ISIS PHARMACEUTICALS

B. LYNNE PARSHALL, COO & CFO

September 2011 Corporate Presentation

Isis' Focus Today

- Maximizing Innovation & Value Creation
- Commercializing Mipomersen
- Maturing & Expanding the Pipeline
- Maintaining Technology Leadership

Isis' Corporate Strategy

- Create Antisense Technology - A New Platform for Drug Discovery
- Control Technology & Products Through Continued Innovation & Patents
- Use the Efficiency of the Antisense Platform to Create Broad & Expanding Pipeline
- Support a Broad Portfolio of Development & Commercialization Opportunities Through Partnerships
  - License drugs after Phase 2 Proof-of-Concept
  - Stay small, focused & innovative
  - Maintain manageable cost structure
  - Create a consortium of satellite companies to broadly exploit technology

Creating Value from Innovation

Isis Leads the Way in RNA Therapeutics

- Antisense Technology Works
- Efficiency of Antisense Confirmed
- Isis' Business Strategy is Proven
  - Successful mipomersen development
    - Filing for marketing approval this year
  - Sustained financial strength
    - Ended 2010 with >$450 million
  - Small, focused & cost-effective organization that supports large & diverse pipeline
    - 24 drugs in development for multiple diseases

Creating Value from Innovation

Isis Leads the Way in RNA Therapeutics

Isis' Business Strategy is Sustainable

- Future innovation supported with a manageable cost structure
  - Efficient & productive work force
- Partnership strategy maximizes long-term return & minimizes risk
  - Potential to earn >$3.5 billion in future milestone payments on current programs
- Opportunity for new partnerships
  - Broad pipeline of drugs advancing in development to Phase 2 Proof-of-Concept

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Partnered with genzyme

Mipomersen 2011 Milestones

Kynamro™ (Mipomersen): *Significant Commercial Opportunity*

- ✓ EU filing for HoFH & severe HeFH submitted in July 2011

- ➢ United States NDA filing for HoFH planned in 4Q:11

Planned Launch 2012

Focused on the commercialization of mipomersen to treat a potentially fatal cardiovascular disease – hoFH & severe heFH

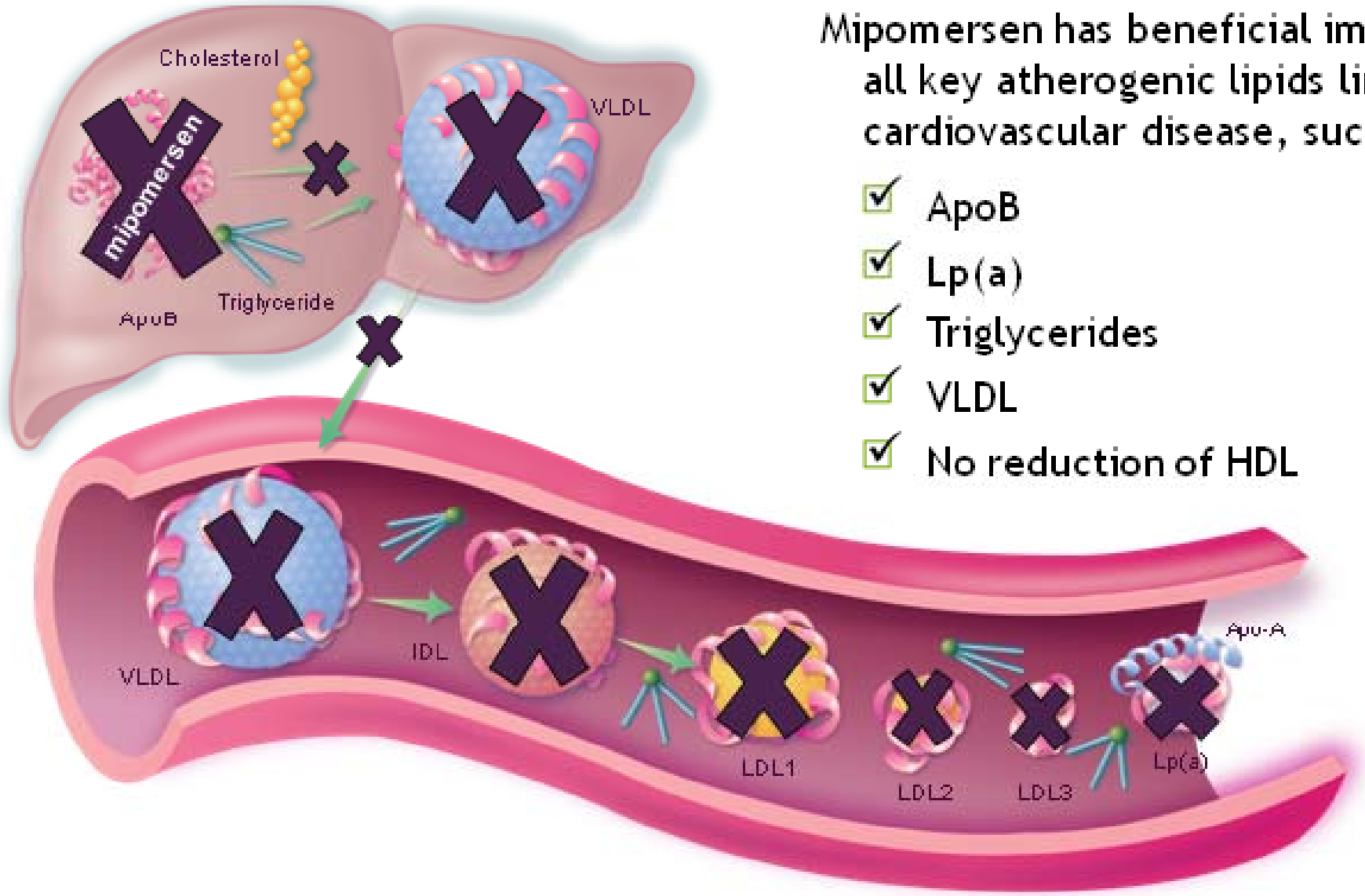
Mipomersen

Novel Treatment for High-Risk Patients with Severely High Cholesterol

- Mipomersen
  - Important first-in-class product opportunity
    - Significant initial commercial opportunity in patients at high risk of CV death
    - Long-term growth potential
  - Four positive placebo-controlled Phase 3 studies
    - All primary, secondary & tertiary endpoints met
    - >700 drug treated patients in initial filing; >100 patients treated over 1 year
  - Robust efficacy combined with emerging safety profile supports focus on planned patient populations

