

# ISIS' ANNUAL SHAREHOLDER MEETING

Stanley T. Crooke, Isis Chairman & CEO

# Isis' Corporate Strategy

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- 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

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- 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

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### 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

## Isis' Focus Today

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

# Mipomersen 2011 Milestones

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## □ Mipomersen: *A Significant Commercial Opportunity*



- EU filing for HoFH & severe HeFH planned in 3Q11



- United States NDA filing for HoFH planned in 2H11

*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

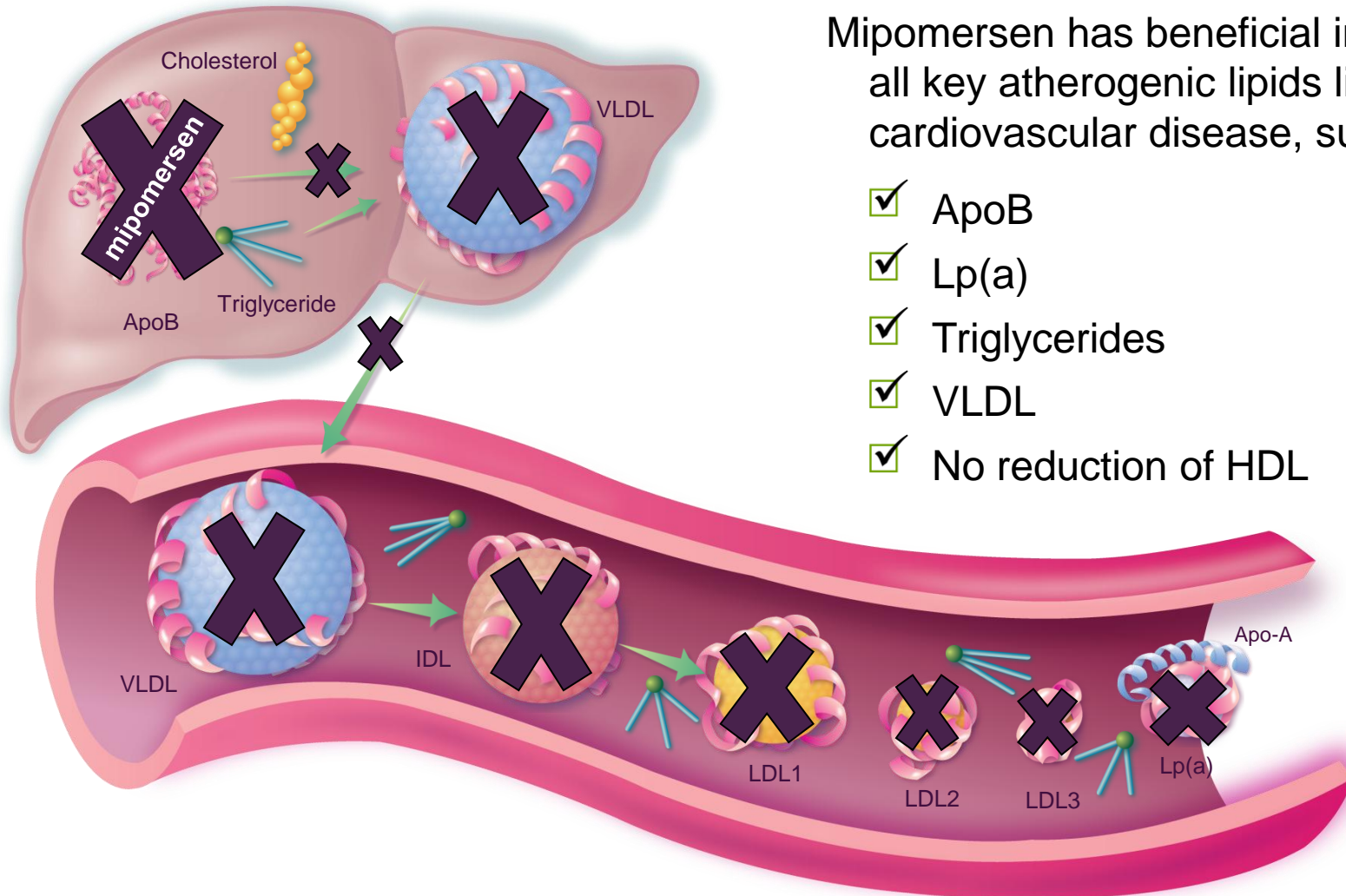
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- Mipomersen
  - Important first-in-class product opportunity
    - Significant initial commercial opportunity in patients at high risk of CV death
    - Long-term growth potential
  - Four positive placebo-controlled Phase 3 studies
    - All primary, 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

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# Mipomersen Reduced All Key Atherogenic Lipids in All Patient Populations Studied

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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)
<b>Homozygous FH</b> (MIPO 5 / n= 51)	<b>426</b>	<b>-24.7%</b> (-106 mg/dL)	<b>- 27%</b> (-77.7 mg/dL )	<b>-31%</b> (-20.5 mg/dL)

*Average LDL-C Reduction in hoFH > 100 mg/dL*

<b>Severe Heterozygous FH</b> (MIPO 35 / n=58)	<b>276</b>	<b>-36%</b> (-101.2 mg/dL)	<b>-36%</b> (-75.3 mg/dL )	<b>-33%</b> (-18 mg/dL)
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*Average LDL-C Reduction in Severe heFH > 100 mg/dL*

# Mipomersen Reduced All Key Atherogenic Lipids in All Patient Populations Studied

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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)
<b>Heterozygous FH</b> (MIPO 7 / n= 124)	<b>153</b>	<b>-28%</b> (-46 mg/dL )	<b>- 26%</b> (-37.8 mg/dL)	<b>- 21%</b> (- 14.4 mg/dL)

