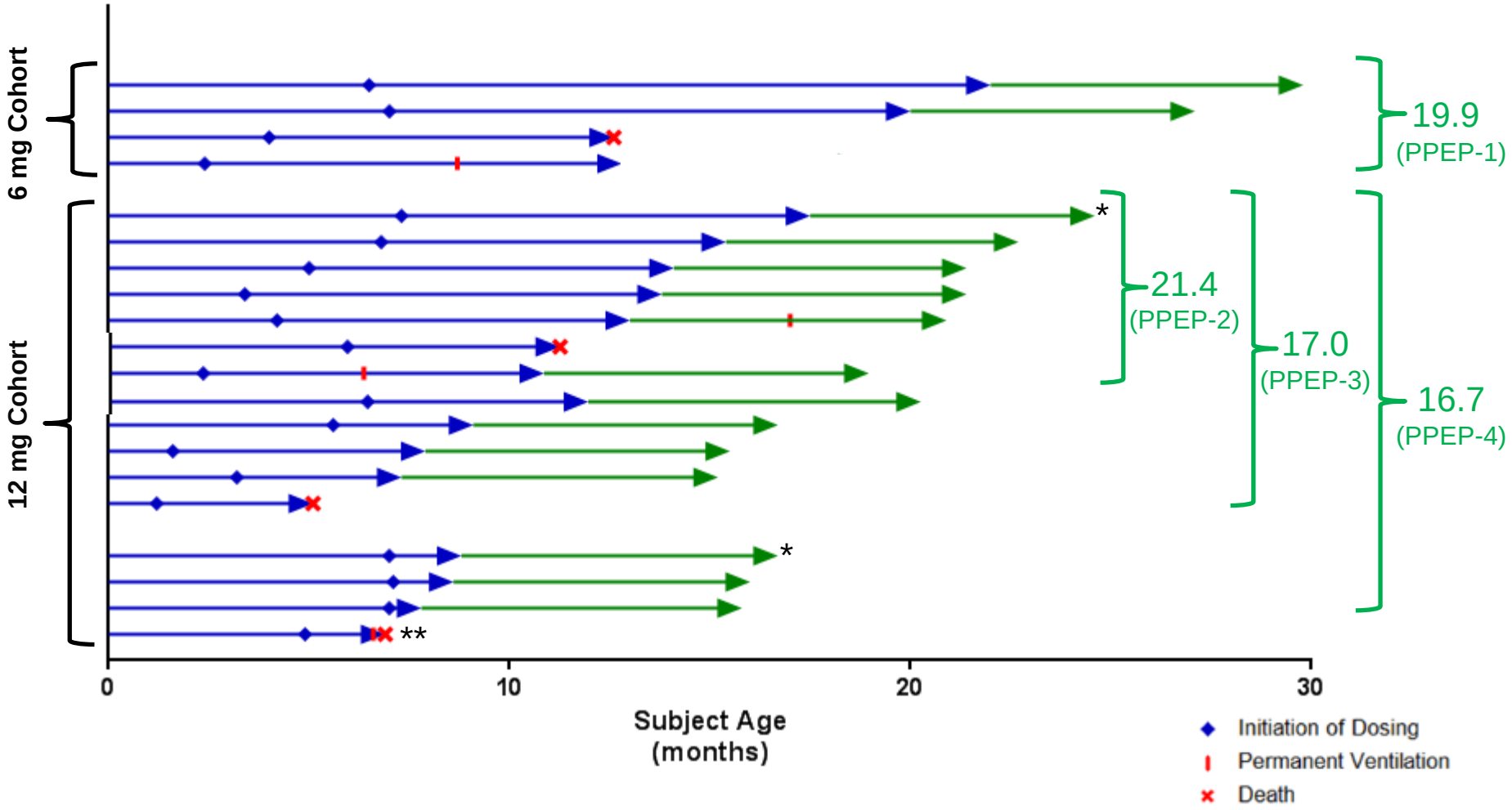
Type I

- 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$_{RX}$

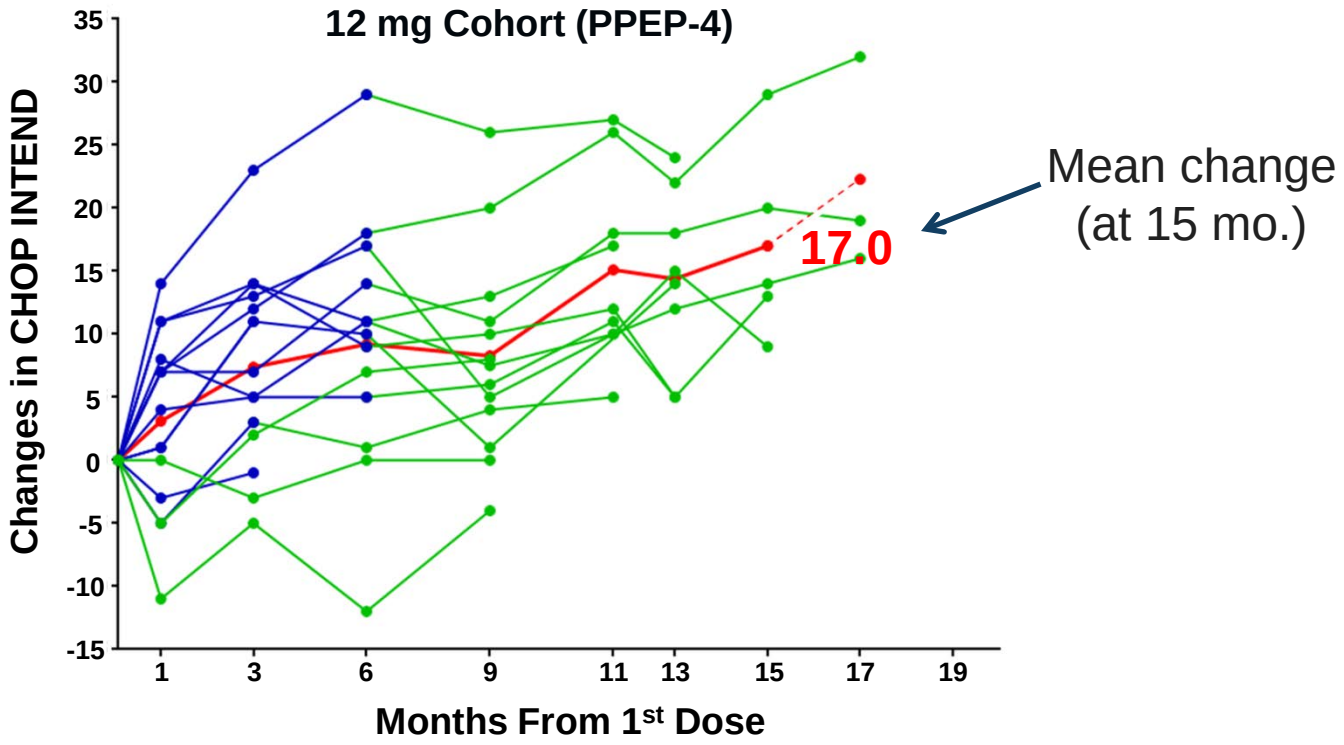
Phase 2 Open-label Study as of Sept 2, 2014 and as of April 17, 2015



*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