Mipomersen

Lowers LDL-Cholesterol & Other Independent Cardiovascular Risk Factors



Mipomersen has beneficial impact on all key atherogenic lipids linked to cardiovascular disease, such as:

- ☑ ApoB
- ☑ Lp(a)
- ☑ Triglycerides
- ☑ VLDL
- ☑ No reduction of HDL

Mipomersen Reduced All Key Atherogenic Lipids in All Patient Populations Studied

Patient Population	Treated Baseline LDL-C (mg/dL)	%Change in LDL-C (mean absolute reduction)	%Change in ApoB (mean absolute reduction)	%Change in Lp(a) (mean absolute reduction)
Homozygous FH (MIPO 5 / n= 51)	**426**	**-24.7%** (-106 mg/dL)	**- 27%** (-77.7 mg/dL)	**-31%** (-20.5 mg/dL)
Average LDL-C Reduction in hoFH > 100 mg/dL				
Severe Heterozygous FH (MIPO 35 / n=58)	**276**	**-36%** (-101.2 mg/dL)	**-36%** (-75.3 mg/dL)	**-33%** (-18 mg/dL)
Average LDL-C Reduction in Severe heFH > 100 mg/dL				

Mipomersen Reduced All Key Atherogenic Lipids in All Patient Populations Studied

Patient Population	Treated **Baseline LDL-C** (mg/dL)	%Change in **LDL-C** (mean absolute reduction)	%Change in **ApoB** (mean absolute reduction)	%Change in **Lp(a)** (mean absolute reduction)
Heterozygous FH (MIPO 7 / n= 124)	**153**	**-28%** (-46 mg/dL)	**- 26%** (-37.8 mg/dL)	**- 21%** (- 14.4 mg/dL)
45% of heFH Patients Achieved LDL-C Levels < 100 mg/dL				
High Cholesterol at High Risk for CAD (MIPO 12 / n=158)	**123**	**-37%** (-47.3 mg/dL)	**-38%** (-44.3 mg/dL)	**-24%** (-14.7 mg/dL)
>50% of High-Risk Patients Achieved LDL-C Levels < 70 mg/dL				

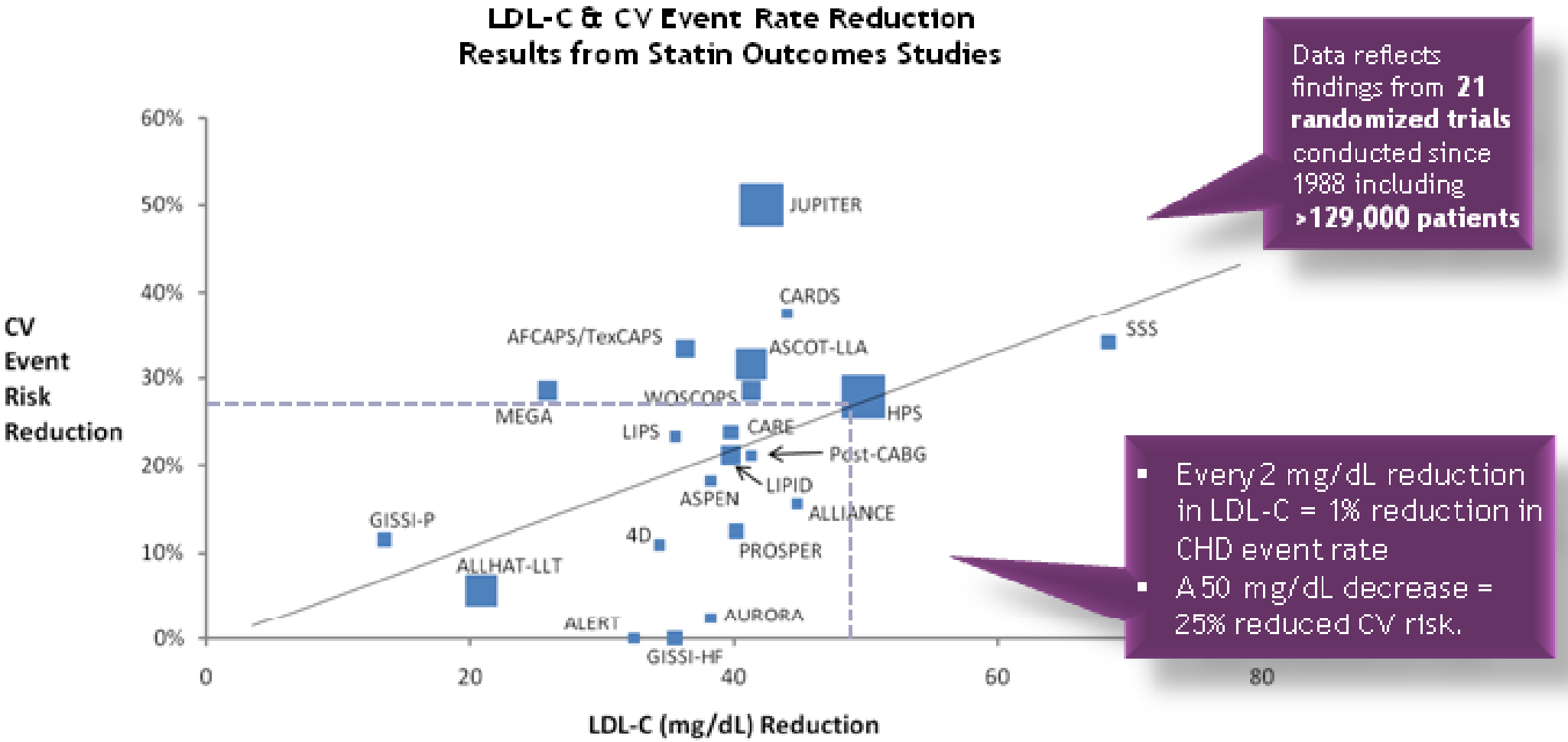
Mipomersen
Safety & Tolerability Profile

