ISIS PHARMACEUTICALS

Barclays Global Healthcare Conference

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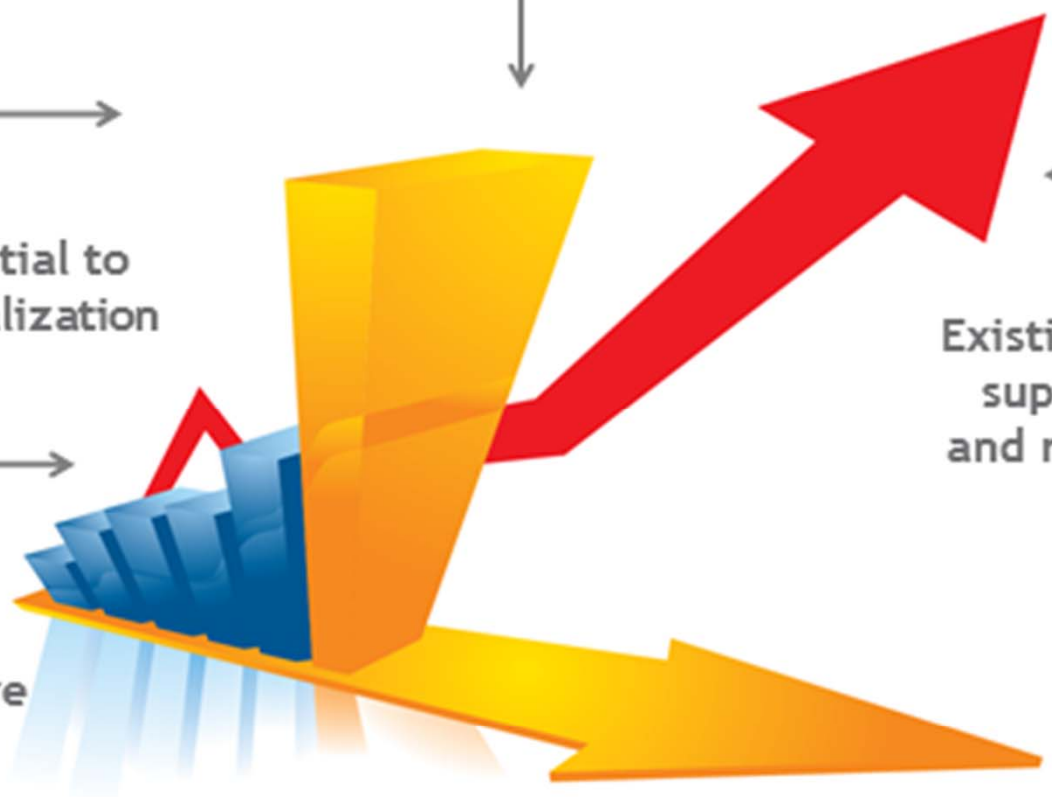
Isis: Significant Opportunities for Near-term Growth and Value

1. KYNAMRO: Launched and sales growing
2. 5 drugs with potential to file for commercialization by 2018
3. Broad, robust, mature pipeline
4. Antisense platform is proven, broadly applicable and efficient
5. Existing partnerships support substantial and reliable revenue stream
6. Business strategy designed to maximize the value of each asset, enables an effective cost structure and limits cash needs



KYNAMRO® (mipomersen sodium) Injection 200 mg/ml

1st Systemic Antisense Drug Approved for Chronic Use

- Marketed in the U.S. and approved in additional countries
- In 2014, Genzyme will continue to invest significantly in KYNAMRO
- Increased sales growth projected in 2014
- Minimal investment by Isis to reach profitability

- Continuing investment in market with FOCUS FH
- FOCUS FH data planned early 2015

Isis' Pipeline

Commercialized

KYNAMRO®	Homozygous FH
Alicaforsen*	Pouchitis
Vitravene®	CMV Retinitis

Phase 3

ISIS-TTR$_{Rx}$	TTR Amyloidosis
KYNAMRO®	Severe HeFH
Custirsen (OGX-011)	Cancer

Phase 2

ISIS-SMN$_{Rx}$	Spinal Muscular Atrophy
ISIS-APOCIII$_{Rx}$	FCS
ISIS-APOCIII$_{Rx}$	Severely High TGs
ATL1103	Acromegaly
ISIS-FXI$_{Rx}$	Clotting Disorders
ISIS-CRP$_{Rx}$	CAD
ISIS-GCGR$_{Rx}$	Diabetes
ISIS-GCCR$_{Rx}$	Diabetes
ISIS-PTP1B$_{Rx}$	Diabetes
ISIS-EIF4E$_{Rx}$	Cancer
Apatorsen (OGX-427)	Cancer
ISIS-STAT3$_{Rx}$	Cancer
Plazomicin	Severe Bacterial Infection
EXC 001	Local Fibrosis
iCo-007	Diabetic Macular Edema
ATL1102	Multiple Sclerosis

Phase 1

ISIS-GCCR$_{Rx}$	Cushing's Syndrome
ISIS-APO(a)$_{Rx}$	Very High Lp(a)
ISIS-FGFR4$_{Rx}$	Obesity
ISIS-GSK3$_{Rx}$	Antiviral
RG-101	Hepatitis C Virus

Preclinical

ISIS-PKK$_{Rx}$	Hereditary Angioedema
ISIS-DMPK$_{Rx}$	Myotonic Dystrophy 1
ISIS-FVII$_{Rx}$	Clotting Disorders
ISIS-ANGPTL3$_{Rx}$	Hyperlipidemia
ISIS-DGAT2$_{Rx}$	NASH
ISIS-AR$_{Rx}$	Cancer
ISIS-GSK4$_{Rx}$	Ocular Disease
RG-012	Alport Syndrome