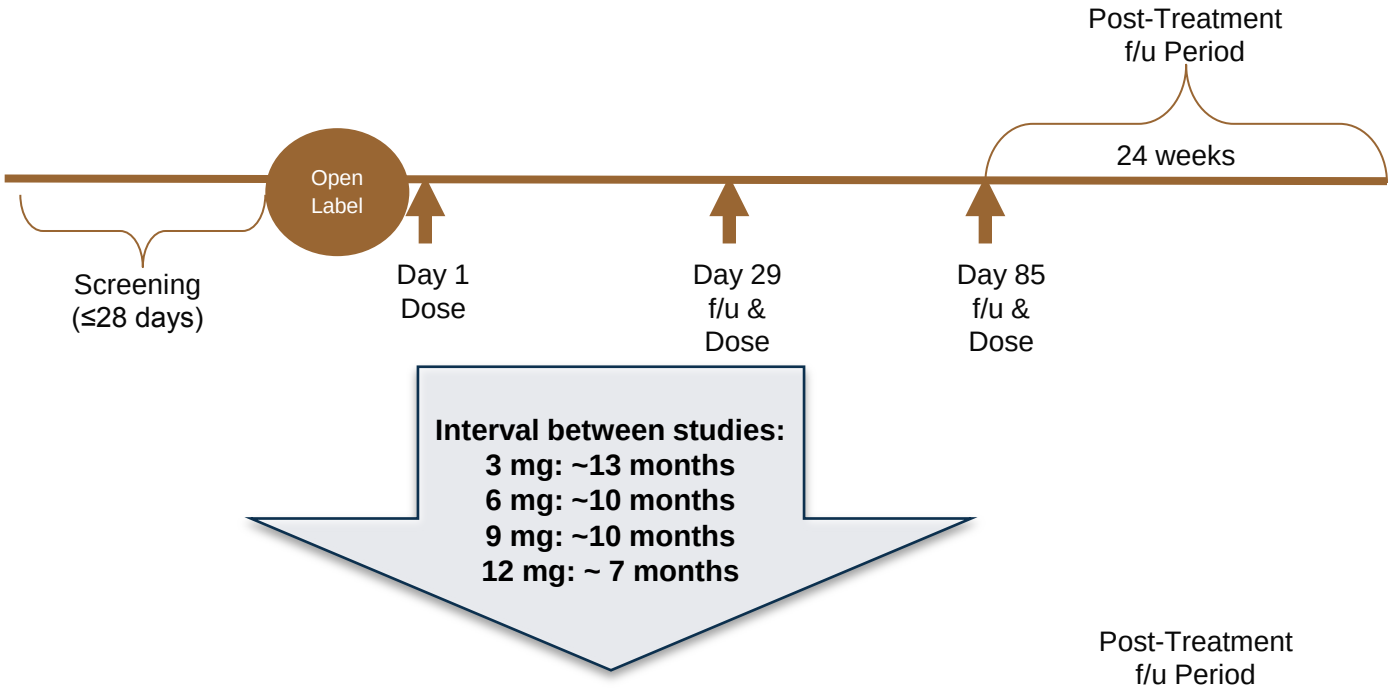
- Prospective studies show continued decline in motor function scores (HFMSE) in children with Type II / Type III SMA, mean change in HFMSE score at:
  - Year 1 = 0.15*
  - Year 2 = - 0.54**
  - Year 3 = - 1.71**