Side Effects	▪ Most common side effects were injection site reactions & flu-like symptoms
Adverse Events	▪ 8% of patients treated with mipomersen had persistent ALT elevations above 3xULN ▪ Moderate median increases in liver fat - Ongoing studies to evaluate long-term clinical significance - Preliminary data from OLE suggest liver fat may stabilize or decline in patients who continue treatment beyond 12 months
Tolerability Profile	▪ Drop-outs: 8% placebo vs. 22% mipomersen - Continuing to treat patients for 24 months and beyond ▪ Plans to improve tolerability include continued physician and patient education, dose site & regimen options
Bottom Line	▪ ***Increases in ALTs & liver fat associated with greatest reductions in LDL-C*** ▪ ***Drop-outs comparable to other s.c. drug trials***

Long-Term Treatment with Mipomersen

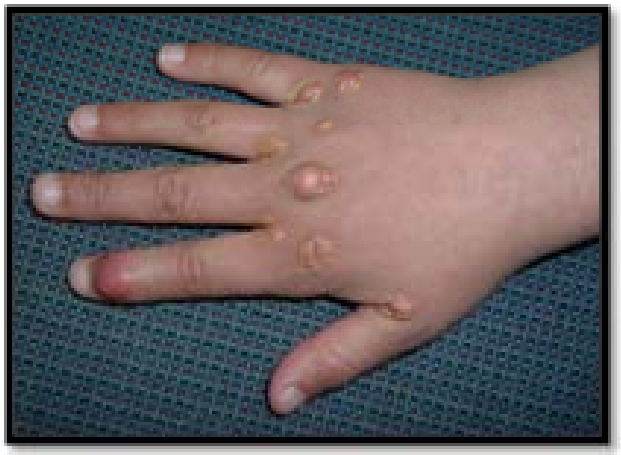
- Continued robust lipid lowering activity with long-term treatment
  - All measured atherogenic lipids remained reduced with continued treatment including apoB, LDL-C, Lp(a), Tg, & non-HDL
  - No loss of activity observed over 2 years of treatment
- Preclinical observations of liver adaptation to reduced lipid transport apparent in long-term clinical experience
  - Liver fat increased in a small subset of patients. With continued treatment (>12 months) liver fat stabilized in all patients & declined in a majority of these patients
  - In general, increases in ALT levels & liver fat appeared to be associated with rapid & larger drops in LDL-C

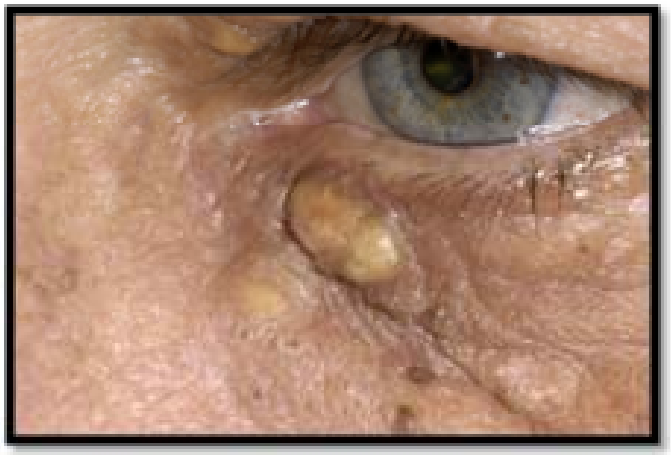
Decreasing LDL Reduces Risk of Adverse CV Outcome

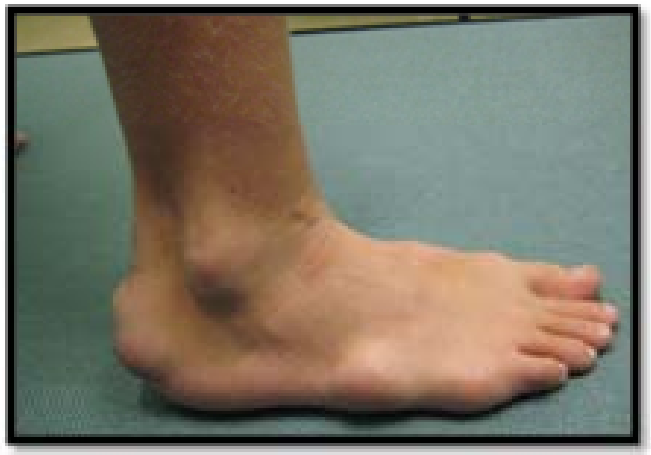


What is FH or Familial Hypercholesterolemia?

