Goldman Sachs Healthcare Conference

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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 ISIS-APOCIII$_{Rx}$. 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: The Leader in RNA-targeted Drug Discovery and Development

Only direct route from genes to drugs	Uniquely specific and broadly applicable
Virtually no undruggable targets	Almost universal applicability
Efficient discovery and early development	Dramatically reduced cost and increased success in R&D
Investment amortized across the entire pipeline	Chemistry, manufacturing, formulation, analytical methods
Multiple antisense mechanisms	Broad versatility: toxic RNA, splicing, direct protein down regulation
Multiple routes of delivery	SubQ, IV, intrathecal, intraocular, intradermal, inhalation, enema, oral
Broad clinical activity	Demonstrated clinical activity in multiple tissues

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$_{Rx}$	Clotting Disorders
ISIS-GCGR$_{Rx}$	Diabetes
ISIS-GCCR$_{Rx}$	Diabetes
ISIS-PTP1B$_{Rx}$	Diabetes
Apatorsen (OGX-427)	Cancer
ISIS-STAT3-2.5$_{Rx}$	Cancer
ISIS-AR-2.5$_{Rx}$	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-ANGPTL3$_{Rx}$	Hyperlipidemia
ISIS-APO(a)-L$_{Rx}$	Very High Lp(a)
ISIS-FGFR4$_{Rx}$	Obesity
ISIS-HBV$_{Rx}$	HBV

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$_{Rx}$	b-Thalassemia
ISIS-DGAT2$_{Rx}$	NASH
ISIS-GSK4-L$_{Rx}$	Ocular Disease
ISIS-GSK6-L$_{Rx}$	Antiviral

Severe & Rare · Cardiovascular · Metabolic · Cancer · Other

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

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

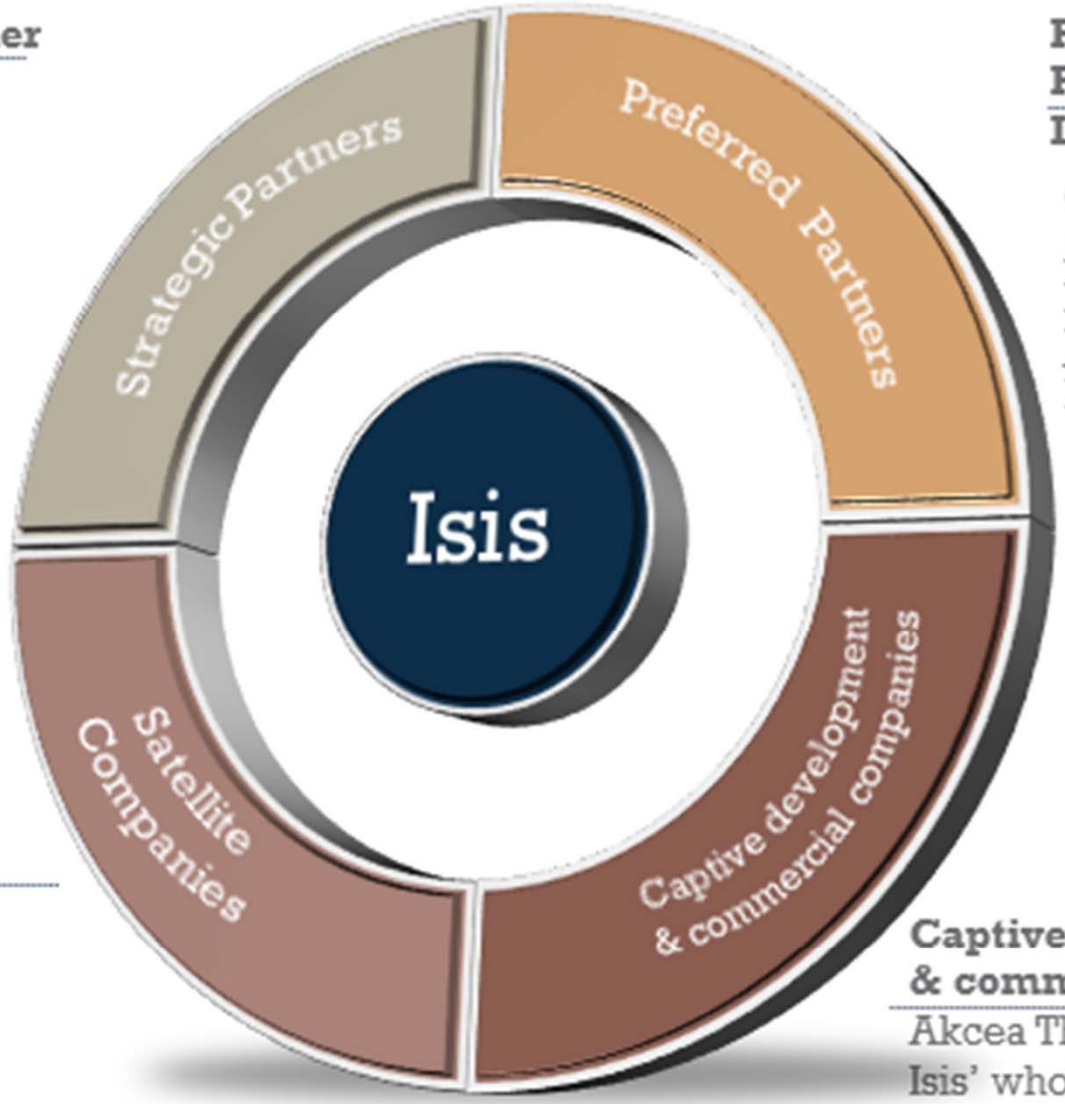
Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