* 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

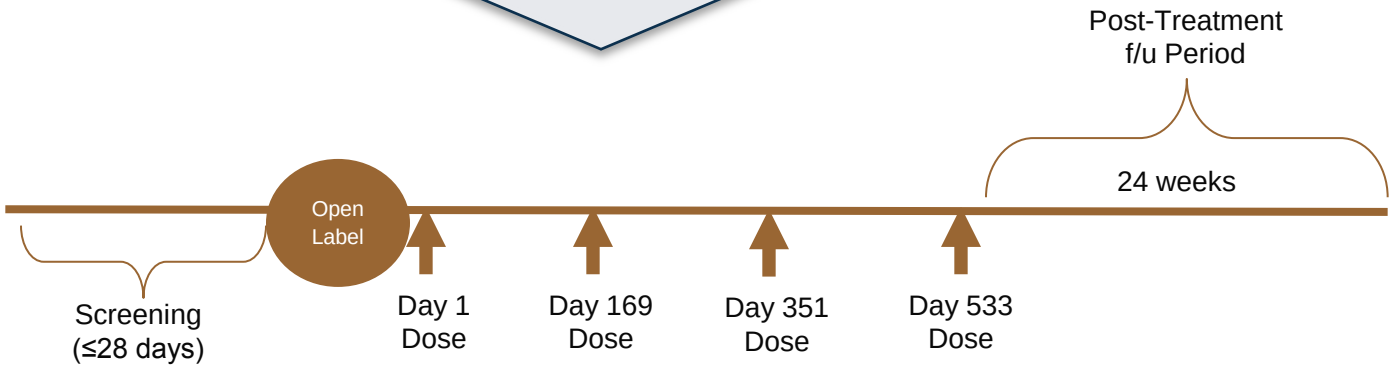
Phase 2 Study

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

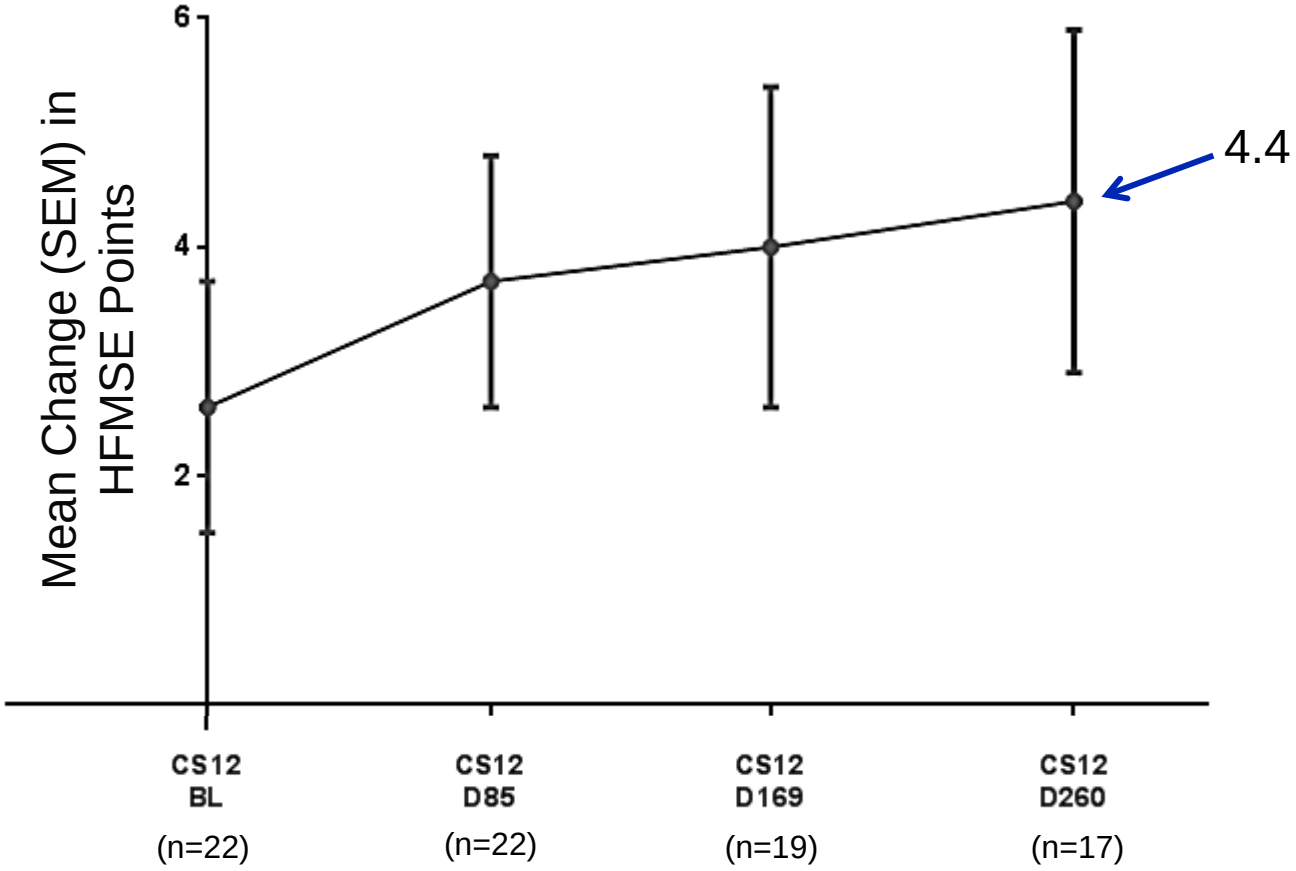
As of May 15, 2015

- 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$_{Rx}$

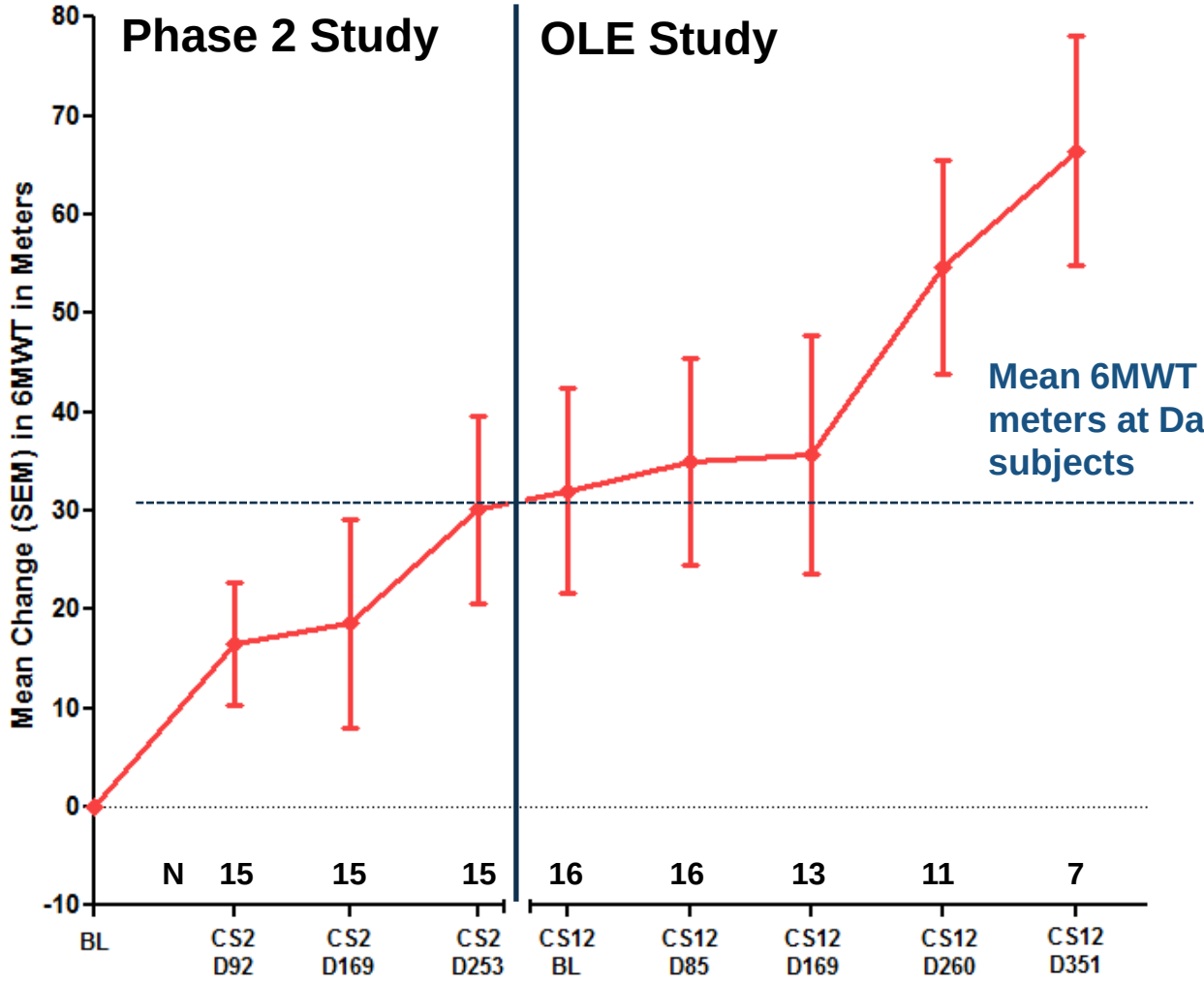
As of May 15, 2015



