13 December 2012
EMA/792736/2012
EMEA/H/C/002429

Questions and answers

Refusal of the marketing authorisation for Kynamro (mipomersen)

On 13 December 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Kynamro, intended for the treatment of patients with certain forms of familial hypercholesterolaemia.

The company that applied for authorisation is Genzyme Europe B.V. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Kynamro?

Kynamro is a medicine that contains the active substance mipomersen. It was to be available as a solution for injection under the skin.

What was Kynamro expected to be used for?

Kynamro was expected to be used to treat patients with an inherited disease causing high blood cholesterol levels, called familial hypercholesterolaemia. It was initially expected to be used to treat two closely related forms of the disease called 'severe heterozygous' and 'homozygous' familial hypercholesterolaemia. During the assessment of Kynamro, the indication was restricted to patients with homozygous familial hypercholesterolaemia only.

It was expected to be used together with other cholesterol-lowering medicines and a low-fat diet.

How is Kynamro expected to work?

The active substance in Kynamro, mipomersen, is an 'antisense oligonucleotide', a very short fragment of DNA designed to block the production of a protein called apolipoprotein B, by attaching to the genetic material of cells responsible for producing it. Apolipoprotein B is the main component of 'low

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density lipoprotein' (LDL) cholesterol, commonly known as 'bad cholesterol', and of two closely related types of cholesterol called 'intermediate density lipoprotein' (IDL) and 'very low density lipoprotein' (VLDL) cholesterol. Patients with homozygous familial hypercholesterolaemia have high blood levels of these types of cholesterol, which increases the risk of coronary heart disease (heart disease caused by the obstruction of the blood vessels that supply the heart muscle). By blocking the production of apolipoprotein B, Kynamro was expected to reduce the levels of these types of lipoproteins in the blood of patients.

What did the company present to support its application?

The effects of Kynamro were first tested in experimental models before being studied in humans.

The company submitted the results of two main studies. One involved 51 patients with homozygous familial hypercholesterolaemia and the other involved 58 patients with severe heterozygous familial hypercholesterolaemia. The studies compared the effects of Kynamro with placebo when added onto treatment with other cholesterol-lowering medicines and a low-fat diet, for a treatment period of 26 weeks. The main measure of effectiveness was the reduction in the patients' LDL cholesterol levels.

What were the CHMP's main concerns that led to the refusal?

The CHMP noted that Kynamro was effective at reducing LDL cholesterol levels in patients with homozygous and severe heterozygous familial hypercholesterolaemia. After 26 weeks, the approximate average reduction seen in patients taking Kynamro was between 25% and 36%, while it was between 3% and 13% in patients taking placebo.

However, the CHMP was concerned about the medicine's safety. The Committee noted that a high proportion of patients stopped taking the medicine within two years, even in the restricted group of patients with homozygous familial hypercholesterolaemia, mainly due to side effects such as flu-like symptoms, injections site reactions and liver toxicity. This was considered important because Kynamro is intended for long-term treatment in order to maintain the cholesterol-lowering effect. The CHMP was also concerned by liver test results in patients taking Kynamro showing a build-up of fat in the liver and increased enzyme levels, and was not convinced that the company had proposed sufficient measures to prevent the risk of irreversible liver damage. Moreover, the Committee was concerned that a greater proportion of patients taking Kynamro experienced serious cardiovascular events (problems with the heart and blood vessels) than patients taking placebo. This prevented the CHMP from concluding that Kynamro's intended cardiovascular benefit, in terms of reducing cholesterol levels, outweighed its cardiovascular risk.

Therefore, at that point in time, the CHMP was of the opinion that the benefits of Kynamro did not outweigh its risks and recommended that it be refused marketing authorisation.

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that patients receiving the medicine in clinical trials will continue to do so as planned. Patients applying for compassionate use programmes will continue to be evaluated and will receive the medicine if eligible.

If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.