- FH is a genetic disorder characterized by very high levels of LDL-cholesterol, the "bad cholesterol," in the blood leading to heart attacks & stroke at an unsually young age
- FH is one of the most common inherited metabolic disorders, with homozygous the most severe form of the disease
- Patients with untreated FH have a 50% mortality rate by age 60
- New NLA recommendations promote early diagnosis, aggressive treatment & lifelong monitoring to reduce cardiovascular risk
- NLA recommendations emphasize the importance of "cascade screening"







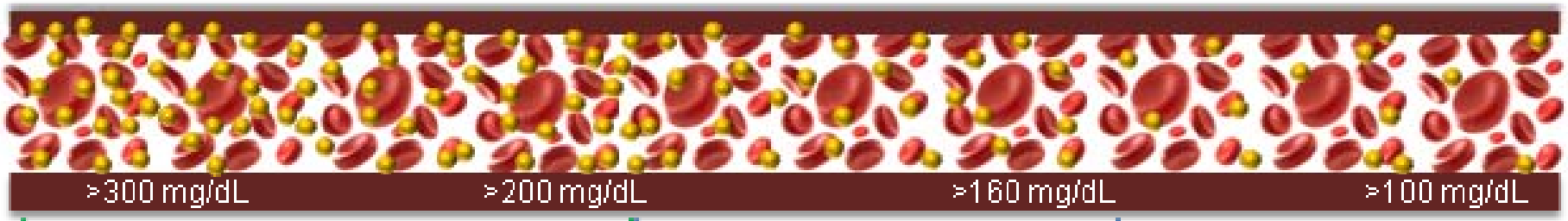
Kynamro™ (Mipomersen): Near-Term Commercial Opportunities

~3,000 patients

~15,000 patients

1st US Filing
hoFH

2nd US Filing
Severe heFH



1st EU Filing
hoFH & Severe heFH

2nd EU Filing
heFH

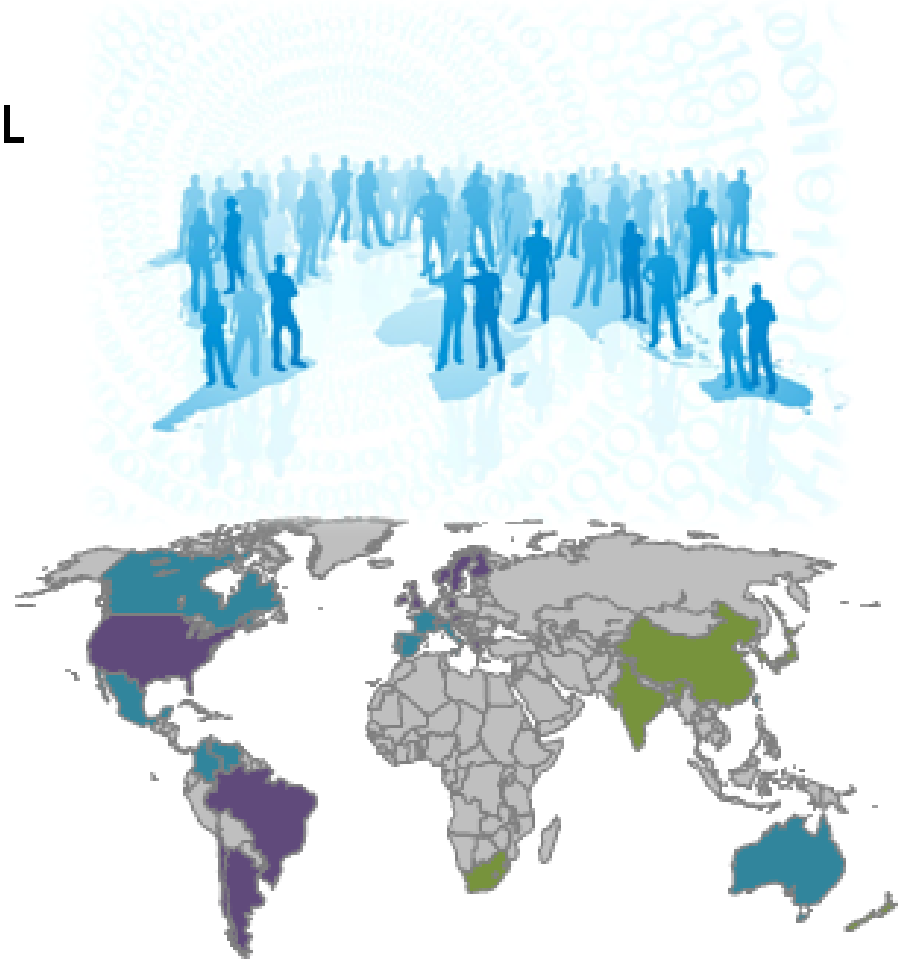
~18,000 patients

>65,000 patients

Kynamro™ (Mipomersen): A Transforming Therapy

Addressing A Significant Unmet Medical Need

- On track for MAA & NDA filings
- Competitive advantage: uniquely targets ALL atherogenic particles
- NLA recommendations for early diagnosis & aggressive treatment of FH patients by lipid specialists
- Genzyme's commercial focus to improve disease awareness & treatment of severe FH patients
- Genzyme experienced in the rare disease market & supported by global infrastructure