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



Mean 6MWT scores increased by 55 meters at Day 260 in all ambulant subjects

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

ISIS-TTR$_{Rx}$

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

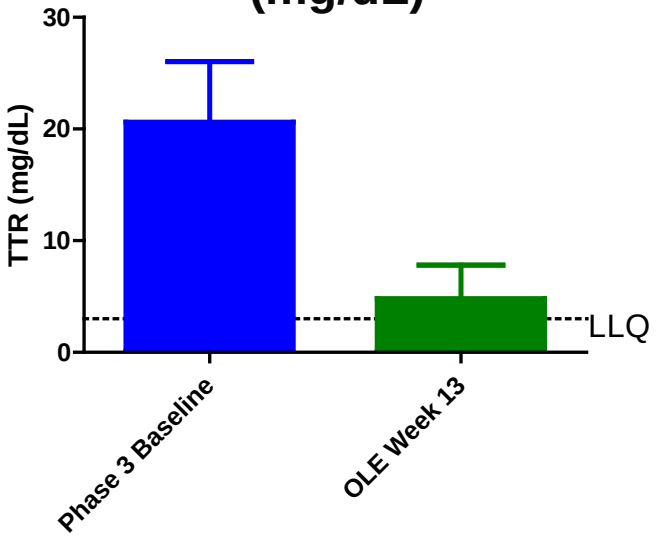
Potentially First-In-Class & Best-In-Class