ISIS PHARMACEUTICALS INC.
13 G FILINGS OCCURING SINCE THE FIRST OF THE YEAR

Increased ownership in Isis

February 14, 2013	SC 13G/A	FMR LLC (Fidelity)	15.51%	15,812,207 shares
February 14, 2013	SC 13G/A	ClearBridge Investments LLC	6.15%	6,223.056 shares
February 13, 2013	SC 13G/A	BB Biotech AG	8.0%	8,043,140 shares
February 13, 2013	SC 13G	The Vanguard Group	5.5%	5,437,039 shares
February 8, 2013	SC 13G/A	Blackrock Inc.	7.48%	7,565,293 shares
February 6, 2013	SC 13G	Artisan Partners	5.8%	5,862,500 shares

Decreased ownership in Isis

February 13, 2013	SC 13G/A	Columbia Wagner Asset Management	Less than 5%

Information listed above was prepared from SEC documents included on the Isis Pharmaceuticals website (Investors & Media section)

KYNAMRO™ (mipomersen sodium) Injection

First Systemic Antisense Drug Approved

KYNAMRO mipomersen sodium genzyme A SANOFI COMPANY

- **KYNAMRO approved by FDA for homozygous FH** (Jan 29)
  - $25M milestone earned

- **Commercial activities underway**
  - Physicians qualified, scripts written
  - Focus on improving disease awareness and treatment of homozygous FH patients

www.KYNAMRO.com

- **Re-examination of CHMP opinion requested by Genzyme; anticipate new opinion in 2Q 2013**

- **Investing in the future – FOCUS FH study in severe FH patients ongoing (under SPA); projected completion by 2014**

FOCUS FH

Isis: FDA Approval Of Kynamro Promises A Bright Future For Company

Feb 1 2013, 11:21 by: Prohost Biotech | about: ISIS, includes: ALNY, SNY, SRPT

The FDA has approved Isis' (ISIS) Drug Kynamro (mipomersen sodium) for Homozygous Familial Hypercholesterolemia (HoFH). Genzyme, a Sanofi (SNY) company, and Isis Pharmaceuticals announced the news on Wednesday January 30, 2013. The FDA approved Kynamro's 200 mg weekly subcutaneous injection as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (Apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

The market is small? We know that. Yet we did not miss the fact that January 30, 2013, the day Kynamro's was granted approval, will be recorded in the textbooks of pharmaceutical sciences as the day the first systemically administered antisense therapeutic has been approved by the FDA. This approval is insinuation to a large market, very large as a matter of fact, considering the nature of the therapeutic molecules and the nature of the targets. The approval has officially confirmed the feasibility of creating therapeutic molecules out of Isis' chemically transformed antisense molecules. We also did not miss the fact that the successful development of an antisense molecule will really highlight the firm's pipeline that is full of products - all represent genetic disease that are intractable and life-threatening with unmet treatment needs.

Isis' success was anything but easy. The firm and its scientists had to struggle for around two decades to overcome the multitude of hurdles the antisense technology is known to face. The problems were, indeed, grave. They sounded unsolvable, which led chemists and molecular biologists to classify antisense among the most ambitious, yet, the most difficult to translate into safe and effective therapeutics. That is the main reason analysts believed and some would continue to propagate that the time, effort and money biotech firms have been spending on developing antisense drugs will be washed-out. The same scientists, however, recognized the tremendous value antisense therapeutics would gather if successfully produced.

The FDA approval of Isis' systemically used antisense drug confirmed that the time, effort and money it spent did not go in vain. The impossible was made possible and the firm was capable of bringing to patients an entirely new class of drugs capable of overcoming the limitations of conventional treatments. HoFH patients will soon have in hand a therapeutic called Kynamro, the first drug that works at the root-cause of their inherited disease. HoFH is a rare inherited condition that makes the body unable to dispose of the bad LDL cholesterol, causing abnormally high levels of circulating LDL cholesterol. In the United States, HoFH occurs in approximately one in one million individuals who are threatened with cardiovascular complications and death at an early age - as early as 30 years old.

The Beef?