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

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' 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, difficult, expensive Phase 2 program ▪ Challenging endpoints ▪ Expertise from partner could provide increased likelihood of success	▪ Complex, expensive Phase 3 development ▪ Straightforward, effective Phase 2 program with definitive endpoints ▪ Multiple indications ▪ Large patient population ▪ Large marketing and sales effort	▪ 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$_{Rx}$** Biogen **ISIS-DMPK-2.5$_{Rx}$** **ISIS-STAT3-2.5$_{Rx}$ (AZD9150)** AstraZeneca **ISIS-AR-2.5$_{Rx}$ (AZD5312)**	**ISIS-FXI$_{Rx}$** BAYER	**Volanesorsen** **ISIS-APO(a)$_{Rx}$** **ISIS-ANGPTL3$_{Rx}$** **+ follow-on drugs** AKCEA THERAPEUTICS

Isis — Bayer License Agreement

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

ISIS-FXI$_{Rx}$: Phase 2 Data Support a Potential Breakthrough Therapeutic Opportunity for Thrombosis

- Lowest reported incidence of VTE and 7-fold reduction vs. enoxaparin in total knee replacement surgery (4% vs. 30%)
  - Without prophylaxis, patients undergoing knee arthroplasty are at high risk for postoperative venous thromboembolism
- Numerically fewer bleeding events in ISIS-FXI$_{Rx}$-treated patients than with enoxaparin treatment
  - Clear dissociation between thrombosis and bleeding for the first time
  - Enoxaparin efficacy and bleeding rates were within expected ranges in this patient population
- Safety and tolerability profile supportive of continued clinical development

Near-term Drivers of Value

Isis' Late-stage Programs

Volanesorsen

AKCEA THERAPEUTICS

- Phase 3 in FCS patients
- Phase 3 in familial partial lipodystrophy patients

ISIS-SMN$_{Rx}$

Partnered with: Biogen

- Phase 3 in SMA infants
- Phase 3 in SMA children

ISIS-TTR$_{Rx}$

Partnered with: gsk

- Phase 3 in FAP patients

Volanesorsen

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

Familial Chylomicronemia Syndrome (FCS)

An Ultra-Orphan Disease Caused by 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 Lipoprotein Lipase 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

Volanesorsen: Ideal Profile as a Potential Treatment for Patients with FCS and FPL

- Results from a broad Phase 2 program showed significantly improved lipid profile:

- Patients with high triglycerides and type 2 diabetes treated with volanesorsen showed improvements in measures of glucose control