*45% of heFH Patients Achieved LDL-C Levels < 100 mg/dL*

<b>High Cholesterol at High Risk for CAD</b> (MIPO 12 / n=158)	<b>123</b>	<b>-37%</b> (-47.3 mg/dL )	<b>-38%</b> (-44.3 mg/dL)	<b>-24%</b> (-14.7 mg/dL)
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*>50% of High-Risk Patients Achieved LDL-C Levels < 70 mg/dL*

# Mipomersen

## Safety & Tolerability Profile

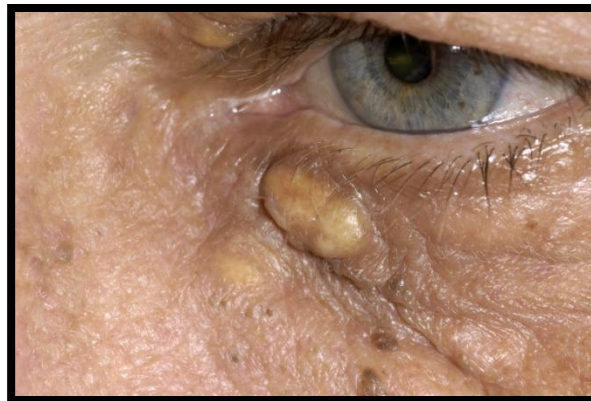
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Side Effects	<ul style="list-style-type: none"><li>▪ Most common side effects were injection site reactions &amp; flu-like symptoms</li></ul>
Adverse Events	<ul style="list-style-type: none"><li>▪ 8% of patients treated with mipomersen had persistent ALT elevations above 3xULN</li><li>▪ Moderate median increases in liver fat<ul style="list-style-type: none"><li>- Ongoing studies to evaluate long-term clinical significance</li><li>- Preliminary data from OLE suggest liver fat may stabilize or decline in patients who continue treatment beyond 12 months</li></ul></li></ul>
Tolerability Profile	<ul style="list-style-type: none"><li>▪ Drop-outs: 8% placebo vs. 22% mipomersen<ul style="list-style-type: none"><li>- Continuing to treat patients for 24 months and beyond</li></ul></li><li>▪ Plans to improve tolerability include continued physician and patient education, dose site &amp; regimen options</li></ul>
Bottom Line	<ul style="list-style-type: none"><li>▪ <b><i>Increases in ALTs &amp; liver fat associated with greatest reductions in LDL-C</i></b></li><li>▪ <b><i>Drop-outs comparable to other s.c. drug trials</i></b></li></ul>

# What is FH or Familial Hypercholesterolemia?

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- ❑ 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 usually 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”



# The Need:

Patients with Severe FH Initially Appear Asymptomatic

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**Referral for Lipid Care**  
FH Diagnosis