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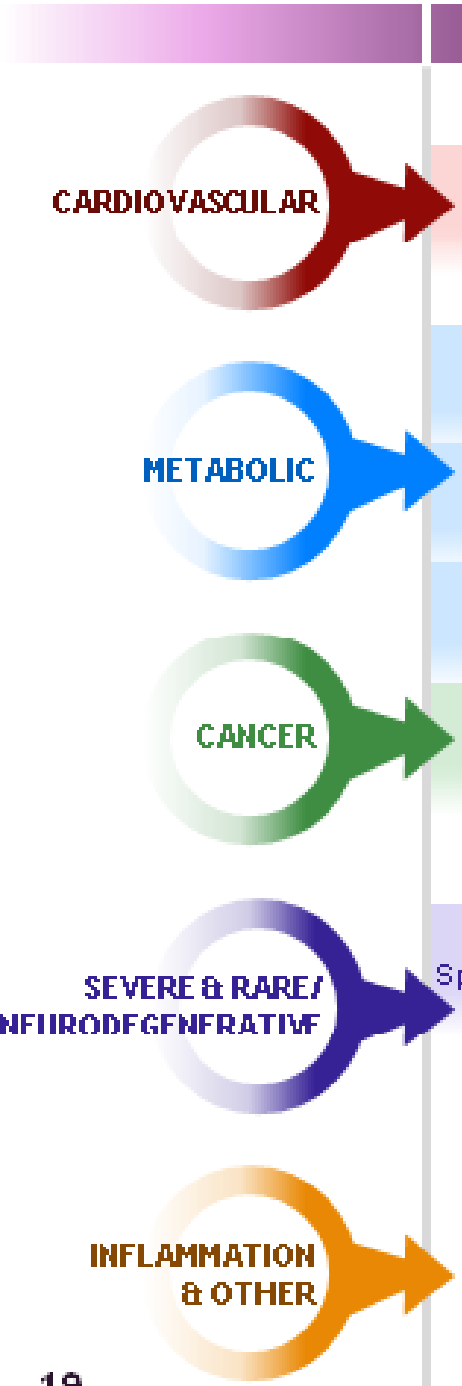
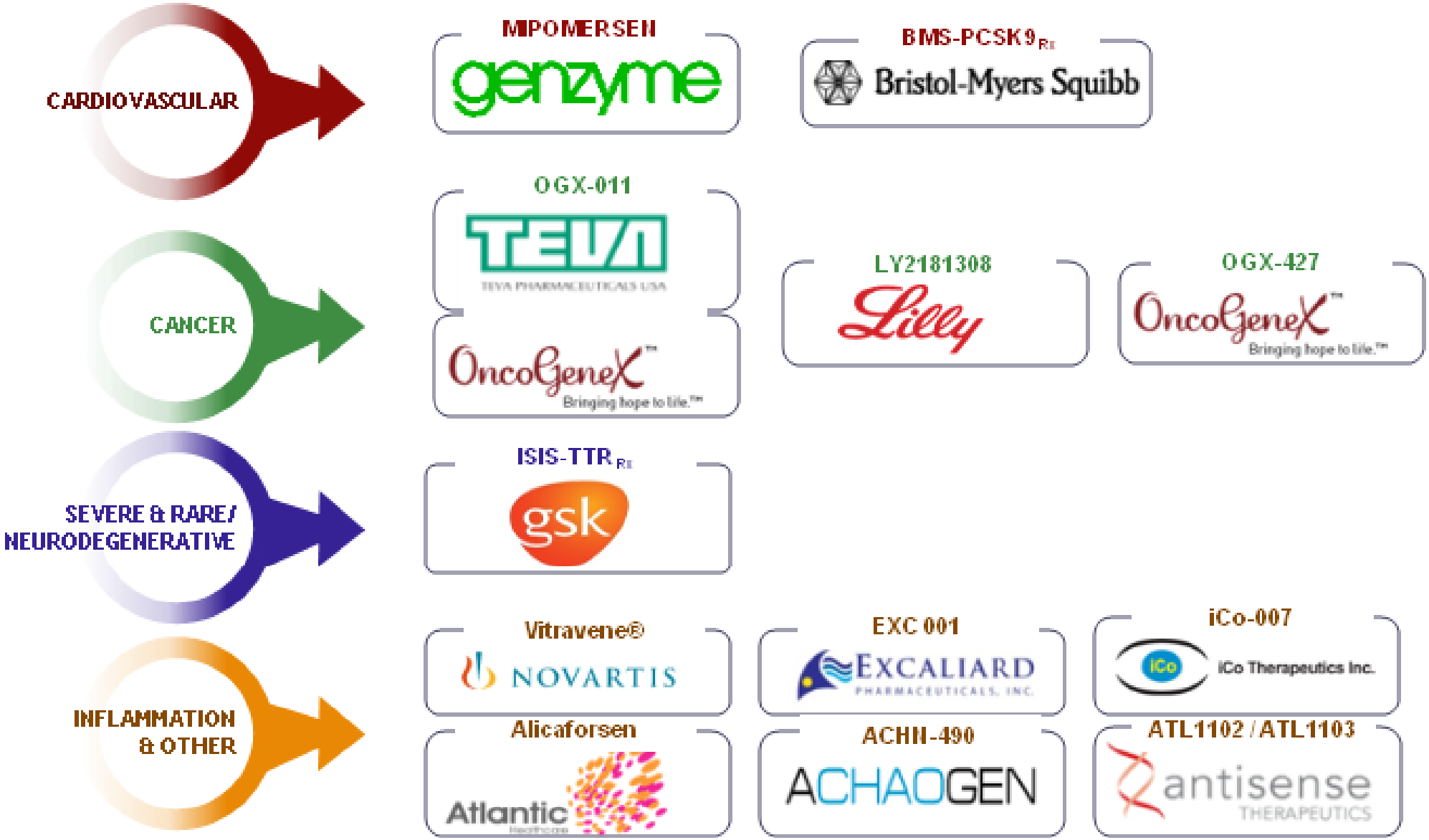
Pipeline

● PARTNERED



Partners


CARDIOVASCULAR
MIPOMERSEN
genzyme
BMS-PCSK9 RI
Bristol-Myers Squibb
CANCER
OGX-011
TEVA
TEVA PHARMACEUTICALS USA
OncoGeneX
Bringing hope to life.™
LY2181308
Lilly
OGX-427
OncoGeneX
Bringing hope to life.™
SEVERE & RARE/ NEURODEGENERATIVE
ISIS-TTR RI
gsk
INFLAMMATION & OTHER
Vitravene®
NOVARTIS
EXC 001
EXCALIARD
PHARMACEUTICALS, INC.
iCo-007
iCo
iCo Therapeutics Inc.
Alicaforsen
Atlantic
ACHN-490
ACHAOGEN
ATL1102 / ATL1103
antisense
THERAPEUTICS