Severe & Rare Cardiovascular Metabolic Cancer Other

** Named Patient Supply*

Near-term Drivers of Value

5 Drugs with Potential to File for Commercialization by 2018

Phase 3 1H 2014

ISIS-SMN$_{Rx}$

SMA: ~35,000 US, EU & Japan

biogen idec

Phase 3 1H 2014

ISIS-APOCIII$_{Rx}$

FCS: 3,000-5,000 WW
Severe TG: ~50,000 in US/EU

ISIS PHARMACEUTICALS

Phase 3 ongoing

ISIS-TTR$_{Rx}$

FAP: ~10,000 WW
FAC: ~40,000 WW

gsk GlaxoSmithKline

Value Drivers over Next Few Years

Phase 3 data 2014

Custirsen (OGX-011)

CRPC : ~315,000 in US & EU

TEVA OncoGenex™ Bringing hope to life.™

Phase 2 ongoing

EXC 001

Anti-scarring drug with potential for multibillion dollar market

EXCALIARD PHARMACEUTICALS, INC. Pfizer

ISIS-SMN$_{Rx}$

For Infants and Children with Spinal Muscular Atrophy

Partnered with: biogen idec

ISIS-SMN$_{Rx}$ for Spinal Muscular Atrophy (SMA)

Severe Genetic Neuromuscular Disease Affecting 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
  - Characterized by progressive muscle atrophy and loss of motor function
- **Caused by genetic defects in the SMN1 gene that result in the lack of functional SMN protein**
- **No currently approved therapies for SMA**

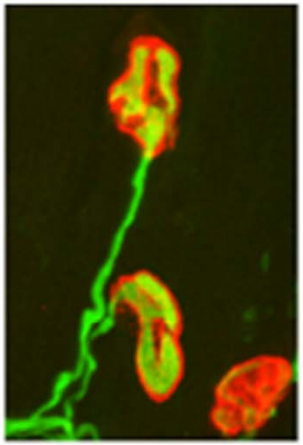
Partnered with: biogen idec

ISIS-SMN$_{Rx}$

Elegant Solution Restores Neuromuscular Activity

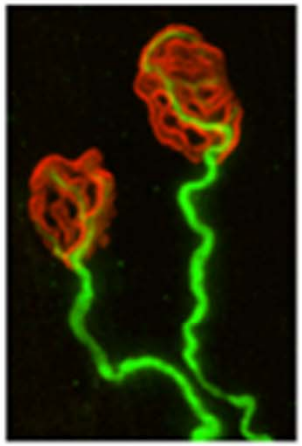
- A related gene, SMN2, normally produces only a small amount of functional SMN protein because of inappropriate RNA processing
- ISIS-SMN$_{Rx}$ increases the production of functional SMN protein by promoting correct RNA processing

SMA Neuromuscular Junction



Diseased

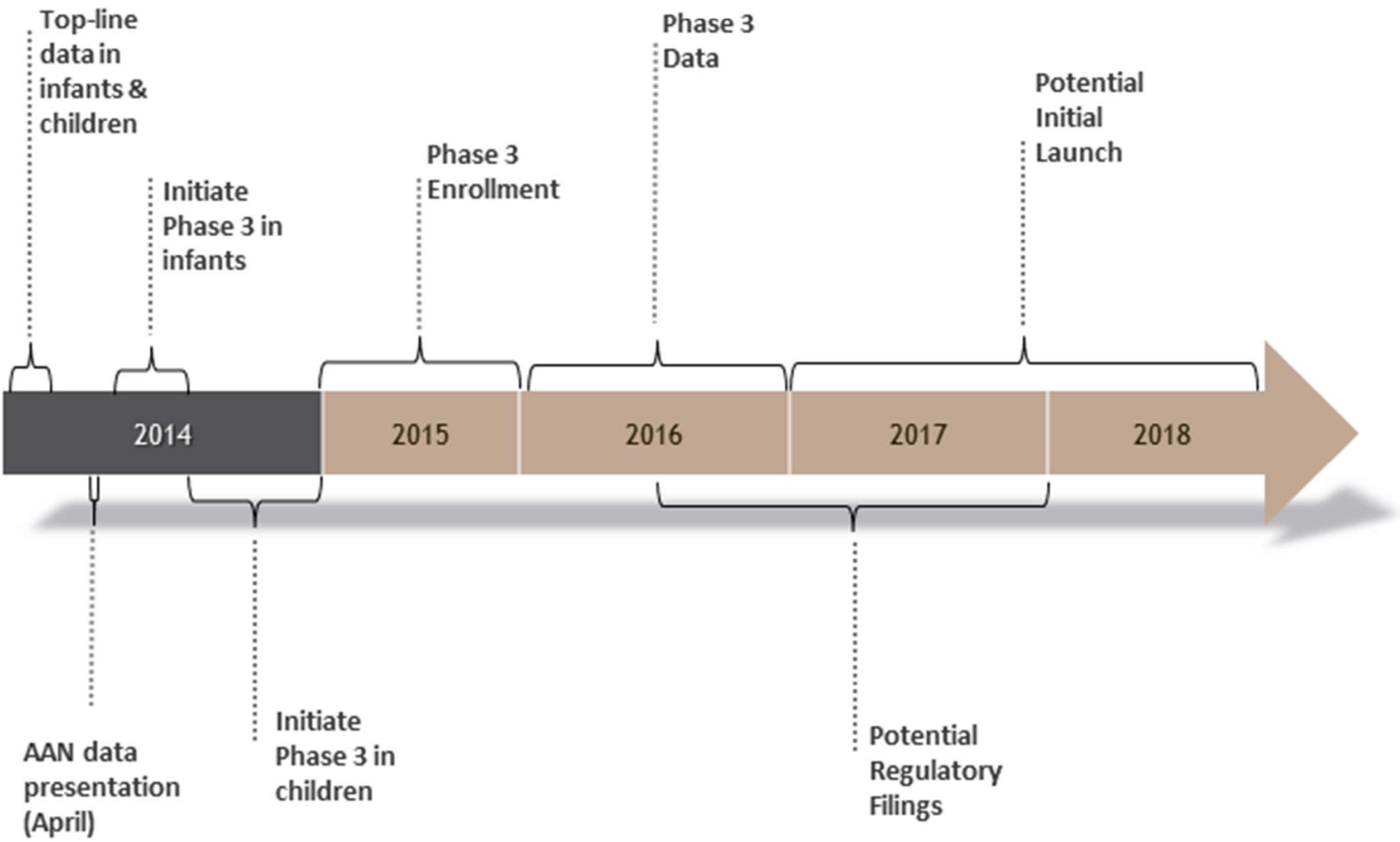
ISIS-SMN$_{Rx}$ Treated Neuromuscular Junction