- 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

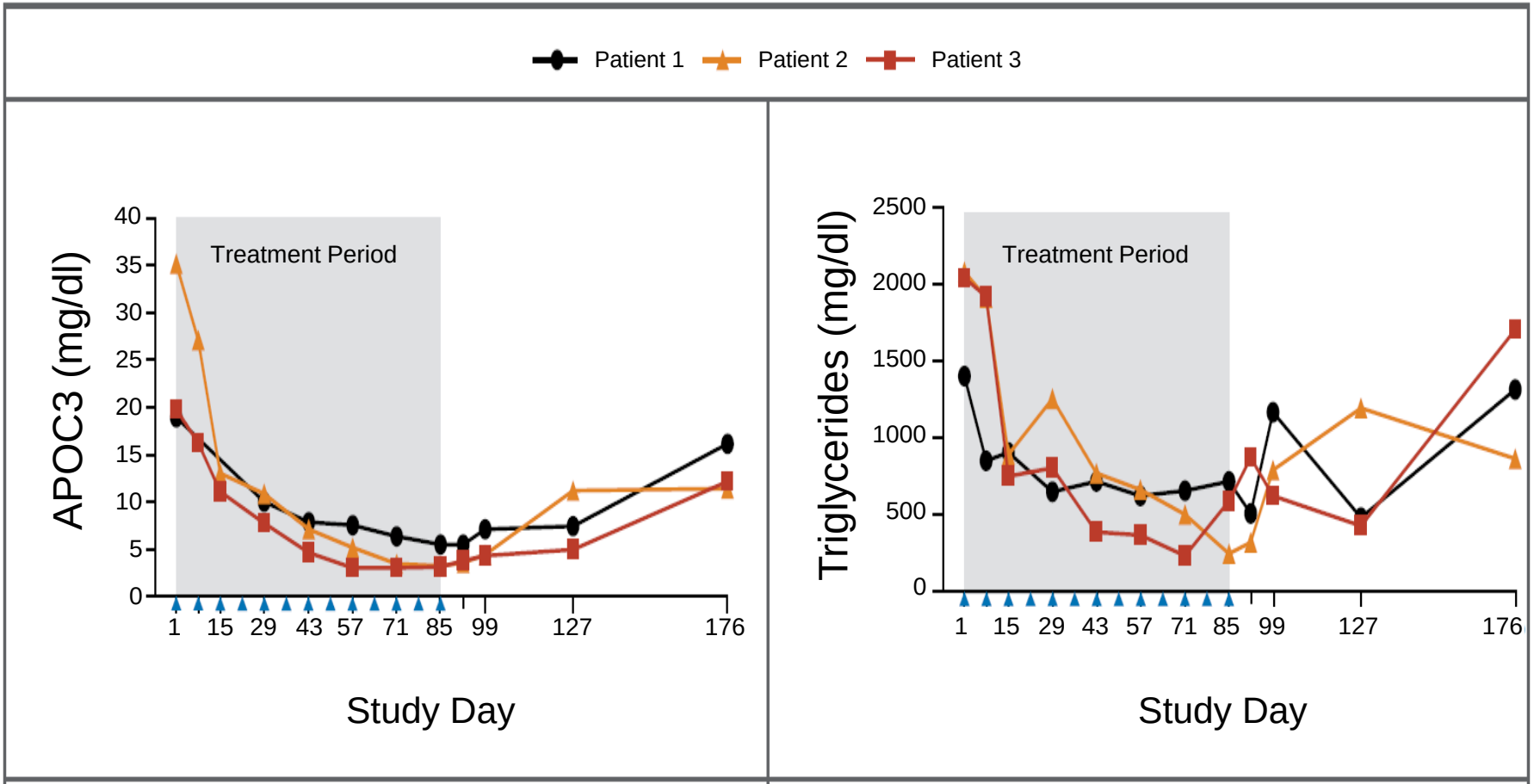
- FPL is a rare lipid disorder (~3-5K patients) characterized by elevated levels of ApoC-III and triglycerides
  - FPL is distinct from generalized lipodystrophy, which is a disease primarily driven by inadequate leptin activity
- Patients with FPL exhibit:
  - Loss of fat from extremities, trunk and 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

-Andra

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.



Volanesorsen Phase 2 Program

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

Triglyceride Reductions

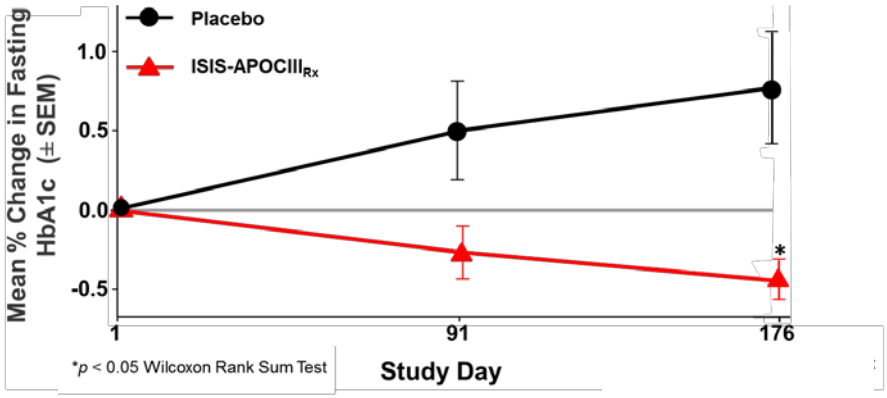
Mean % Decrease from Baseline

MONOTHERAPY	ADD-ON TO FIBRATE	HIGH TG WITH T2D	FCS
			
-71%	-64%	-69%	-69%

Volanesorsen: Potential for Additional Profile Benefits

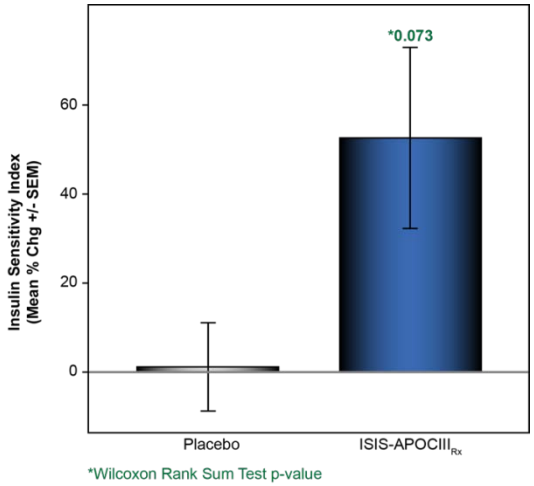
Improved Glucose Control By Multiple Measures