Isis' Cardiovascular Franchise

Multiple Approaches to Cardiovascular Disease

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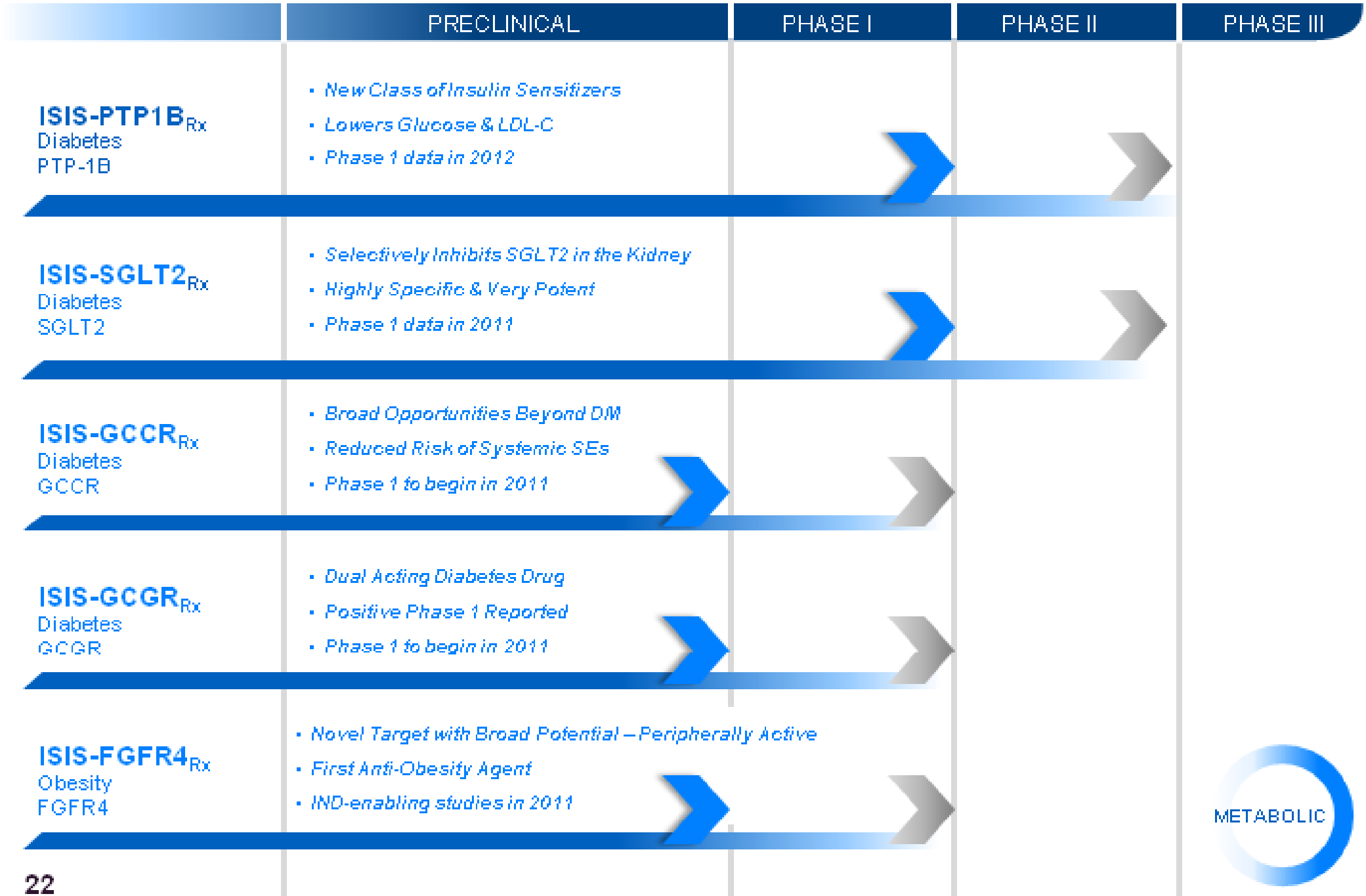
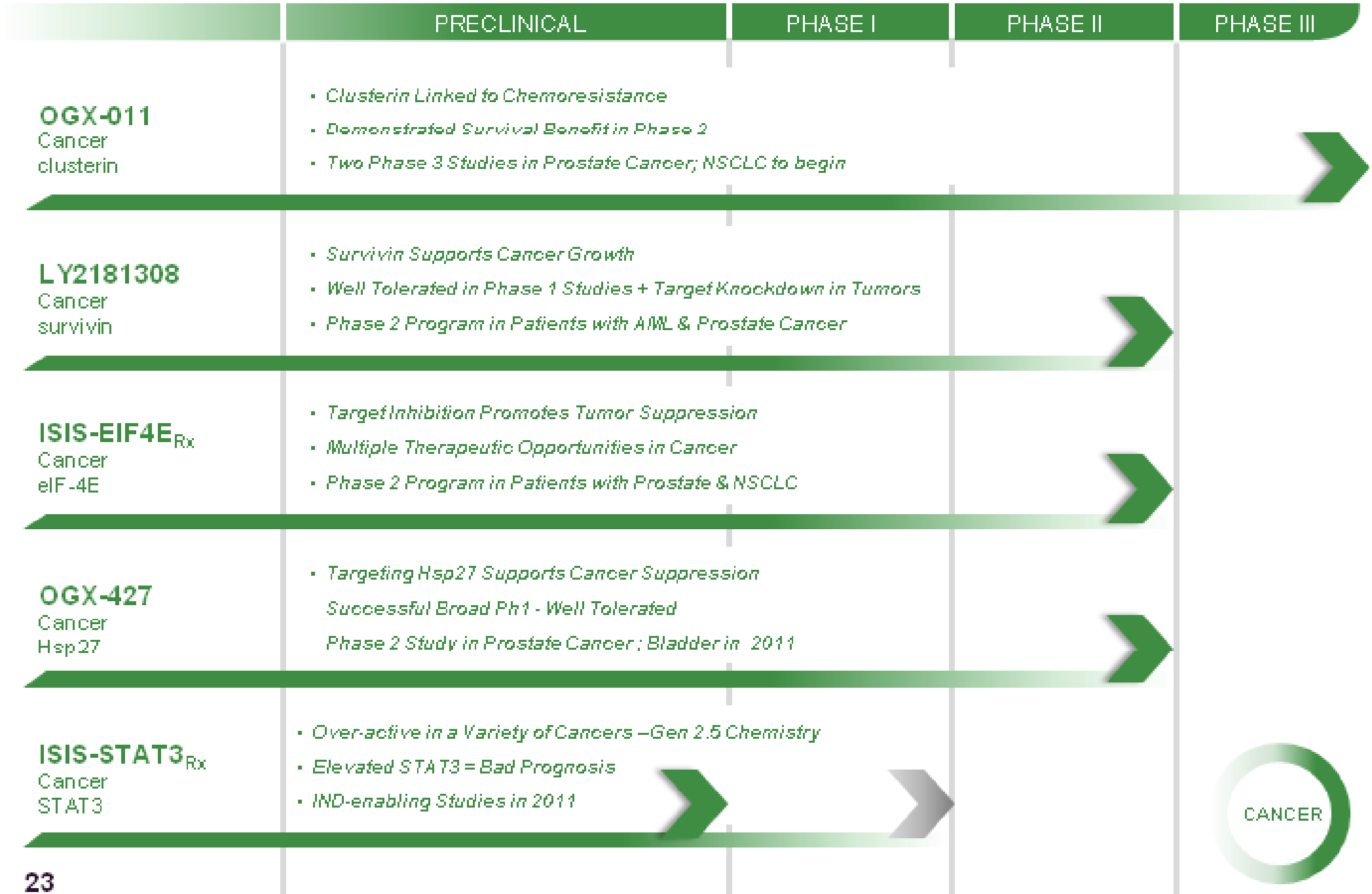
Isis' Metabolic Franchise