Increase Awareness,  
Diagnosis & Treatment

**Statins**  
Second & Third  
Line Agents

Add-on to Current  
Treatments

**No Treatment**  
or  
**Apheresis**

Need for Therapeutic  
Options

# Mipomersen: Near-Term Commercial Opportunities

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~3,000 patients

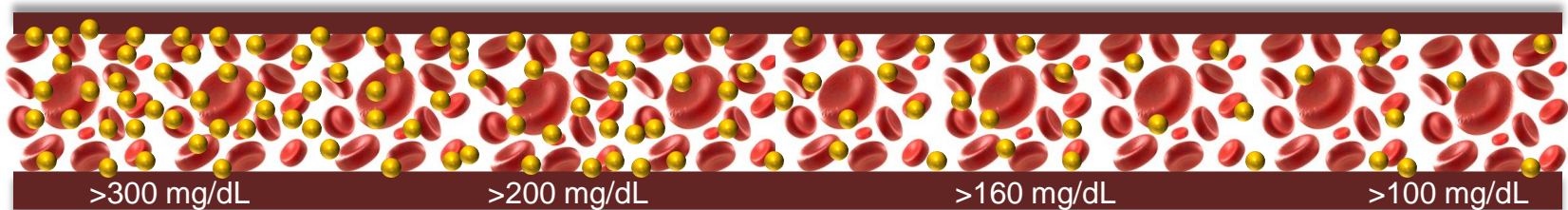


1<sup>st</sup> US Filing  
hoFH

~15,000 patients



2<sup>nd</sup> US Filing  
Severe heFH

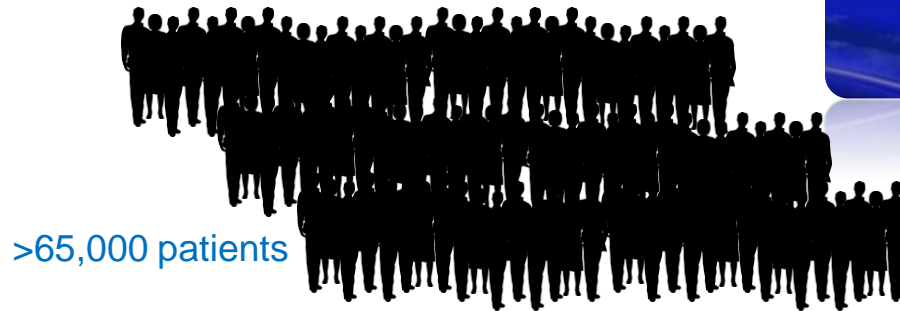


1<sup>st</sup> EU Filing  
hoFH & Severe heFH



~18,000 patients

2<sup>nd</sup> EU Filing  
heFH

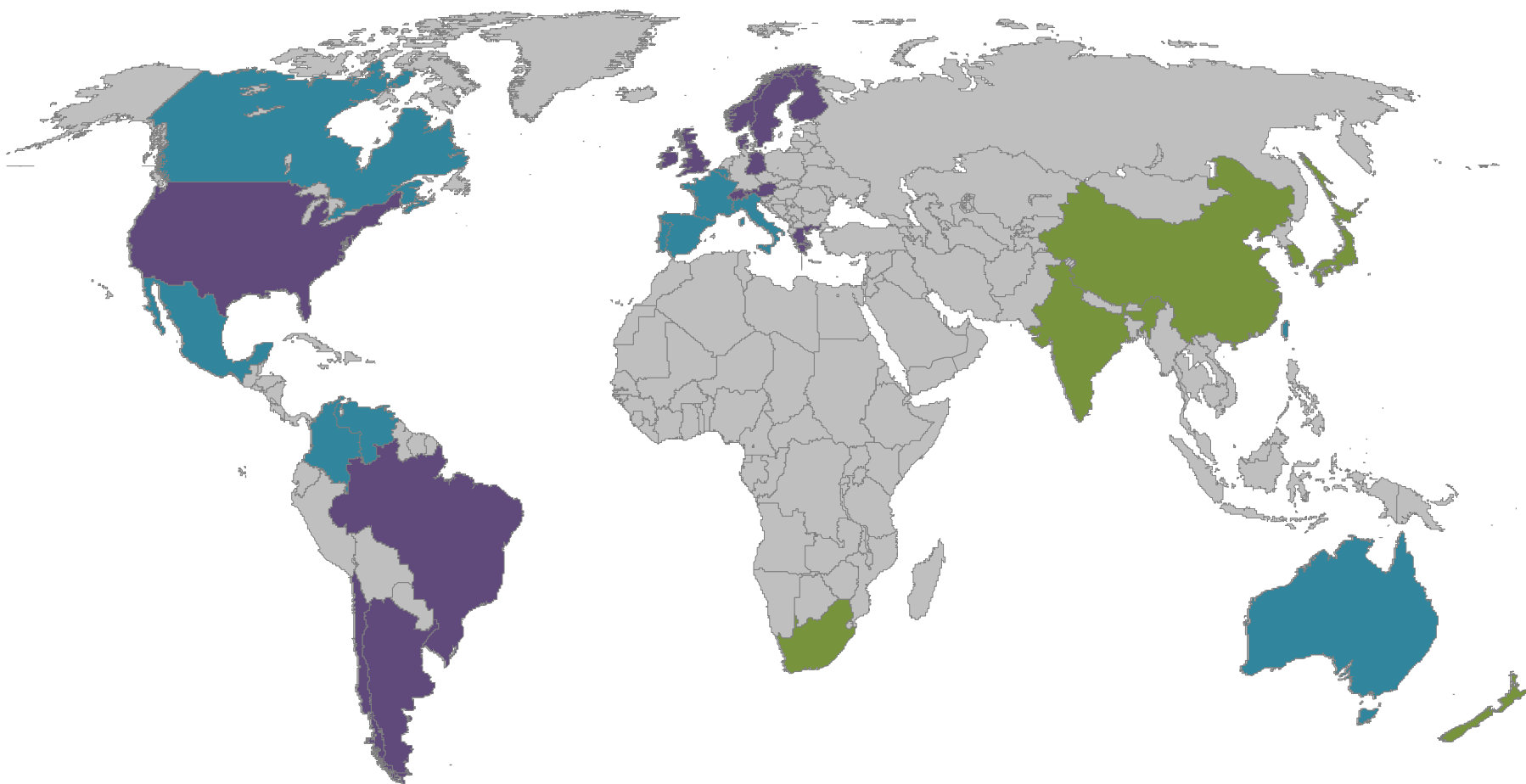


>65,000 patients



# Mipomersen: A Global Commercial Opportunity

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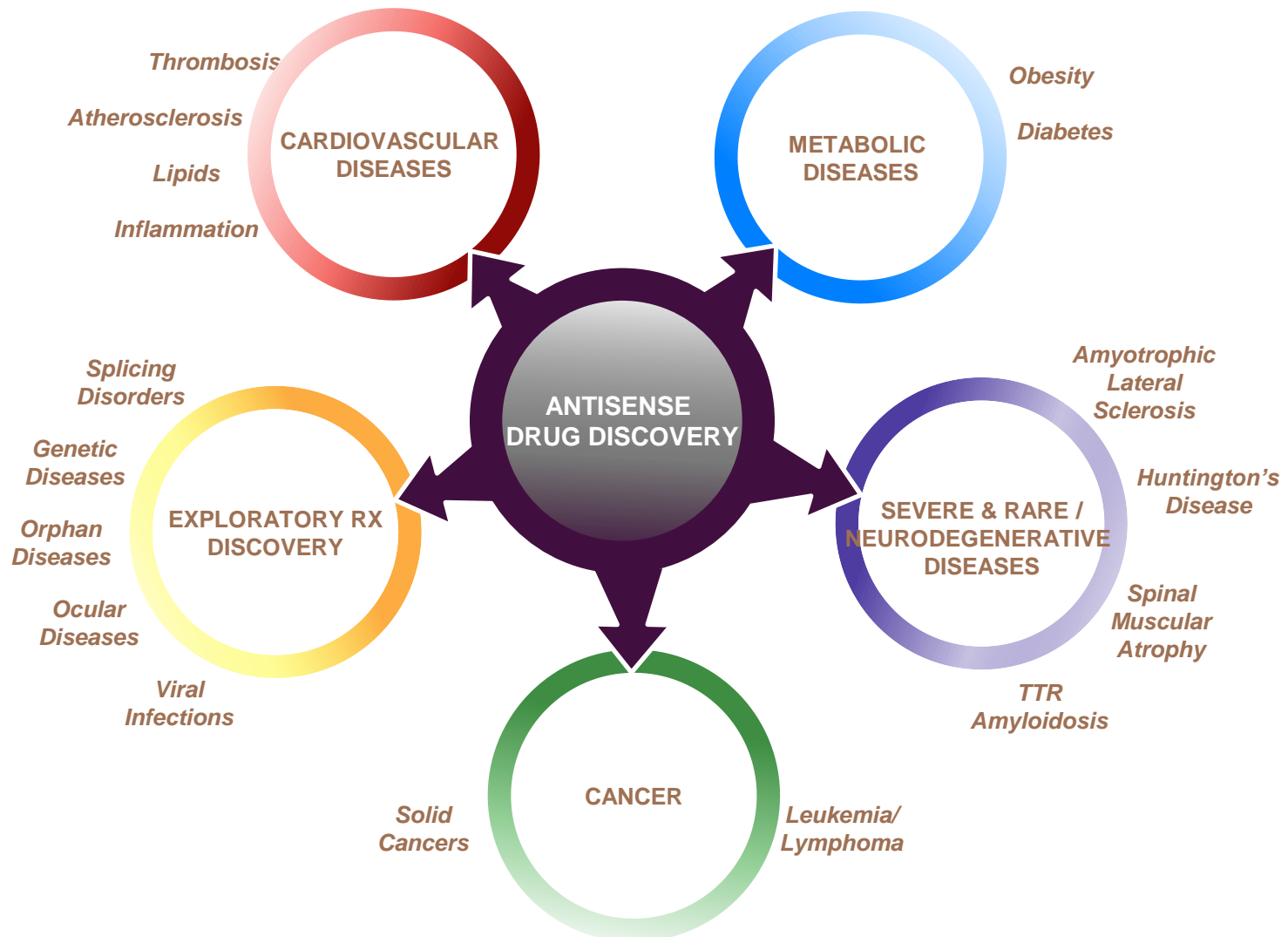
## Isis' Focus Today