Of course negative analysts will discourage buying ISIS with the pretext that the HoFH market is too small. For investors to know better, they must understand that the success of therapeutic antisense molecules is extremely helpful in creating more antisense successful molecules. All the products have the same molecules, but directed against various targets. The money, investors realize, resides in the

Efficiency of Antisense Platform

	Antisense Drugs			Small Molecule Drugs		
Idea to Phase 1	Cost $5-10M	Time 2 - 5 yrs	FTE/yr 3 - 5	Cost $40-100M	Time 7 - 10 yrs	FTE/yr 20 - 40
Preclinical Development	~90% probability of reaching clinical trials			~10% probability of reaching clinical trials		
CMC Investments	Investments amortize over entire pipeline			Unique investments required for each drug		
TOX/PK	Similar for all drugs No drug interactions			Unique for each drug		
Breadth of Opportunities	All genes Major tissues			Only “druggable” targets		

ISIS PHARMACEUTICALS

Isis' Unique Business Strategy

Key Principles

- Create a New Platform for Drug Discovery
  - Antisense Technology Works
  - Continuing advances enhance performance & prolong proprietary control
- Control Technology & Products Through Continued Innovation & Patents
  - Over 1,500 Patents
- Use the Efficiency of the Antisense Platform to Create Broad & Expanding Pipeline
  - 25 drugs in development
- Small Innovation Focused Organization Supporting a Diverse Pipeline
  - Fewer than 350 people→ Manageable cost structure
- Employ a Unique Business Strategy
  - Partnership strategy maximizes long-term return & minimizes risk
  - Sustained financial strength
  - Simplified organization
  - Sustained innovation

Overview

Key Messages

- **Kynamro: Commercialization on the Horizon**
- **Maturing Pipeline**
  - Five drugs with launch potential in next five years
  - Nine drugs with Phase 2 or Phase 3 data planned for 2013/early 2014
  - Two to three Phase 3 programs planned to initiate in 2013/early 2014
- **Expanding Pipeline**
  - Three new drugs in development
  - Growing severe and rare disease program
- **Antisense Advances**
  - Generation 2.0 drugs more potent and better tolerated
  - Generation 2.5 drugs significantly more potent than Generation 2.0
- **Partnering Success: Significant Interest Continues**
- **2013 Goals**

Isis' Partnering Progress

Business Strategy Maximizes Value and Minimizes Risk

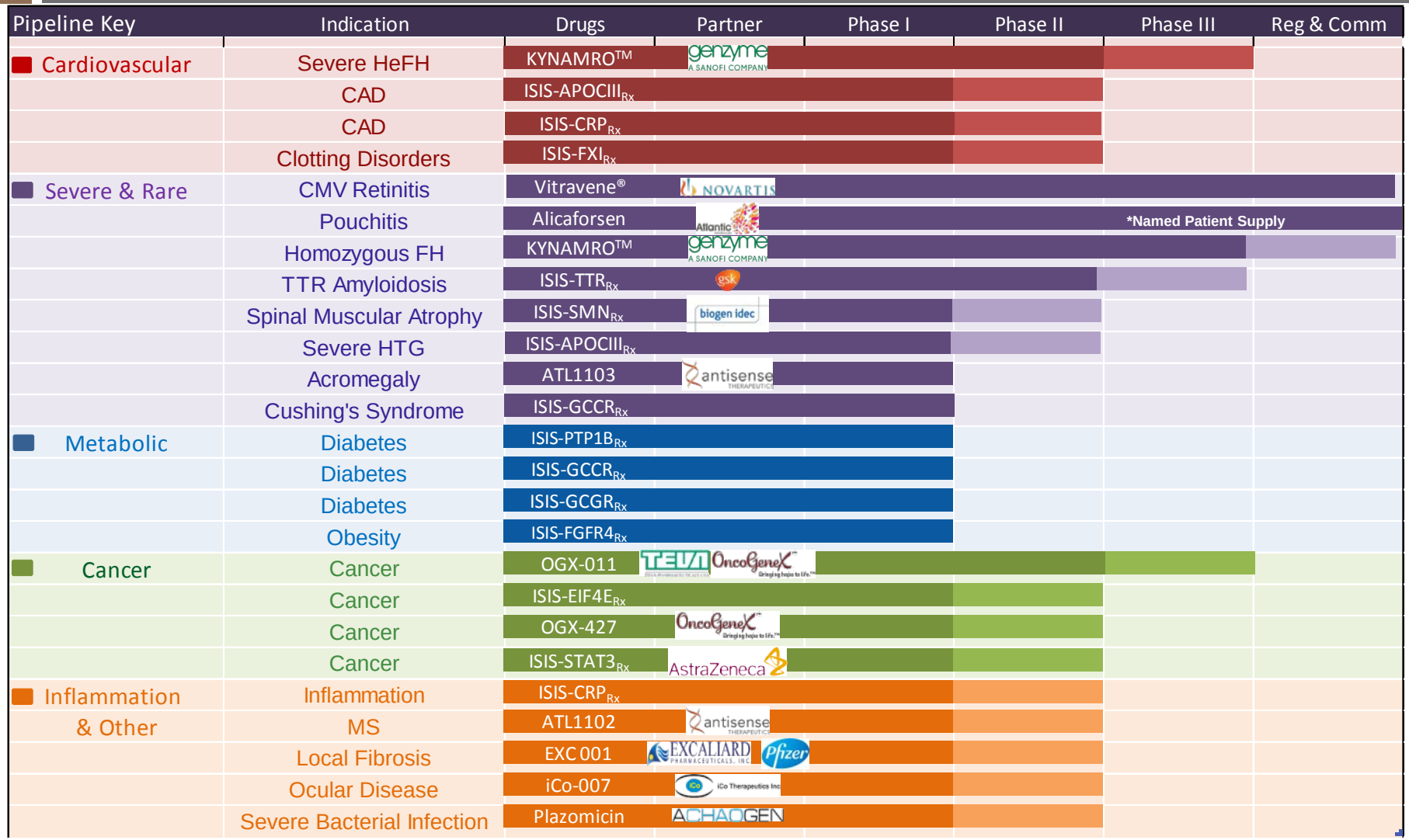
- Partner programs at earlier stages of development in therapeutic areas with higher risk (e.g., neuro and cancer) and where Phase 2 data will not provide a large increase in value
- Defer license fees with manageable and relatively inexpensive Phase 2 programs where results will cause significant value inflection
  - Unique partner strategy for each program to maximize value
  - Superior down stream economics
  - Isis controls earlier-stage development
- ~$2B in cash from partnerships to date