Treated

ISIS-SMN$_{Rx}$ preserves neuromuscular junctions in a mouse model of SMA

ISIS-SMN$_{Rx}$: Path to Market



Partnered with: biogen idec

ISIS-SMN$_{Rx}$
Attractive Economics with Significant Upside

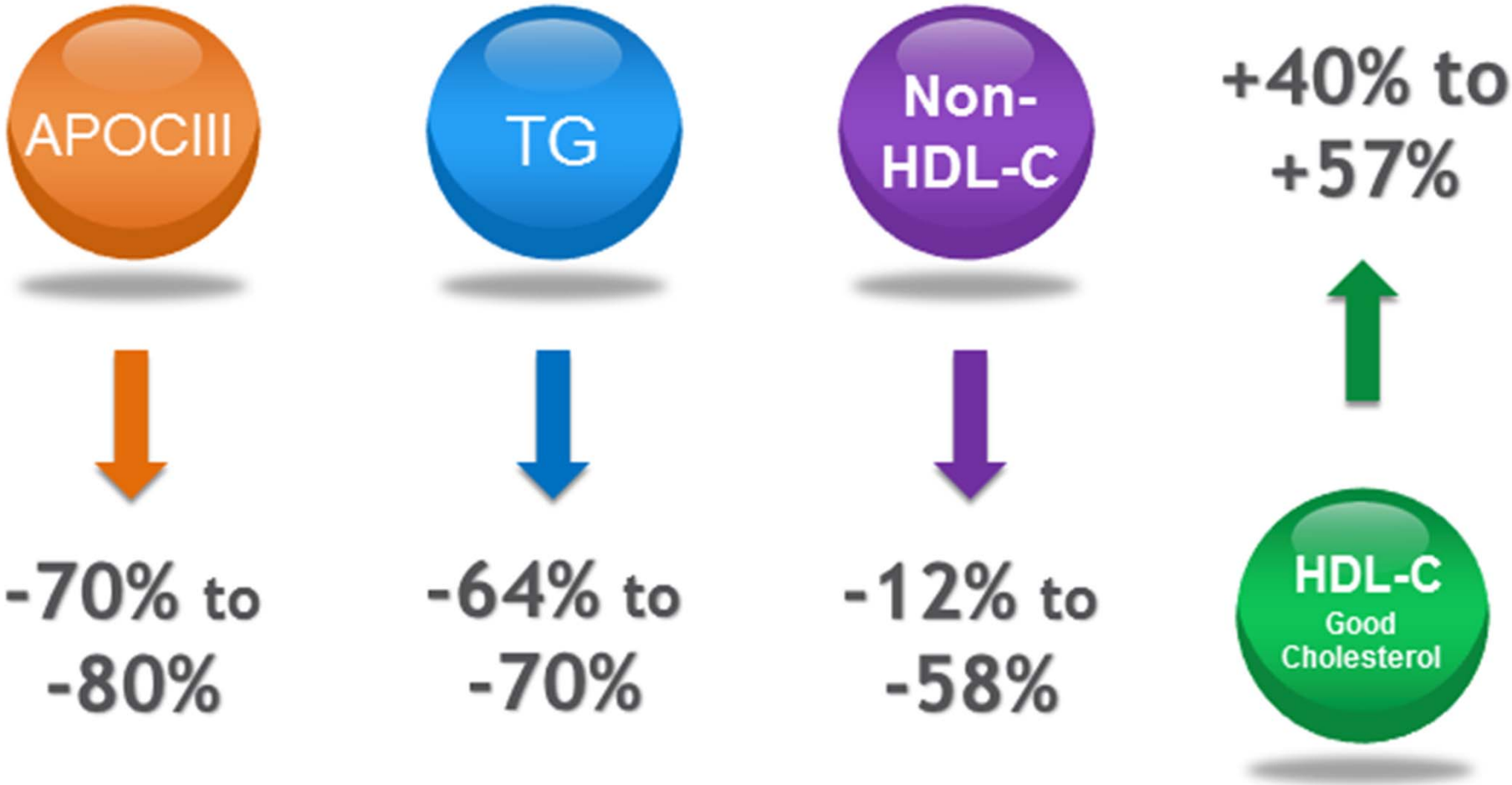
- **Partnered with Biogen Idec:**
  - Global development & commercial capabilities
    - Recognized world leader in commercializing specialty neurological drugs
    - Both companies are committed to the most rapid path to market
- **Biogen Idec has the option to license ISIS-SMN$_{Rx}$ upon completion of the first successful Phase 2/3 trial**
  - Upfront option payment, $29M
  - License fee and milestone payments, $304M
    - Clinical development milestone payments, $79M
      - >$16M received
      - Next milestone payment for initiation of infant Phase 3 study, $18M
      - Additional milestones as the Phase 3 program advances, including initiation of childhood SMA Phase 3 study
    - Regulatory approval milestone payments, $150M
  - Double-digit royalties on sales