HbA1c Analysis in Diabetic Patients



Euglycemic Clamp

A Measure of Tissue Insulin Sensitivity



Important Added Benefit

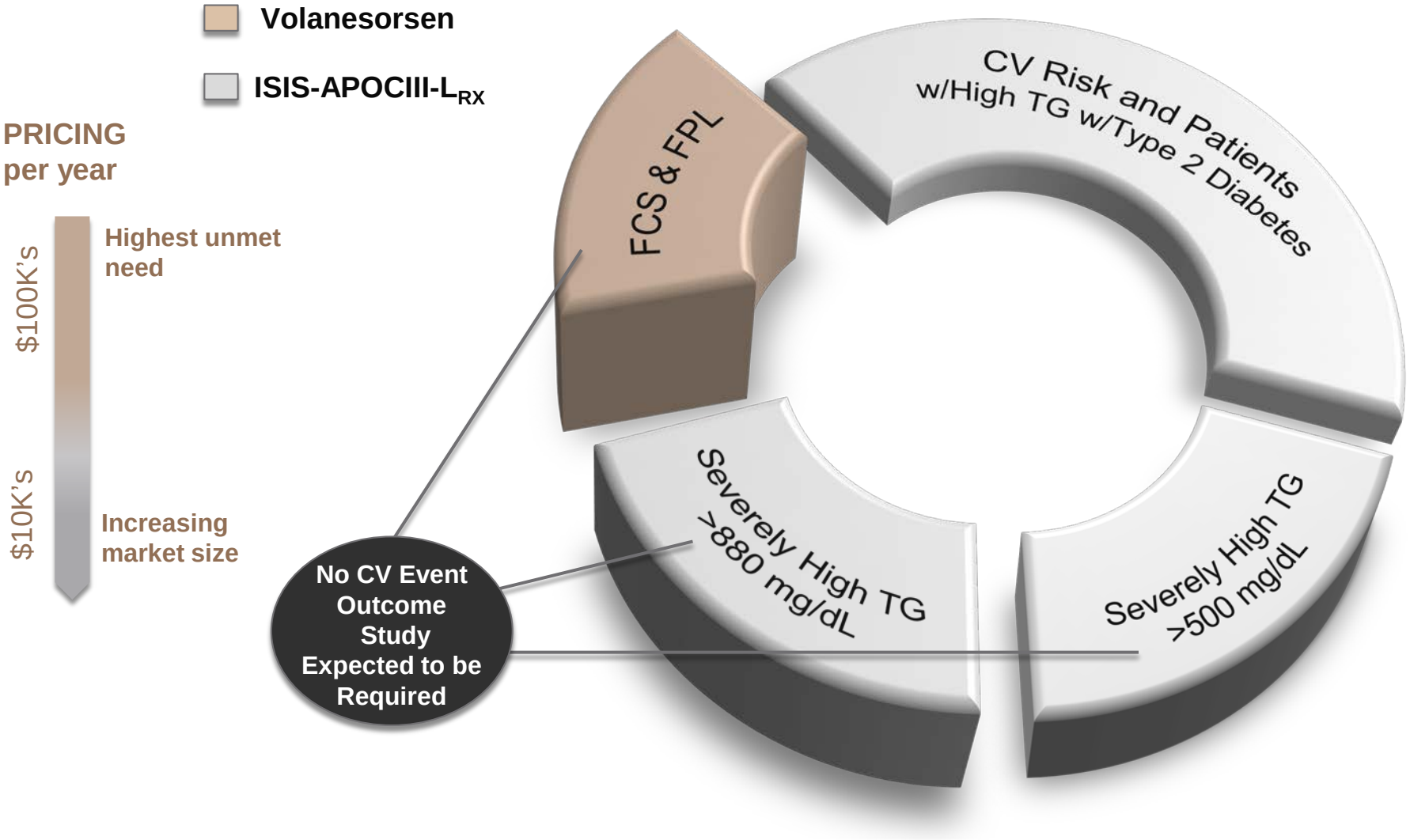
Reduced ApoC-III Improved Glucose Control