Partners


CARDIOVASCULAR
MIPOMERSON
genzyme
BMS-PCSK9Rx
Bristol-Myers Squibb
CANCER
OGX-011
TEVA PHARMACEUTICALS USA
OncoGeneX™
Bringing hope to life.™
LY2181308
Lilly
OGX-427
OncoGeneX™
Bringing hope to life.™
SEVERE & RARE/
NEURODEGENERATIVE
ISIS-TTRRx
gsk
INFLAMMATION
& OTHER
Vitravene®
NOVARTIS
EXC 001
EXCALIARD
PHARMACEUTICALS, INC.
iCo-007
iCo
iCo Therapeutics Inc.
Alicaforsen
Atlantic
Healthcare
ACHN-490
ACHAOGEN
ATL1102 / ATL1103
antisense
THERAPEUTICS

Isis' Clinical-Stage Pipeline

January 2013



Isis' Pre-clinical Stage Pipeline

January 2013

Pipeline Key	Indication	Drugs	Preclinical	Phase I	Phase II	Phase III	Reg & Comm
Cardiovascular	CAD	ISIS-APOA$_{Rx}$					
	Clotting Disorders	ISIS-FVII$_{Rx}$					
Severe & Rare	AAT Liver Disease	ISIS-AAT$_{Rx}$		gsk			
	Hereditary Angioedema	ISIS-PKK$_{Rx}$	←				
Metabolic	NASH	ISIS-DGAT2$_{Rx}$					
Cancer	Cancer	ISIS-AZ1$_{Rx}$	←	AstraZeneca			
Inflammation	Anemia of Inflammation	XEN701		XENON			
& Other	Antiviral	ISIS-GSK3$_{Rx}$	←	gsk			

← **New Development Candidates**

Potential Drug Launches Through 2017

Drug	Indication/Market	Economics
ISIS-TTR$_{Rx}$ GlaxoSmithKline	Familial Amyloid Polyneuropathy (FAP) ~10,000 patients	License fee, sales milestone payments and double-digit royalties
ISIS-SMN$_{Rx}$ biogen idec	Spinal muscular atrophy (SMA) ~35,000 patients worldwide	License fee, milestone payments and double-digit royalties
ISIS-APOCIII$_{Rx}$ ISIS PHARMACEUTICALS	Severe triglyceridemia (>880 mg/dL) at increased risk of recurrent pancreatitis ~200,000 patients in US & EU	Isis Owned
OGX-011 TEVA PHARMACEUTICALS USA OncoGeneX Bringing hope to life.™	Castration-resistant prostate cancer (1st line) ~315,000 patients in US/EU	Milestone payments and single-digit royalties
EXC 001 Pfizer	Anti-scarring treatment estimated to be multibillion dollar market	Milestone and other payments and single-digit royalties