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

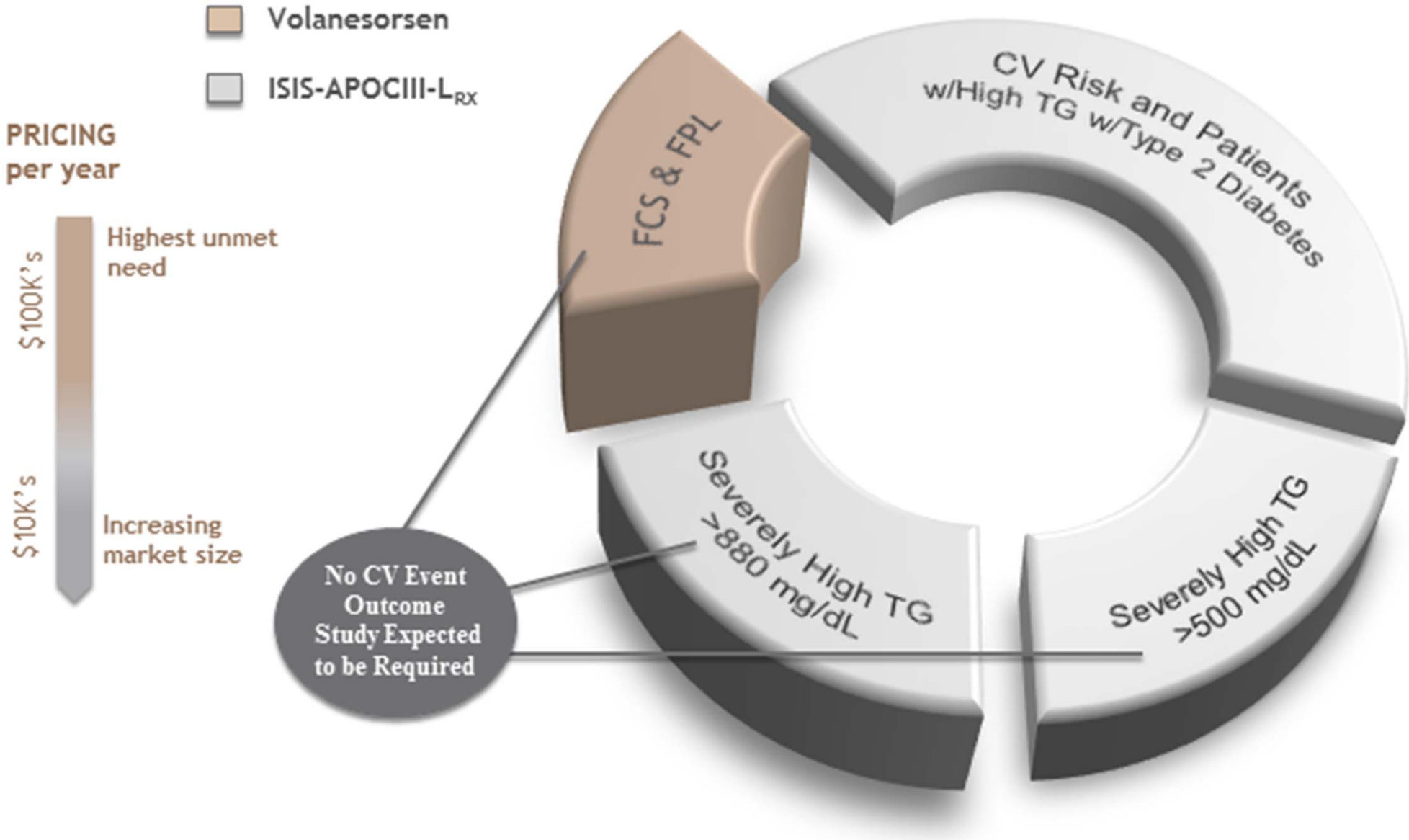
FPL

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

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

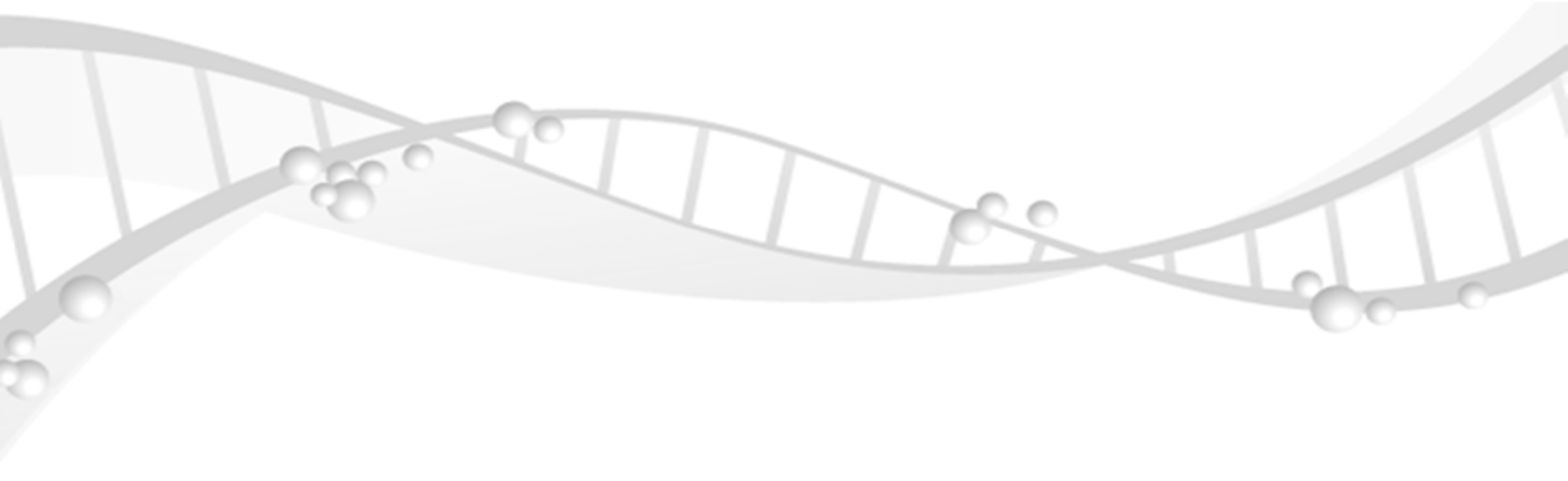
- **ISIS-APOCIII-L_{Rx} incorporates our LICA technology**
  - Up to 10-fold increase in potency
  - Potential for monthly dosing – enhance patient convenience
- **Enhanced profile for broader utility in patients with severely high triglycerides and patients with high triglycerides and type 2 diabetes**
- **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



ISIS-SMN$_{Rx}$

For Infants and Children 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: ~ 30-35K children in U.S., Europe and Japan
  - Number one genetic cause of death in infants
  - Characterized by progressive muscle atrophy and loss of motor function
- Caused by genetic defects in the SMN1 gene that result in a lack of functional SMN protein
- No currently approved therapies for SMA

Broad Phenotypic Spectrum of Spinal Muscular Atrophy

Type 1
- Most severe form of disease
- Age of symptom onset <6 months
- Never able to sit
- Very short life expectancy
- Most have two SMN2 genes

Type 2
- Symptom onset >6 months