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- Commercializing Mipomersen
- **Maturing & Expanding the Pipeline**
- Maintaining Technology Leadership



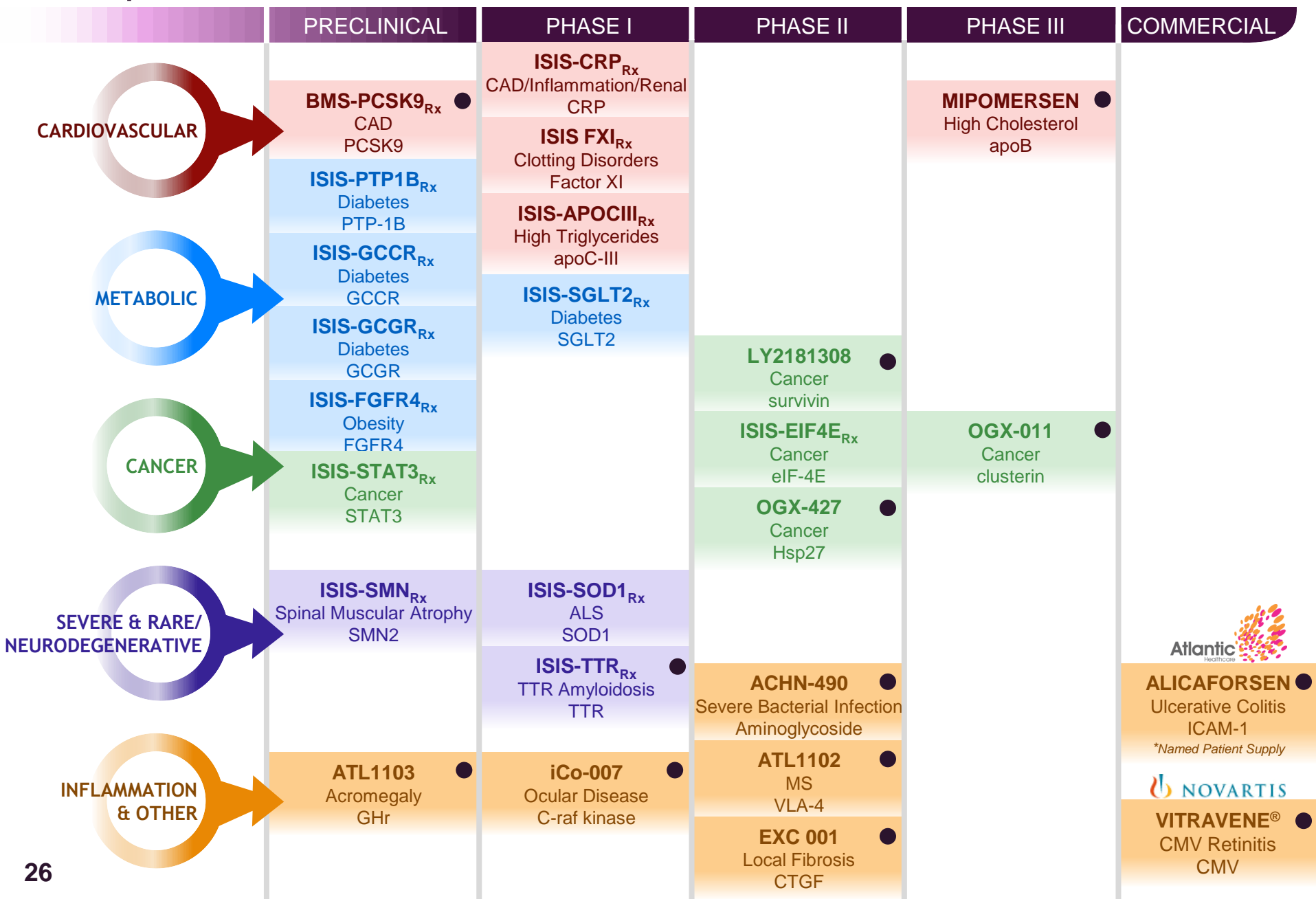
# Isis' Drug Discovery & Development Programs