ISIS-APOCIII$_{Rx}$

For Patients with Familial Chylomicronemia Syndrome and Patients with Severely High Triglycerides

ISIS-APOCIII$_{Rx}$: Improved Lipid Profile in All Patient Groups as a Single Agent or in Combination

Mean % Lipid Changes in Phase 2 Studies*



** Data from 13 weeks 300mg ISIS-APOCIII$_{Rx}$ treatment*

ISIS-APOCIII$_{Rx}$: Excellent Safety and Tolerability Profile

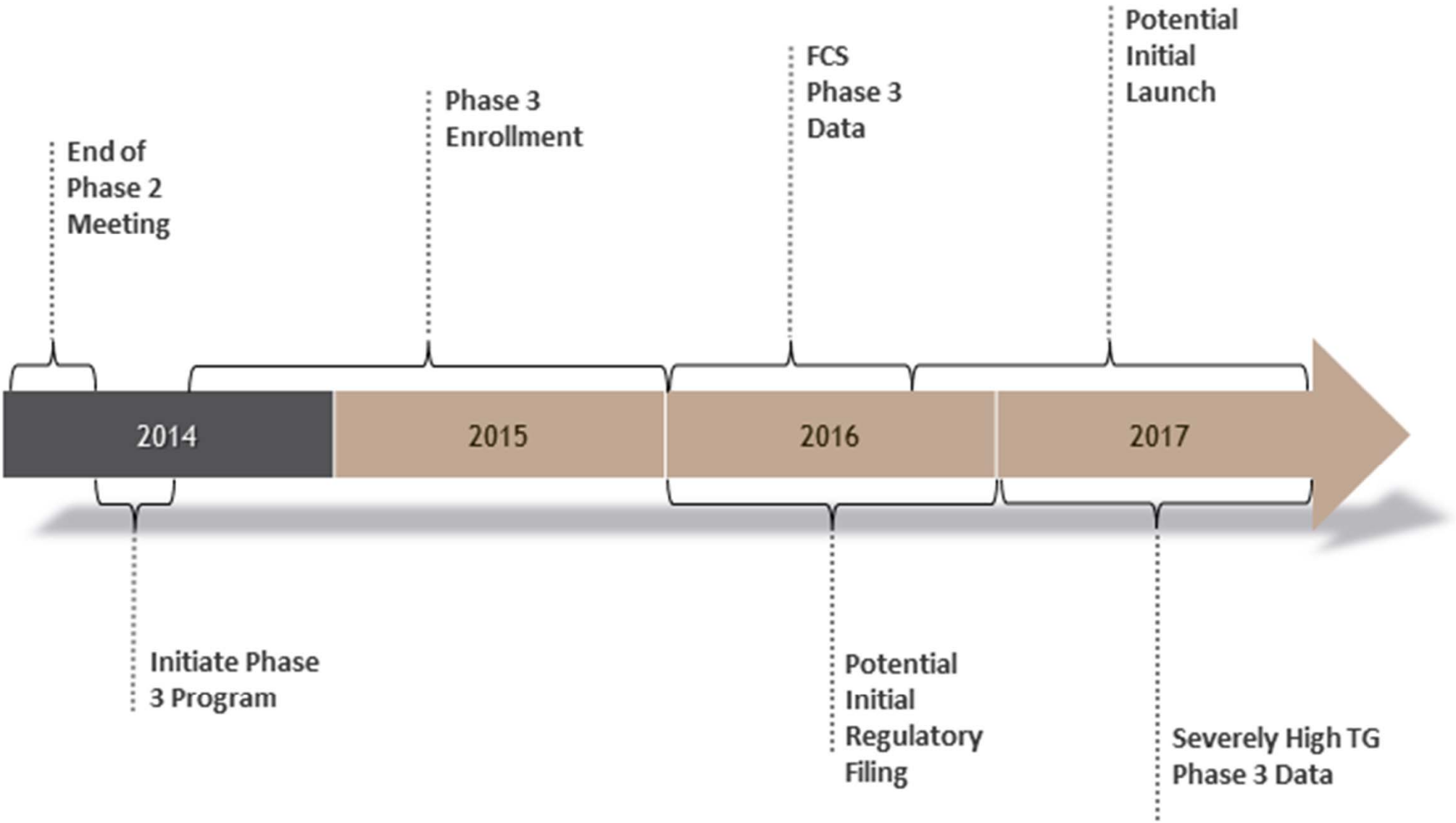
- Well tolerated in ~100 patients
- No ALTs >3x ULN
- No changes in renal function
- No clinically meaningful changes in other biochemical or hematological laboratory values
- Injection site reactions were mild and infrequent
- No flu-like symptoms

ISIS-APOCIII$_{Rx}$: Next Steps

- **Two Phase 3 programs planned to run in parallel: One in FCS patients and another in patients with severely high triglycerides (> 880 mg/dL)**
  - End of Phase 2 meetings with US and EU regulators – 1H 2014
  - Finalize Phase 3 plan – 1H 2014
  - Initiate Phase 3 studies – Mid 2014
- **FCS Phase 3 data planned for 2016**
- **Severely high triglycerides Phase 3 data planned for 2017**
- **Potential initial regulatory filing – 2016**
- **Potential initial commercial launch – 2016/2017**