- Able to sit or stand, but not walk
- Muscle weakness/skeletal deformities
- Shortened life expectancy
- Most have 3-4 SMN2 genes

Type 3
- Symptom onset >6 months
- Able to walk with difficulty
- Muscle weakness/skeletal deformities
- Close to normal life expectancy
- Most have 3-4 SMN2 genes

Type 4
- Adult onset

Summary of ISIS-SMN$_{Rx}$ Phase 2 Infant Data

- Median event-free age in infants treated with ISIS-SMN$_{Rx}$ compares favorably to that of patients in a recently published natural history study
- ISIS-SMN$_{Rx}$-treated SMA infants continue to demonstrate increases in motor function tests (e.g., CHOP INTEND and motor milestones)
- Clinical data are consistent with the mechanism by which ISIS-SMN$_{Rx}$ was designed to work
  - Tissue concentration of ISIS-SMN$_{Rx}$ in spinal cord of treated SMA infants is greater than the concentration that produced biological activity in animal studies
  - Greater amount of full length SMN2 mRNA observed in spinal cord analyzed from ISIS-SMN$_{Rx}$-treated SMA infants compared to untreated SMA infants
  - Greater amount of SMN protein observed in spinal cord tissues analyzed from ISIS-SMN$_{Rx}$-treated SMA infants compared to untreated SMA infants
- Safety and tolerability profile supportive of continued development