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# Pipeline

● PARTNERED



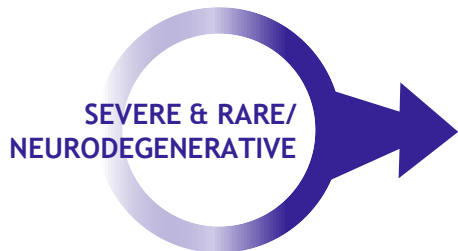
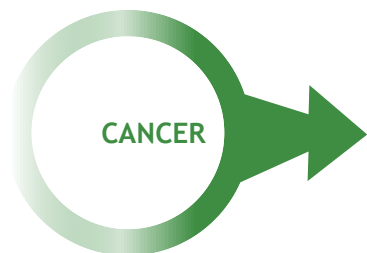
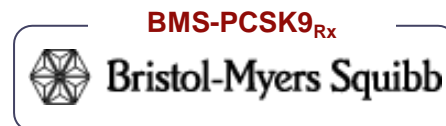
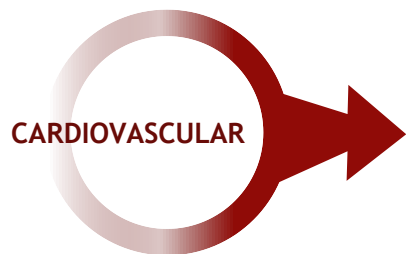
**ALICAFORSEN** ●  
Ulcerative Colitis  
ICAM-1  
*\*Named Patient Supply*