Distinct Novel Complementary Approaches to Diabetes



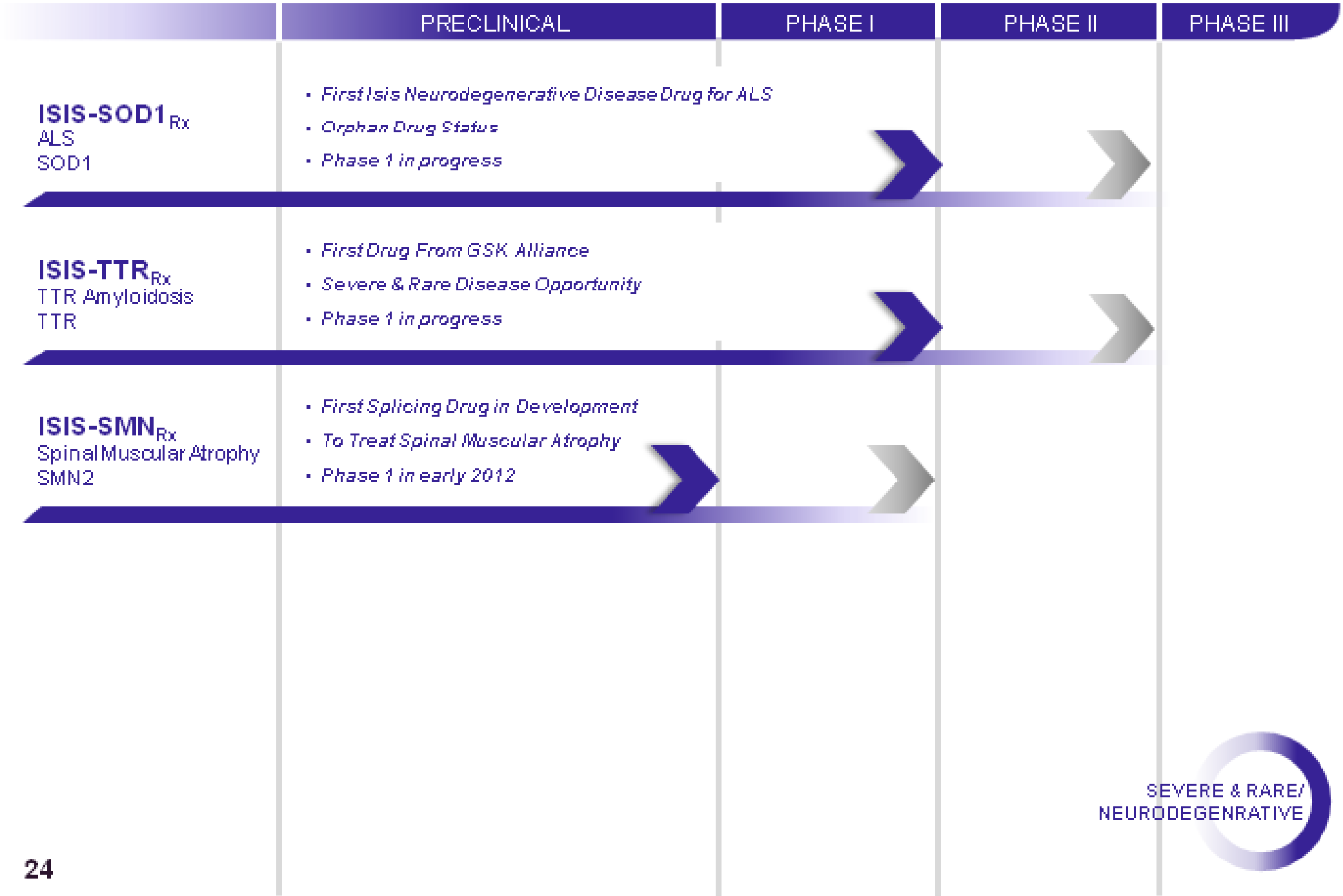
Isis' Cancer Franchise

Novel, Undruggable & Broadly Applicable Cancer Drugs



Isis' Severe & Rare / Neurodegenerative Franchise

Drugs for Severe Rare Diseases



SEVERE & RARE/
NEURODEGENRATIVE

Isis' Focus Today

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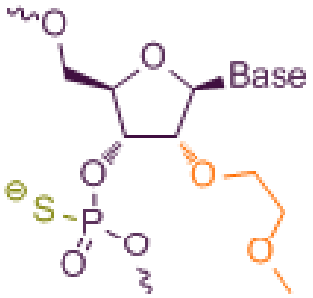
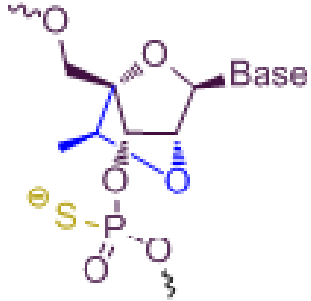
Antisense Technology:
Improving Productivity & Creating Better Drugs