ISIS-APOCIII$_{Rx}$: Rapid Path to Market

FCS and Severely High Triglycerides



ISIS-TTR$_{Rx}$

Transthyretin (TTR) Amyloidosis Program

Transthyretin (TTR) Amyloidosis
Phase 3 Study in FAP Well Underway

Partnered with: GlaxoSmithKline

Unmet Medical Need	Mutant TTR forms amyloid deposits in nerves, heart and other organs, resulting in death
Patient Population (worldwide)	FAP: ~ 10,000 FAC: ~ 40,000
Current Tx Options	• Treatments limited • Liver transplant is the most effective treatment

Partnered with: GlaxoSmithKline

ISIS-TTR_{Rx}: Significant Reductions in TTR

Phase 1 Study in Healthy Volunteers

- **ISIS-TTR_{Rx} produced robust, dose-dependent and significant sustained reductions in TTR levels**
  - Undetectable levels of TTR in some subjects; ~ 90% reduction in some subjects; > 75% reduction on average
- **Excellent Safety and Tolerability Profile**
  - Very low incidence of flu-like symptoms and mild injection site reactions
- **Phase 1 data supported moving directly to Phase 3**

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

Potential Best-in-Class Treatment for TTR Amyloidosis

Partnered with: GlaxoSmithKline

- **Most advanced TTR-specific drug in development**
  - International study with 20 global sites open and enrolling well
  - Phase 3 study in FAP patients well underway with some patients treated for almost a year
  - Initiated OLE study for FAP patients who have completed dosing in the Phase 2/3 study of ISIS-TTR_{Rx}
- **Excellent safety, well tolerated to date**
  - Convenient, easy to use, weekly, at-home low-volume s.c. injection
- **Study on track to complete enrollment in 2015**