- **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

:Phase 3 Study in Patients with FCS

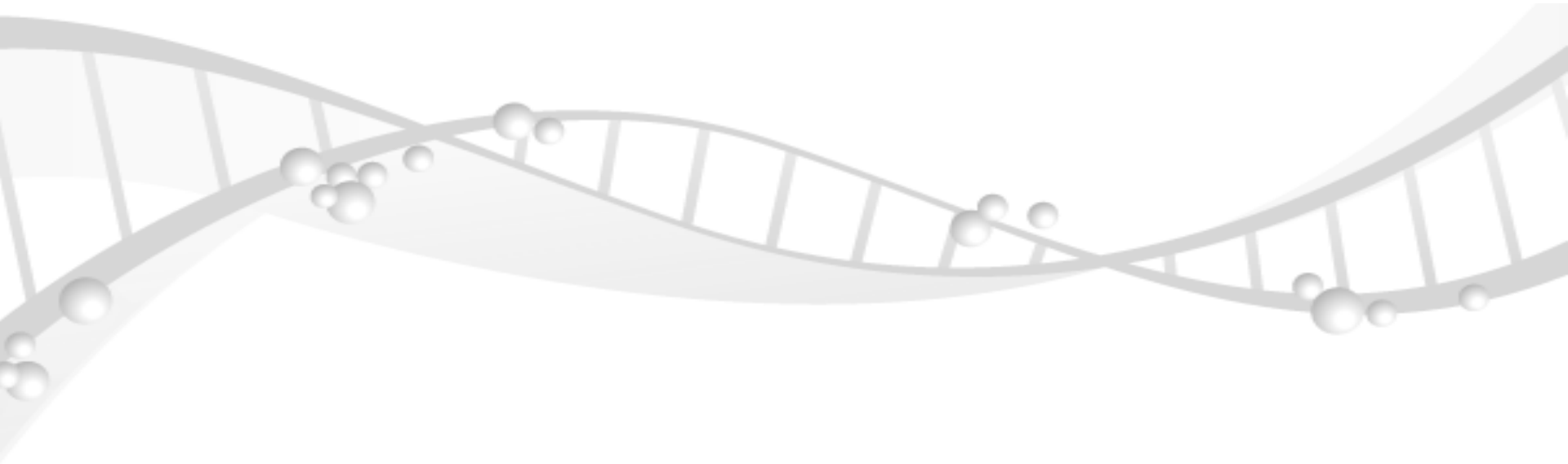
- Initiated August 2014
- 52-week study designed to evaluate the efficacy and safety of 300 mg volanesorsen in patients diagnosed with FCS
- Data planned late 2016/early 2017

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



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

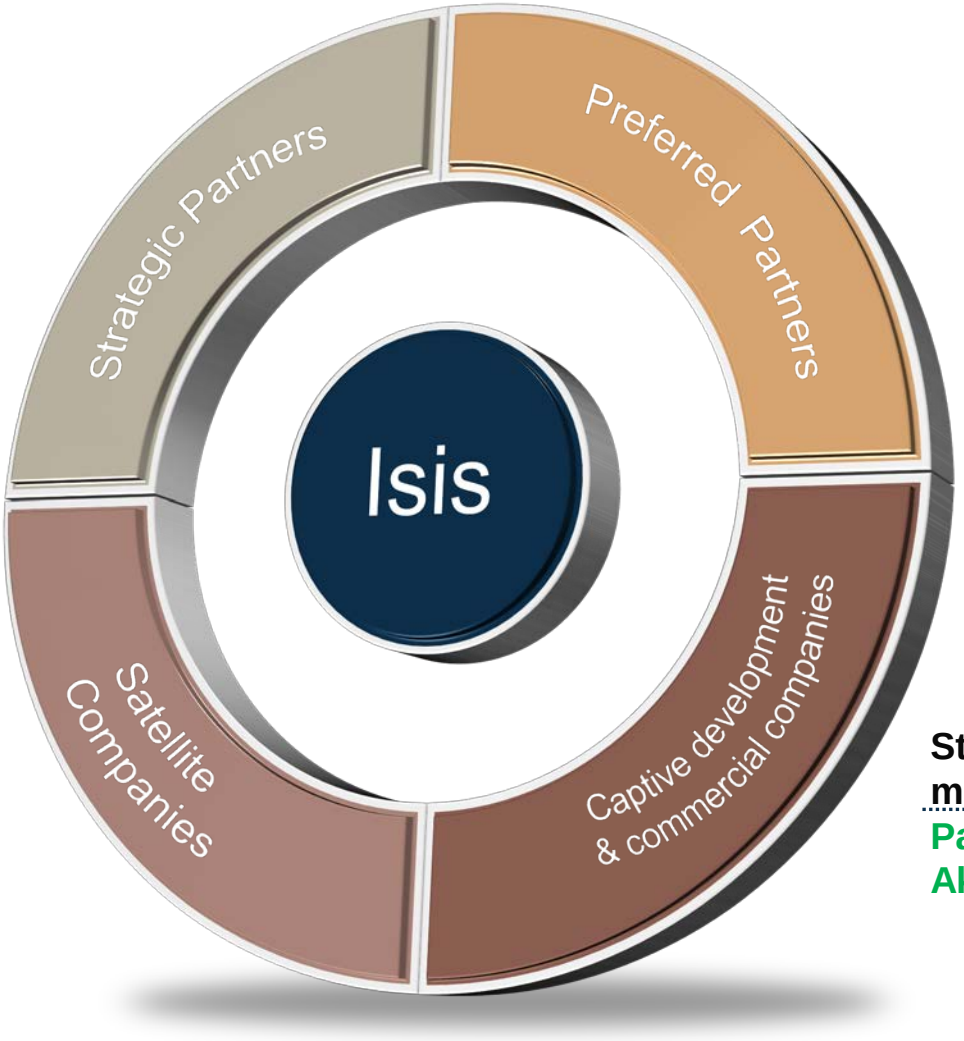
‡Safety set for time period from first study drug administration to end of study

***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 ***Triglycerides***	Familial Chylomicronemia Syndrome – Phase 3	Severe High Triglycerides (SHTG)
	Familial Partial Lipodystrophy – Phase 3	High Triglycerides with Type 2 Diabetes
APO(a) ***Lp(a)***	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