- High specificity for the target
  - The more selectivity a drug has for its target the better the drug
- Broad applicability
  - More potential targets opens up the possibility to treat diseases for which there are no treatment options
- Shared chemistry & features create greater efficiency
  - Rapid inexpensive drug discovery
  - High success rate through Phase 2
- Shared processes across entire pipeline result in greater efficiency

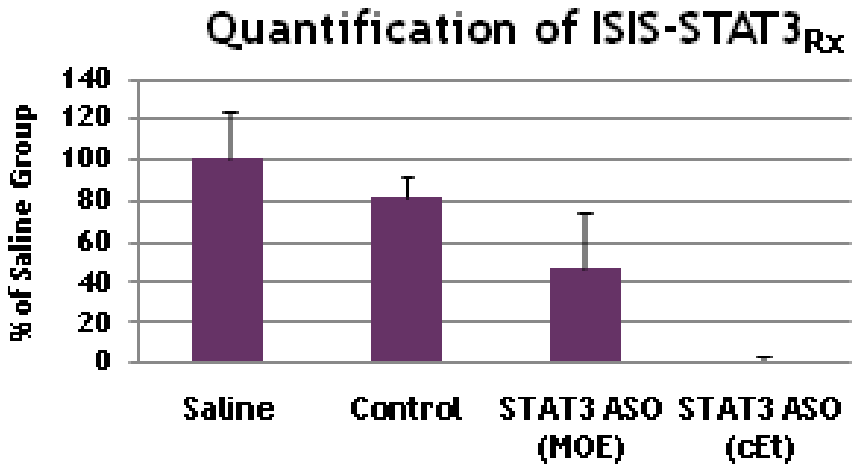
The Evolution of Isis Antisense Drugs

	Second-Generation ***MOE Gapmer***	**Generation 2.5** ***cEt Containing Gapmer***
		
Chemistry Attributes	✓ Increases potency ✓ Increases stability ✓ Reduces non-specific toxicities	✓ Improves potency & therapeutic index ✓ Expands range of targets & tissues
Potency	~200 to 400 mg/week	<5 to 40 mg/week
Routes of Administration	Sub Q, I.V., inhalation, topical, intrathecal	Makes oral delivery feasible

Extends Isis' antisense technology intellectual property position

Generation 2.5 - 'IScEt' Chemistry

- Staged Integration into Isis' Pipeline
  - ISIS-STAT3$_{Rx}$ - The first Generation 2.5 drug
    - In development to treat cancer
  - As safety experience grows, expand into other diseases
    - Use for developing drugs for specific diseases where increase in potency offers unique value



Isis' Future Successes

Isis' Near-Term Events

- Report clinical data evaluating pharmacological effect & safety of multiple drugs
  - ☑ EXC 001 - 3 positive Phase 2 studies reported
  - ☑ ISIS-CRP_{Rx} - Phase 1 reported significant reductions of CRP in normal volunteers
  - ☐ Complete & report Phase 1 data on:

ISIS-$APOCIII_{Rx}$
High Triglycerides
apoC-III

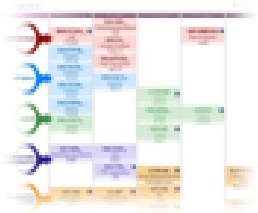
ISIS-$SGLT2_{Rx}$
Diabetes
SGLT2

ISIS FXI_{Rx}
Clotting Disorders
Factor XI

ISIS-$SOD1_{Rx}$
ALS
SOD1

ISIS-TTR_{Rx}
TTR Amyloidosis
TTR

Near-Term Events



- Advance drugs in clinical development toward Phase 2 POC
  - ☑ ISIS-TTR_{Rx} & ISIS-$PTP1B_{Rx}$- initiated Phase 1 study in normal volunteers
  - ☐ Initiate Phase 1 study in:

ISIS-SMN_{Rx}	ISIS-$GCGR_{Rx}$	ISIS-$GCCR_{Rx}$	ISIS-$STAT3_{Rx}$
Spinal Muscular Atrophy	Diabetes	Diabetes	Cancer
SMN2	GCGR	GCCR	STAT3

  - ☑ iCo-007 - Initiate Phase 2 study in patients with diabetic macular edema

- Add 3 to 5 new drugs into Isis' pipeline
  - ☑ ISIS-$STAT3_{Rx}$ - the first Generation 2.5 drug to enter Isis' pipeline

Important Moment for Isis

- Realizing the Potential of Antisense Technology
  - Mipomersen: a near term commercial opportunity to help patients with a fatal cardiovascular disease
  - Evidence of clinical benefit with multiple drugs
  - Numerous opportunities to report clinical data over the next year
  - Solid financial position with mipomersen commercial revenue on the horizon

Business Model at Work

- Strong Balance Sheet and Operating Results
  - Ended second quarter 2011 with nearly $400M in cash
  - Pro forma NOL of $25M for the first half of 2011
- Financial Guidance
  - Projecting 2011 pro forma NOL in the low $40M range
  - Projecting to end 2011 with >$350M in cash

Since 2007, we have generated more than $840M in cash from our partnerships demonstrating that our business strategy is working

Forward Looking Language Statement

This presentation includes forward-looking statements regarding Isis Pharmaceuticals' business, Isis' financial position and outlook, and the therapeutic and commercial potential of Isis' technologies and products in development, including the business of Regulus, Isis' jointly owned subsidiary. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of mipomersen 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, 2010 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 presentation, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries, including Regulus Therapeutics Inc., its jointly owned subsidiary