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

- 3 commercialized drugs

KYNAMRO™
(mipomersen sodium) injection

Approved January 2013

ALICAFORSEN

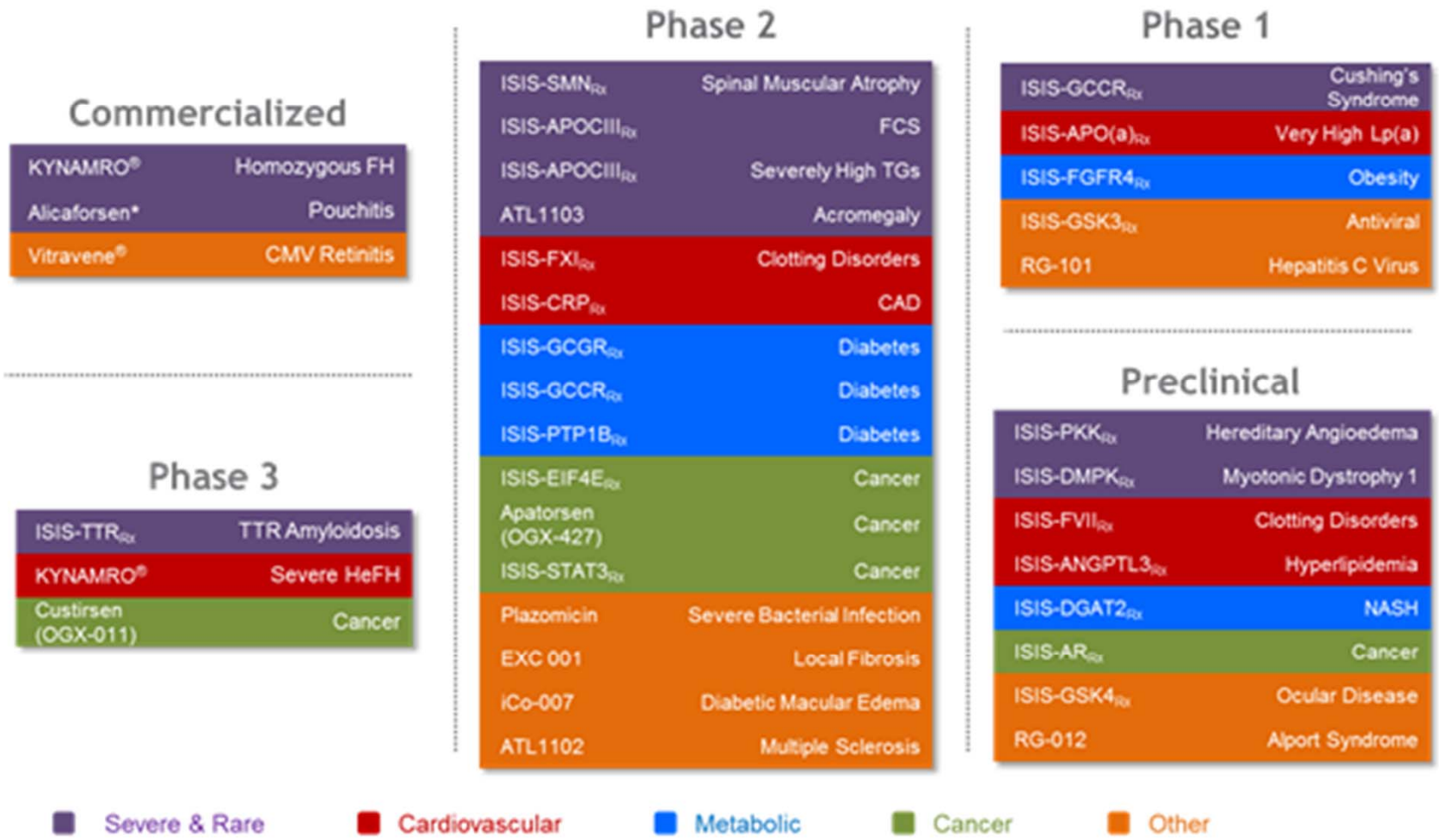
Named Patient Supply

Vitravene®

Approved 1998

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

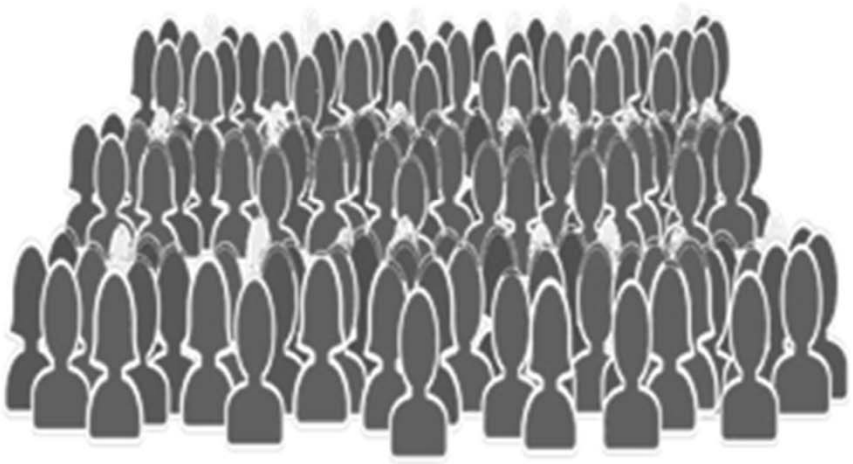
- *3 commercialized drugs*
- **Large mature pipeline**



** Named Patient Supply*

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

- *3 commercialized drugs*
- *Large mature pipeline*
- **Efficient: 1 drug per 12 Isis employees**



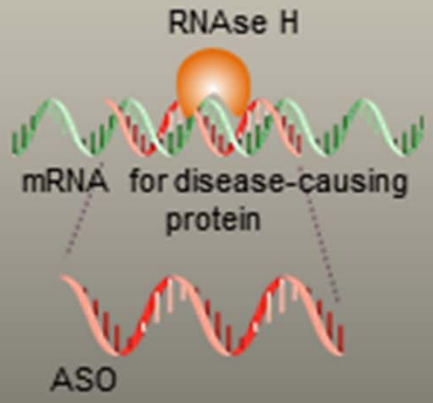
Traditional Pharma
1 drug / ~1,000 employees

ISIS
1 drug / 12 employees

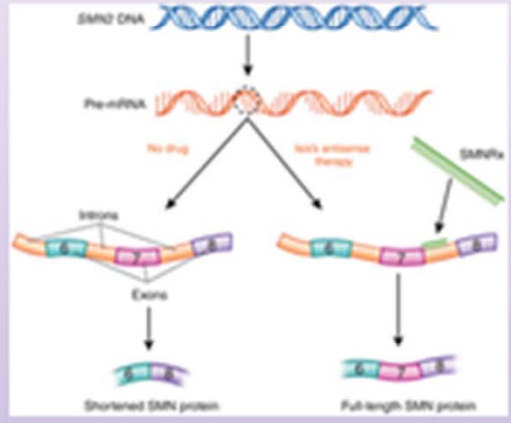
Isis Antisense Technology is a Proven, Efficient Platform for Creating New Drugs

- *3 commercialized drugs*
- *Large mature pipeline*
- *Efficient: 1 drug / 12 Isis employee*
- **Robust – multiple mechanisms**

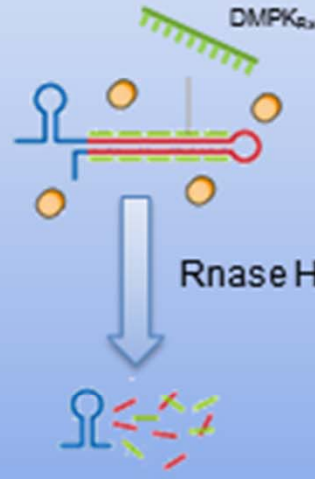
Reduces target RNA & prevents production of protein