Summary of ISIS-SMN_{Rx} Phase 2 Children Data

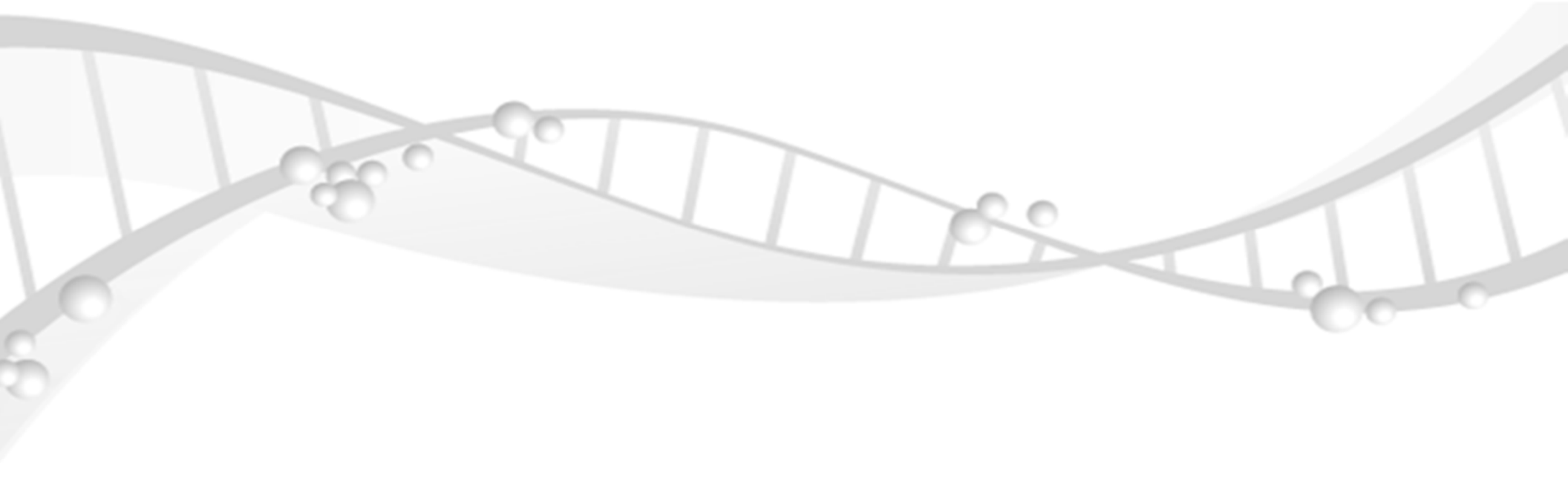
- Evidence of prolonged dose and time dependent increases in muscle function (HMFSE) scores observed (even after 8 to 13 months after last dose) in ISIS-SMN_{Rx}-treated SMA children
- Increases observed in additional measures of muscle function (6MWT and ULM) in ISIS-SMN_{Rx}-treated SMA children
- Increased levels of SMN protein in cerebral spinal fluid (CSF) of ISIS-SMN_{Rx}-treated SMA patients
  - Observation is consistent with designed biological mechanism and is consistent with clinical and preclinical data
- Safety and tolerability profile supportive of continued development

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 and support initiatives that will allow patients to be identified and begin treatment sooner
- 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$_{Rx}$

Toward a Better Treatment for Patients with Transthyretin (TTR) Amyloidosis



Partnered with gsk

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)

→ FAP: ~ 10,000
→ FAC: ~ 40,000

Current Treatment Options

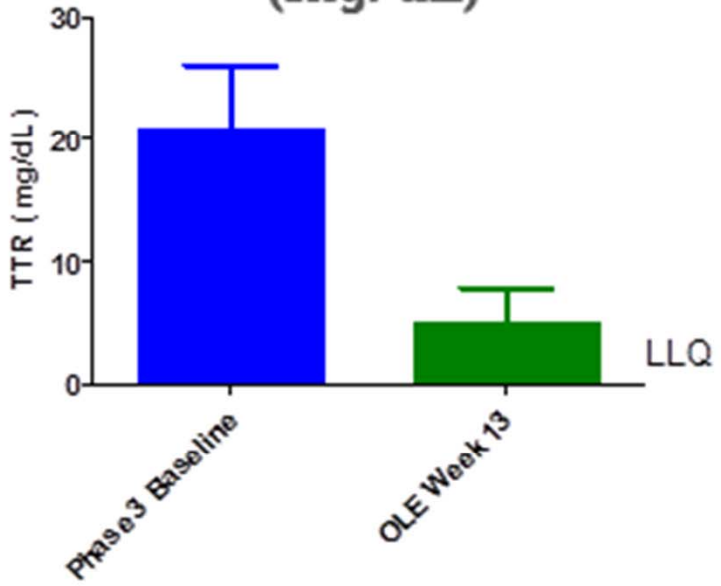
→ Treatments limited
→ No treatments halt or reverse disease
→ Liver transplant for early stage FAP (not FAC)

Partnered with gsk

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

- To date >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

Partnered with gsk

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

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

Planned Data Releases

- 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
- 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

Planned Study Initiations

- 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

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

Mature and robust pipeline of first-in-class or best-in class drugs

UNIQUE BUSINESS STRATEGY MAXIMIZES VALUE

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

ADVANCING TECHNOLOGY

Innovations create more potent drugs, enhance clinical activity and broaden therapeutic reach

FINANCIAL GROWTH

Strong financial position with potential for substantial financial growth in the near-term

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