**VITRAVENE®** ●  
CMV Retinitis  
CMV

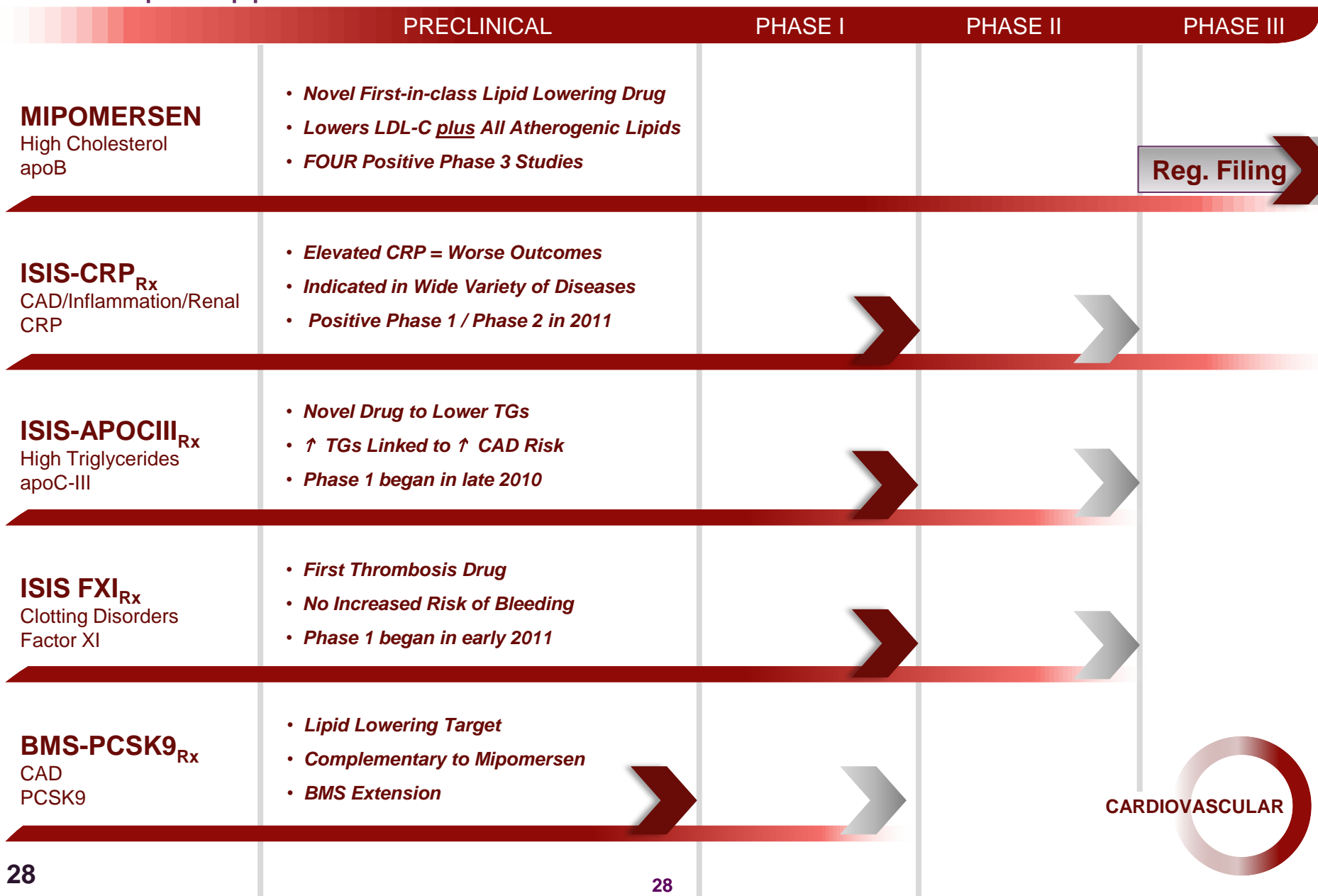
# Partners

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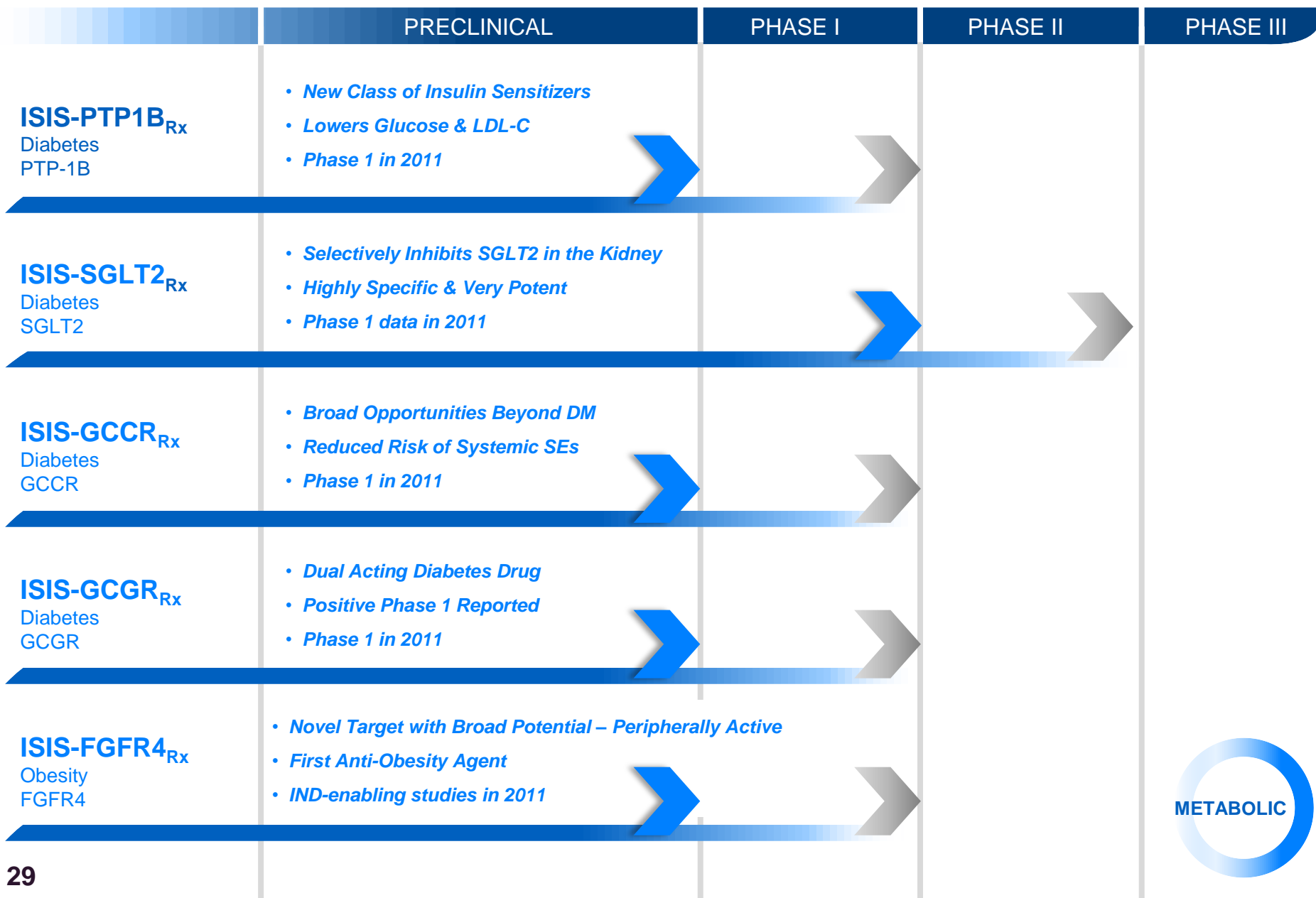
# Isis' Cardiovascular Franchise