Increases production of therapeutic protein



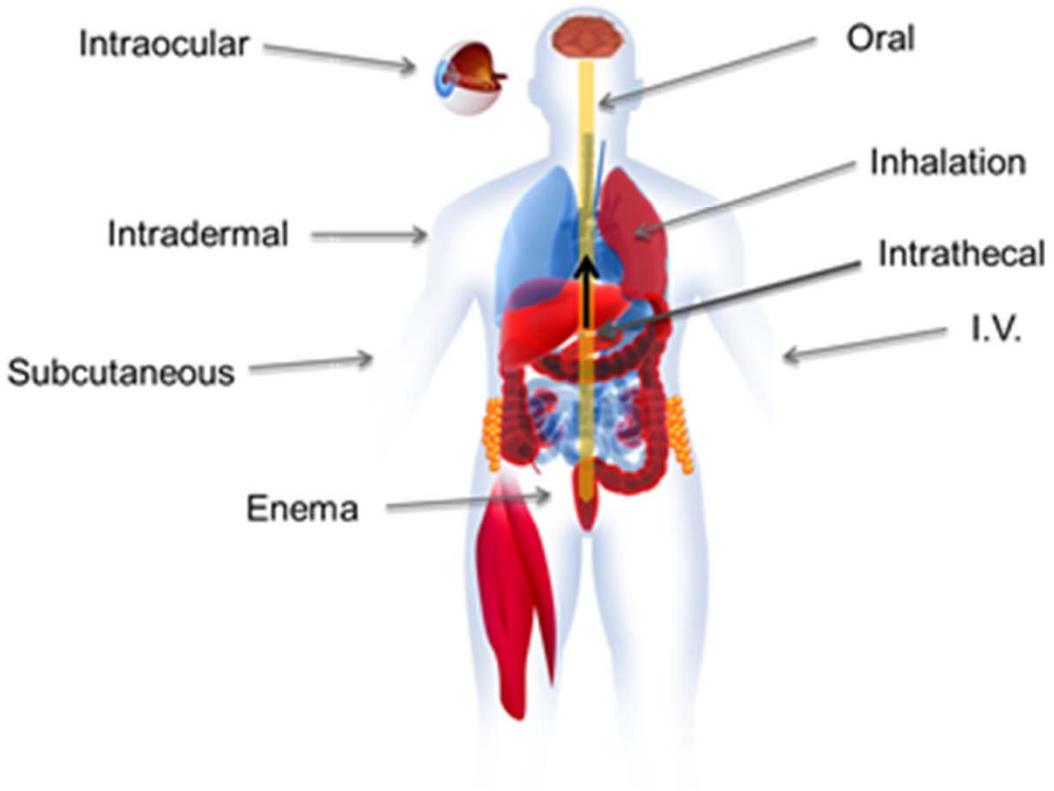
Removes toxic RNA



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

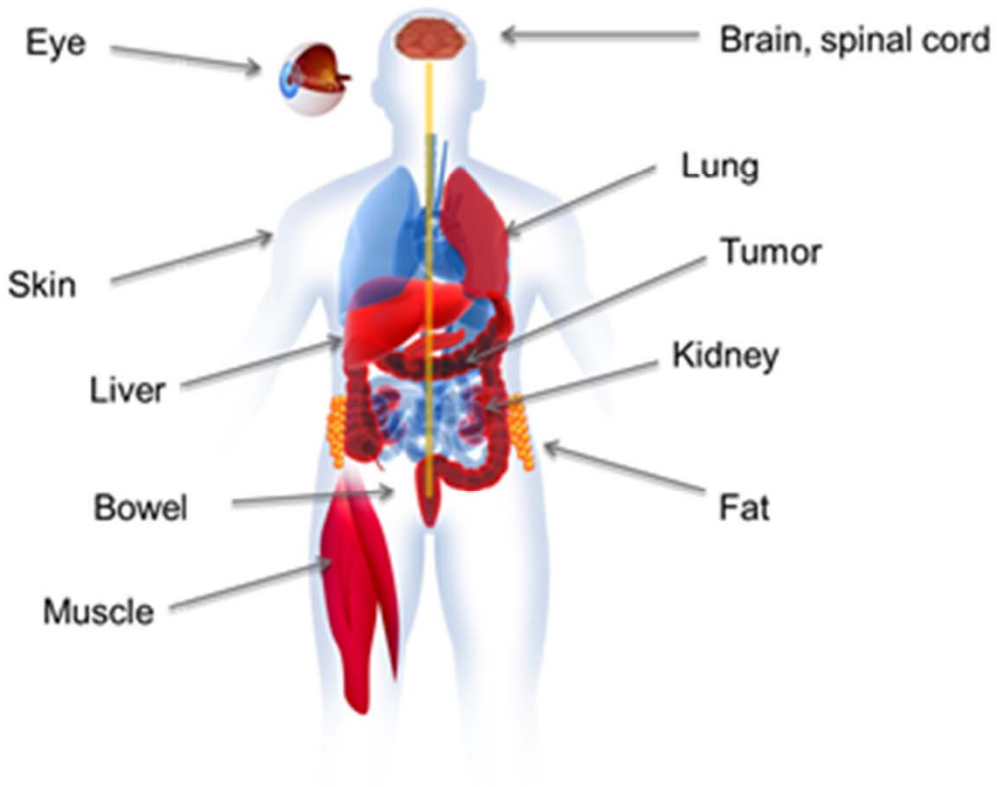
- *3 commercialized drugs*
- *Large mature pipeline*
- *Efficient: 1 drug / 12 Isis employee*
- *Robust – multiple mechanisms*

- **Robust – multiple routes of delivery**



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

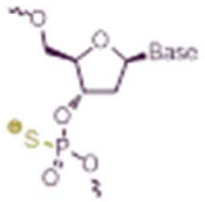
- *3 commercialized drugs*
- *Large mature pipeline*
- *Efficient: 1 drug / 12 Isis employee*
- *Robust – multiple mechanisms*
- *Robust – multiple routes of delivery*
- **Robust – broad clinical activity in multiple tissues**



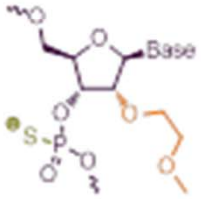
Innovating Antisense Technology

Isis Leads the Field in Advancing Next-Generation Antisense Drugs

1st Generation
Phosphorothioate(PS)



2nd Generation
MOE Gapmer

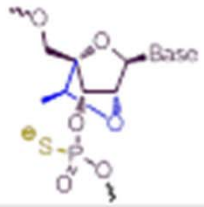


- ✓ Adds stability
- ✓ Improves distribution to tissues

- ✓ Increases potency
- ✓ Increases stability
- ✓ Reduces non-specific toxicities

New Chemistry

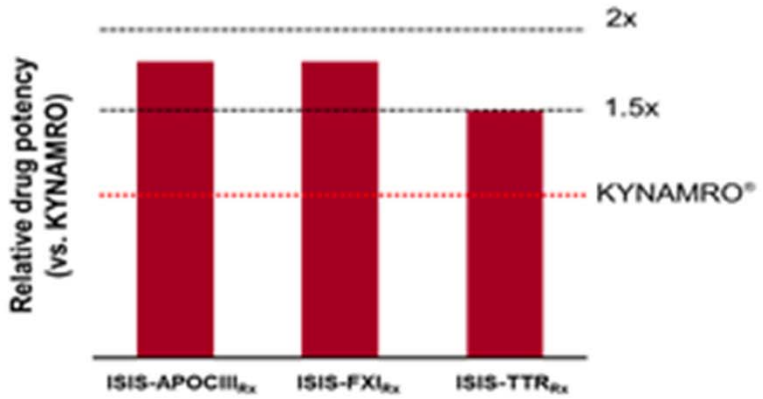
Generation 2.5
cEt Containing Gapmer



- ✓ Improves potency and therapeutic index
- ✓ Expands range of targets and tissues