Advancing the Pipeline

Numerous Drugs with Phase 2 or Phase 3 Data Potentially in 2013/Early 2014

Drug	Indication	Studies	Study Phase
OGX-011	Cancer	Prostate Cancer	Phase 3
ISIS-FXI$_{Rx}$	Thrombosis	Total Knee Replacement	Phase 2
ISIS-CRP$_{Rx}$	Inflammation Cardiovascular Disease	Endotoxin RA Atrial Fibrilation	Phase 2
ISIS-EIF4E$_{Rx}$	Cancer	Lung Cancer Prostate Cancer	Phase 2
ISIS-APOCIII$_{Rx}$	Severe Hypertriglyceridemia (HTG)	Severe HTG Moderate HTG	Phase 2
ISIS-SMN$_{Rx}$	Spinal Muscular Atrophy (SMA)	SMA (childhood onset)	Phase 2
ISIS-STAT3$_{Rx}$	Cancer	Lymphoma	Phase 2
OGX-427	Cancer	Prostate Cancer	Phase 2
iCo-007	Ocular	Diabetic Macular Edema	Phase 2

2013 Partnering Opportunities

Unpartnered Drugs with Phase 2 Efficacy Data Planned in 2013/Early 2014

Drug	Indication(s)	Studies
ISIS-APOCIII$_{Rx}$	Severe Hypertriglyceridemia (HTG)	Severe HTG Moderate HTG
ISIS-FXI$_{Rx}$	Thrombosis	Total Knee Replacement
ISIS-CRP$_{Rx}$	Inflammation Cardiovascular Disease	Endotoxin, RA Atrial Fibrilation
ISIS-EIF4E$_{Rx}$	Cancer	Lung Cancer Prostate Cancer

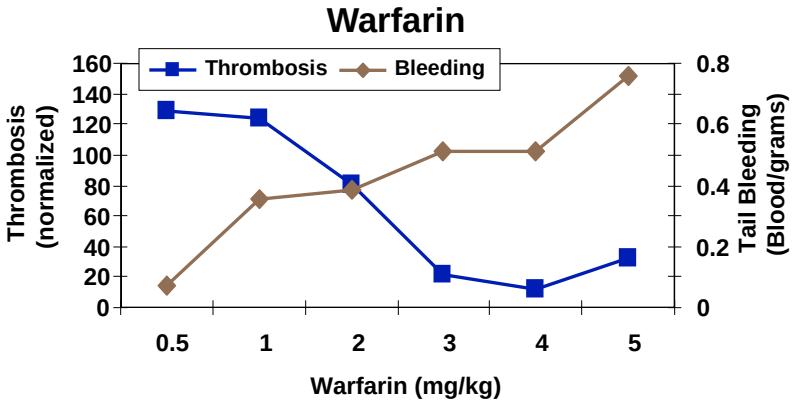
ISIS-FXI$_{Rx}$ for Thrombotic Disorders

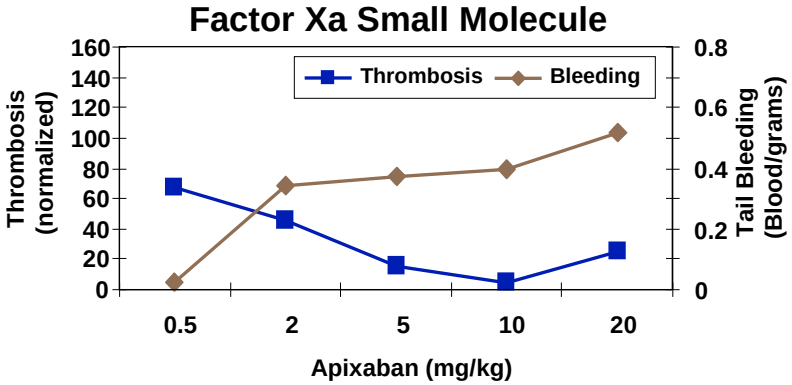
Potential Multibillion Dollar Commercial Opportunity