## Multiple Approaches to Cardiovascular Disease



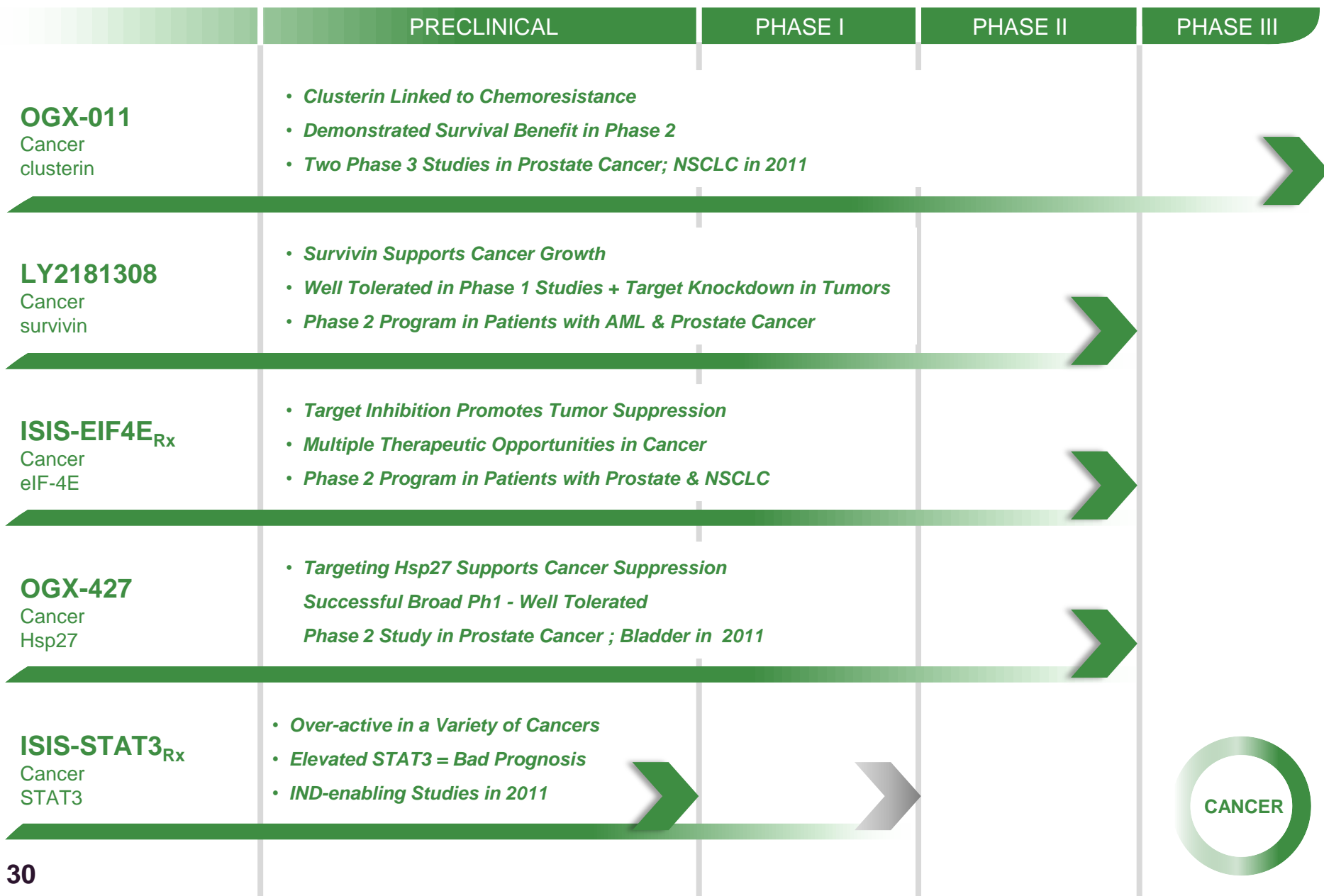
# Isis' Metabolic Franchise

## Distinct Novel Complementary Approaches to Diabetes



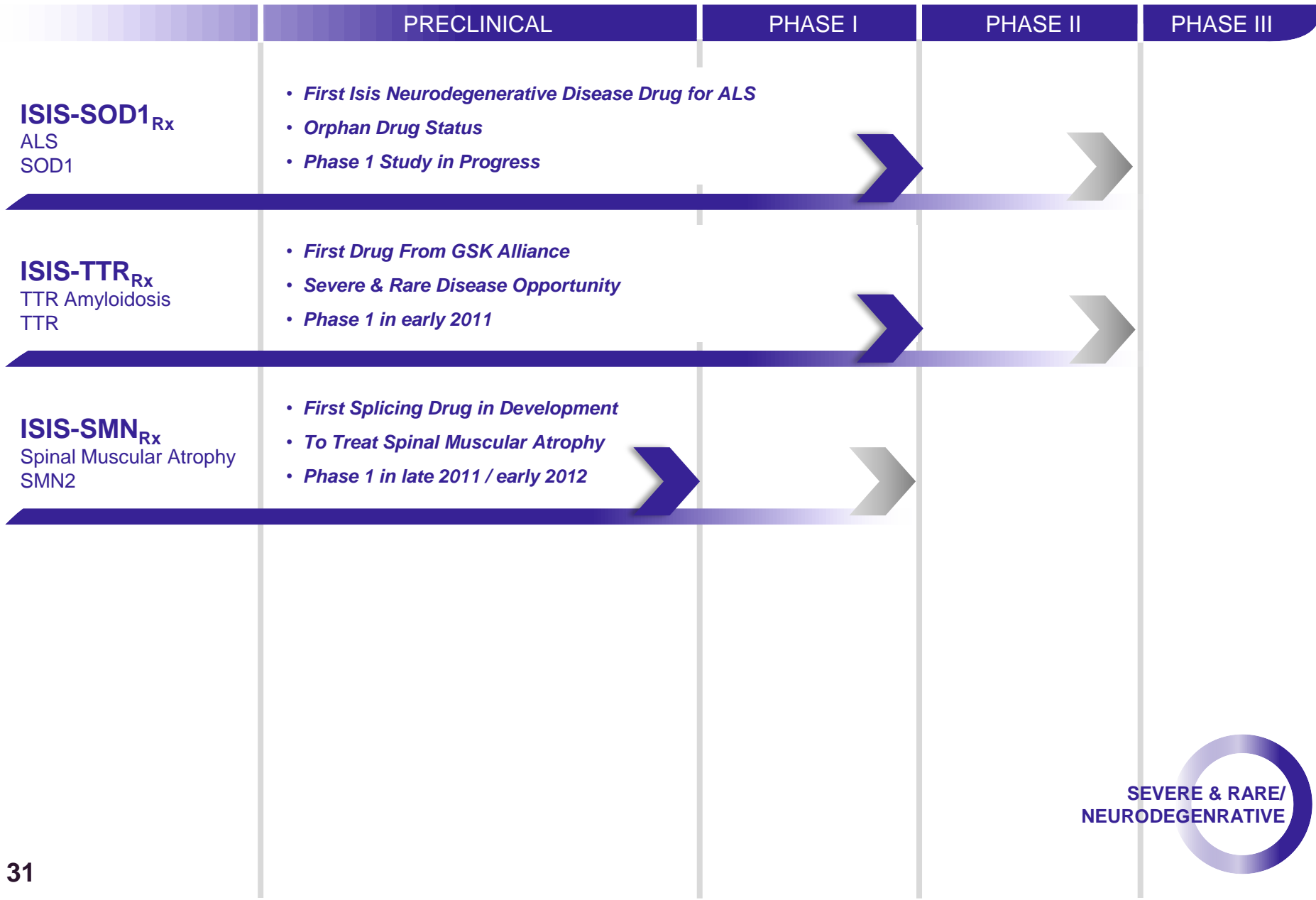
# Isis' Cancer Franchise

## Novel, Undruggable & Broadly Applicable Cancer Drugs



# Isis' Severe & Rare / Neurodegenerative Franchise

## Drugs for Severe Rare Diseases



# Isis' Satellite Company Strategy

## Maximizes Innovation to Create Value

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- Create a consortium of companies that expand the application of antisense technology
- Partner with drug developers who have expertise in areas outside of our core focus to fully exploit our technology
- Isis' SatCo Strategy
  - Uses our technology to broaden our therapeutic focus
  - Supports participation in exciting opportunities with partner's expertise & focus
  - Requires a nominal investment to create important commercial opportunities



XENON



iCo Therapeutics Inc.