Proprietary Screening

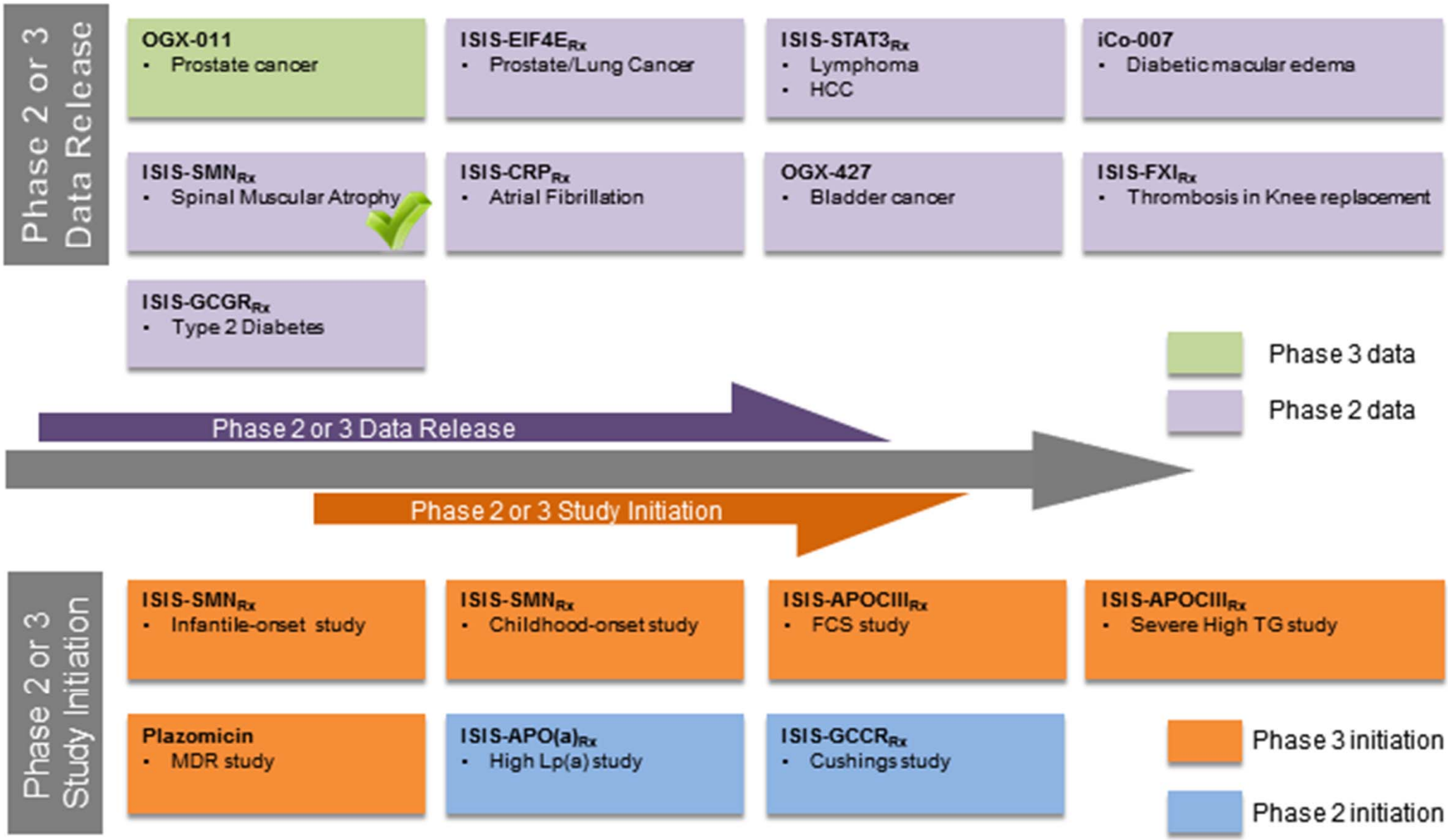
Newer Gen 2.0 antisense drugs are more potent than KYNAMRO



Potency derived from target protein reduction after 4 Weeks of Treatment with 200 mg. Compared to KYNAMRO Phase 1 Studies.

Advancing the Pipeline

Multiple Phase 2 and 3 Data Read Outs & Planned Study Initiations in 2014



Isis' Financial Strength

- **2013 Financial Position (Year end December 31, 2013)**
  - Revenue: $147M
  - Operating Expenses (Pro forma): $187M
  - Cash & Short-term Investments: $657M
- **2014 Guidance**
  - Pro forma NOL in the low $50M range
  - > $575M in year-end cash
    - Revenue:
      - Milestone payments from multiple partners and drugs: > $110M in 2014
      - Amortization of Upfront Fees: > $45M in 2014
    - Expenses:
      - Expected increase in operating expenses over 2013
        - We plan to conduct five Phase 3 studies in 2014
        - We plan to have numerous drugs in later-stage clinical studies
        - We will continue to advance our earlier stage drugs as well as add new drugs to our pipeline

Isis: Successes Today, Potential For Even Greater Success Tomorrow

1. Efficient, proven, broadly useful technology
2. Mature, de-risked pipeline with many near-term commercial opportunities
3. Successful business strategy
4. Strong financial position with potential for substantial financial growth in the near-term
5. Proven senior leadership: committed to future growth