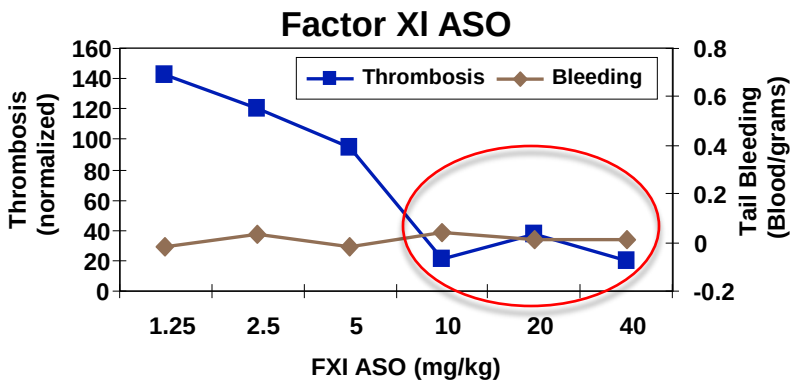
- **Thrombosis, a major component of cardiovascular disease, is one of the leading causes of death in the western world**
  - The formation or presence of a blood clot can occur suddenly and result in death
- **Current treatments to prevent blood clots often result in an unacceptably high risk of bleeding which can also result in death**
- **There is significant need for a treatment to prevent blood clots, with less bleeding, in diseases where warfarin and Factor Xa and Factor IIa are currently used**
  - Acute Coronary Syndromes (ACS)
  - Stroke Prevention
  - Venous Thromboembolism (VTE), including Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT)
- **Potential significant near-term licensing opportunity**

ISIS-FXI$_{Rx}$ Preclinical Data

Efficacy without Increased Bleeding





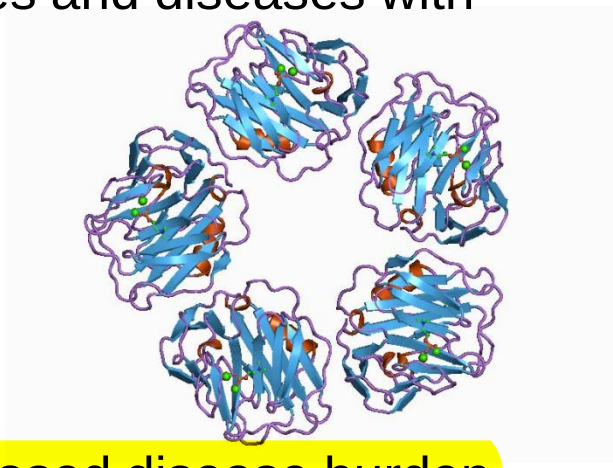


ISIS-FXI$_{RX}$ demonstrated potent antithrombotic activity with no increase in bleeding compared to standard anti-clotting agents, including low-molecular weight heparin, warfarin and Factor Xa inhibitors (all of which increased bleeding)

Targeting C-Reactive Protein (CRP)

Elevated CRP Correlates with Increased Disease Burden

- CRP is elevated in many inflammatory diseases and diseases with inflammatory components, such as
  - Acute Coronary Syndrome
  - Atrial Fibrillation
  - Ulcerative Colitis/Crohn's Disease
  - Chronic Kidney Disease (CKD)
  - End Stage Renal Disease (ESRD)
  - Organ Transplant



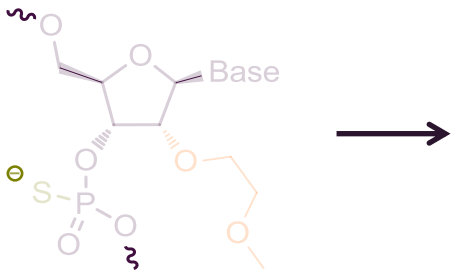
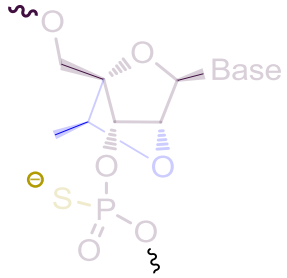
- Elevated CRP levels are associated with increased disease burden
- CRP is a complex glycoprotein, making it difficult to specifically target with small molecule drugs
- Large commercial opportunity
  - Potential broad applications in a number of diseases exacerbated by inflammation
  - Market for inflammatory disease estimated to be > $20B
- Significant partnering opportunity at POC