# Antisense Technology:

## Improving Productivity & Creating Better Drugs

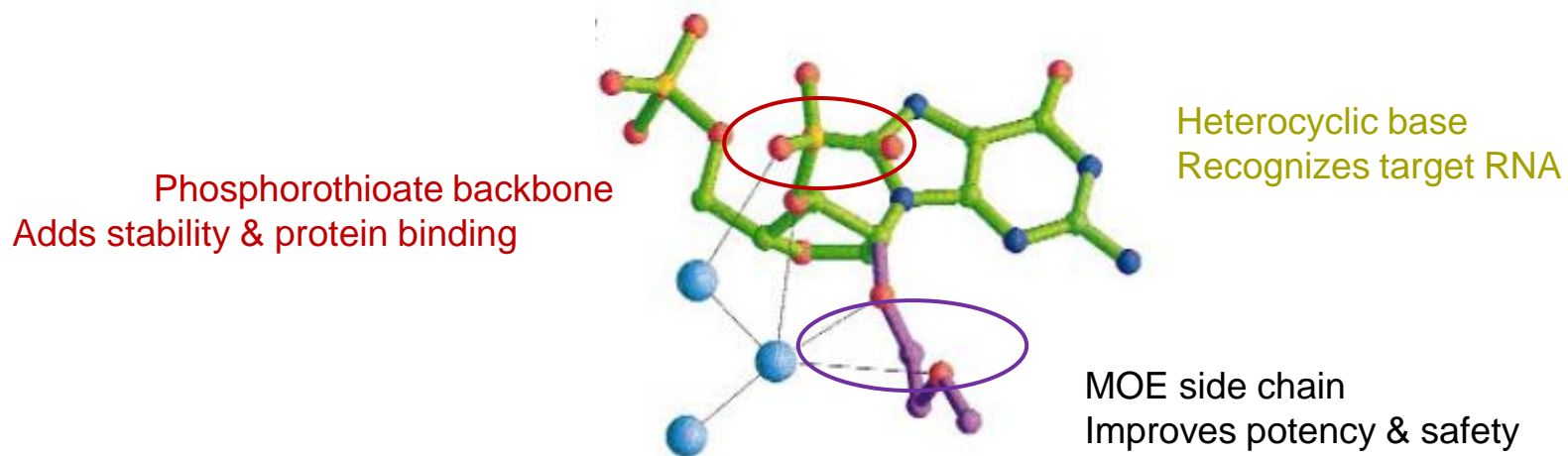
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- High specificity for the target
  - The more selectivity a drug has for its target the better the drug
- Broad applicability
  - More potential targets opens up the possibility to treat diseases for which there are no treatment options
- Shared chemistry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

# Advances in Medicinal Chemistry Are Driving the Technology

## The Magic of MOE Confers Unique Qualities That Make Great Drugs

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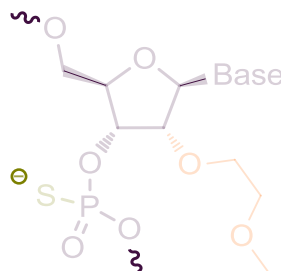
- Extensive clinical experience with second-generation drugs
  - >3,000 subjects dosed
  - Growing experience with chronic administration
  - >20 drugs into the clinic

***2<sup>nd</sup> Generation antisense drugs: Well tolerated in multiple patient populations***

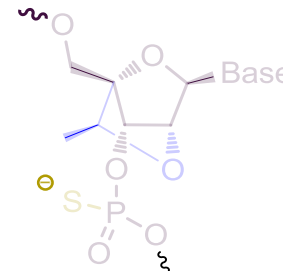
# The Evolution of Isis Antisense Drugs

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## Second-Generation MOE Gapmer



## Generation 2.5 cEt Containing Gapmer



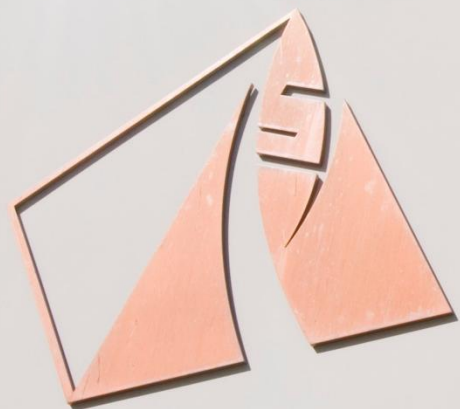
<b>Chemistry Attributes</b>	<ul style="list-style-type: none"> <li>✓ Increases potency</li> <li>✓ Increases stability</li> <li>✓ Reduces non-specific toxicities</li> </ul>	<ul style="list-style-type: none"> <li>✓ Improves potency &amp; therapeutic index</li> <li>✓ Expands range of targets &amp; tissues</li> </ul>
<b>Potency</b>	~200 to 400 mg/week	<5 to 40 mg/week
<b>Routes of Administration</b>	Sub Q, I.V., inhalation, topical, intrathecal	Makes oral delivery feasible

*Extends Isis' antisense technology intellectual property position*

# Important Moment for Isis

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- 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



**ISIS**  

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**PHARMACEUTICALS**

**Thank You for Coming!**