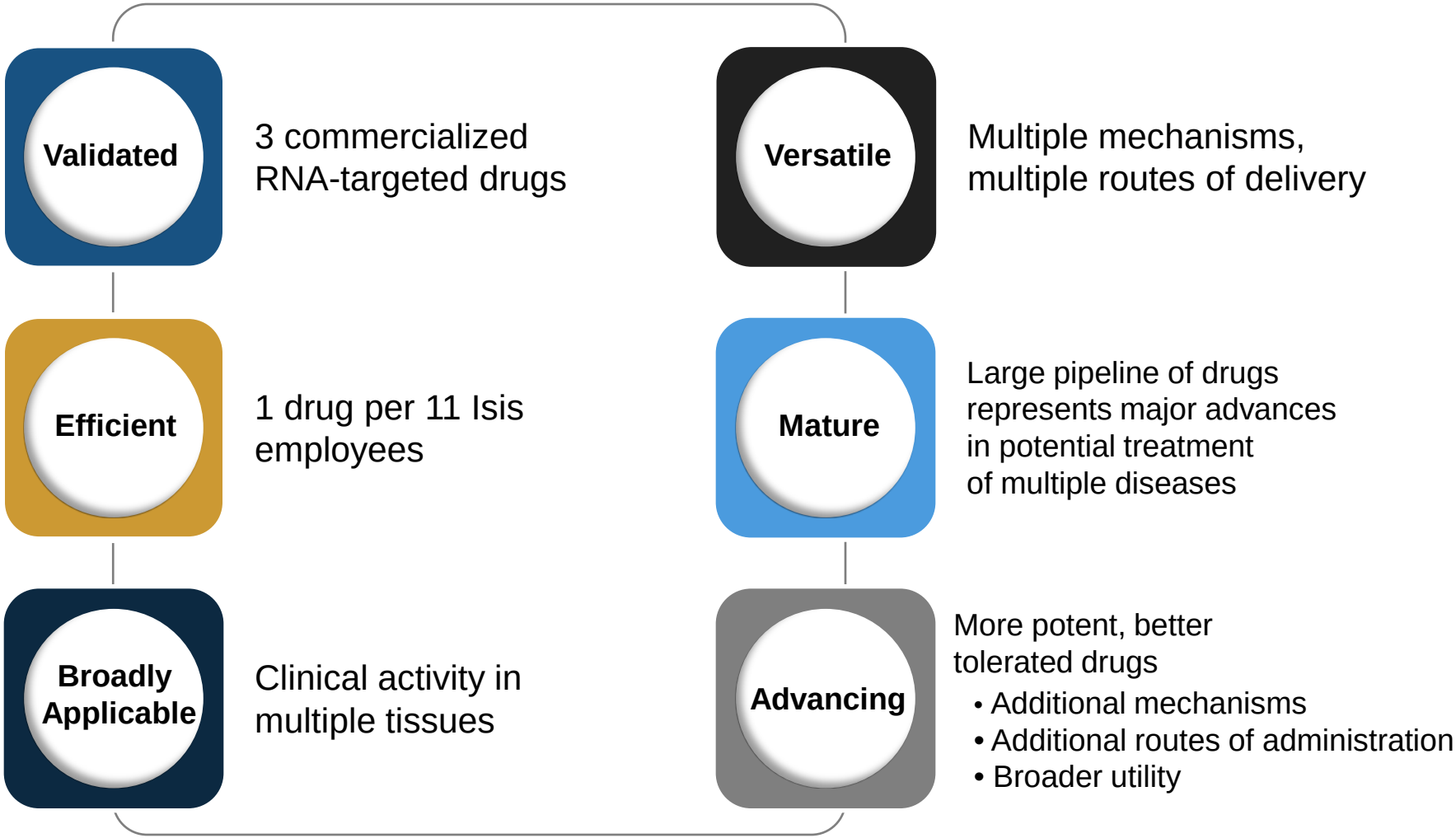
Continue to Advance the Technology

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-PTP1B$_{Rx}$ – P2 in T2D ✓
ISIS-PKK$_{Rx}$ – P1 ✓
RG-101 – P2 in HCV ✓
ISIS-ANGPTL3$_{Rx}$ – P1 ✓
ISIS-TTR$_{Rx}$ – OLE in FAP ✓
ISIS-STAT3-2.5$_{Rx}$ (AZD9150) – P2 in lymphoma ✓
ISIS-SMN$_{Rx}$ – P2 in SMA ✓
ISIS-GCCR$_{Rx}$ – P2 in T2D
KYNAMRO – FOCUS FH
ISIS-AR-2.5$_{Rx}$ (AZD5312)– P1/2 in prostate cancer

Planned Data Releases

ISIS-APO(a)$_{Rx}$ – P2 in High Lp(a)
ISIS-DMPK-2.5$_{Rx}$ – P2 in DM1
Custirsen – P3 in prostate cancer
RG-101 – P2 in HCV

2015 | **2016**

ISIS-APO(a)-L$_{Rx}$ – P1 ✓
RG-012 – P1 ✓
ISIS-FGFR4$_{Rx}$ – P2 in obesity
RG-101 Phase 2 combo and as a single agent in HCV
ISIS-HBV$_{Rx}$ – P2 in hepatitis B
ISIS-PKK$_{Rx}$ – P2 in HAE
ISIS-FXI$_{Rx}$ – P2 in AF pts with ESRD
Volanesorsen – P3 in familial partial lipodystrophy
ISIS-GCGR$_{Rx}$ – P2 dose optimization
ISIS-HTT$_{Rx}$ – P1/2 in HD
ISIS-DGAT2$_{Rx}$ – P1
ISIS-BIIB3$_{Rx}$ – P1
ISIS-GSK4-L$_{Rx}$ – P1

Planned Study Initiations

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