ISIS-CRP$_{Rx}$ – Multiple Clinical Readouts in 2013

Designed to Produce Compelling Data Showing Therapeutic Benefit of Reducing CRP

- **Endotoxin Challenge Study in ~30 Healthy Volunteers (Completed)**
  - Study designed to demonstrate that ISIS-CRP$_{Rx}$ can blunt acute severe increases in CRP
  - Exploring other key inflammatory mediators such as TNF-α, IL-1β, IL-6 and complement
  - **Data planned for 1H 2013**
- **Phase 2 Study in ~ 50 Patients with Rheumatoid Arthritis (Ongoing)**
  - Study designed to demonstrate benefit of lowering CRP in patients with chronically elevated CRP levels
  - **Data planned for mid 2013**
- **Phase 2 Study in ~ 20 Patients with Atrial Fibrillation (Planned Start 1H 2013)**
  - Study designed to demonstrate CRP reduction has a positive effect on the duration and frequency of atrial fibrillation events
  - **Data planned for 1H 2014**

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

Advancing Antisense Technology

Improved Screening Generates More Potent Generation 2.0 Antisense Drugs

Greater Reduction of Target Protein after 4 Weeks of Treatment (Fold Improvement vs. Kynamro)

Dose Level (mg)	ISIS-APOCIII$_{Rx}$	ISIS-FXI$_{Rx}$	ISIS-TTR$_{Rx}$
100	-25% (1.2X)	-49% (2X)	-23% (1.1X)
200	-71% (1.8X)	-71% (1.8X)	-53% (1.5X)
300/400	>-78% (>1.5X)	>-90% (>1.8X)	>-75% (>1.5X)

Conclusion: Newer Generation 2.0 antisense drugs are more potent than Kynamro

Advancing Antisense Technology

Improved Screening Enhances Tolerability Profile of Gen 2.0 Antisense Drugs

Improvement in Nuisance Side Effects Observed in Newer 2nd Generation Antisense Drugs Compared to Kynamro

Parameter	ISIS-APOCIII$_{Rx}$	ISIS-FXI$_{Rx}$	ISIS-TTR$_{Rx}$
Injection-site Reactions (% SC Injections)	89% fewer ISRs	64% fewer ISRs	65% fewer ISRs
Flu-like Symptoms	None reported	None reported	None reported

Advancing Antisense Technology

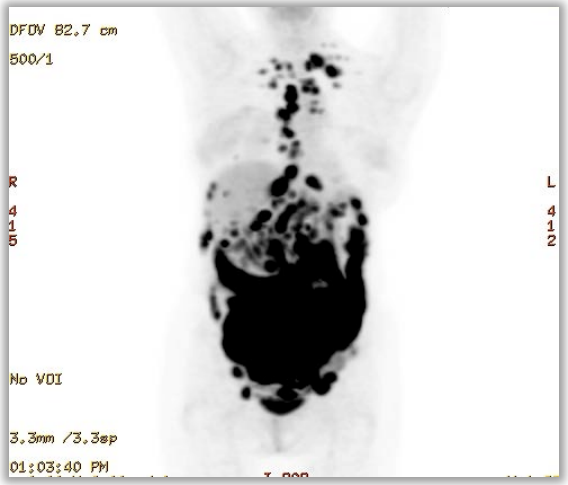
Improved Potency Demonstrated with Generation 2.5 Antisense Drugs

Partnered with: AstraZeneca

- **Experience with ISIS-STAT3$_{Rx}$ demonstrates:**
  - Gen 2.5 drugs are up to 10x more potent than previous Gen 2.0 drugs
  - Gen 2.5 drugs have good tolerability with evidence of durable response in patients with diffuse large B-cell lymphoma
- **Data planned for 2013**

55% response observed in 63 year old female with diffuse large B-cell lymphoma

Before Treatment



After Treatment (2 mg/kg)