Multiple Approaches to Cardiovascular Disease

Cardiovascular Franchise:

- ISIS FXI
- High Triglycerides
- High Cholesterol

Risk Factors for Lipid Metabolism
- Complement Components
- Acute Phase Reactants

Further expanding into thrombosis

Expanding program to inflammation in cardiovascular disease

ISIS-CRP Rx in Phase 1; initiating Phase 2 program in rheumatoid arthritis & multiple myeloma

Liver

Advancing others (PCSK9; Lp(a); apoC-III)

First Thrombosis Drug

Bile

Atherosclerosis

Contributing to CAD

Liver-derived coagulation factors

- Elevated Triglycerides
- Elevated LDL-C

Hypertension

Inflammatory targets


In what diseases will reducing elevated CRP result in benefits to patients?

Elevated CRP levels associated with worse outcome in many diseases

- Organ Transplant/Graft vs. Host Disease
- Dementia
- Periodontal Infections
- End-Stage Renal Disease (ESRD)
- Chronic Kidney Disease (CKD)
- Inflammatory Bowel Disease (IBD)

Inflammation opening up a wide range of disease

Completed a Phase 1 clinical study

CRP levels associated with worse outcomes

Functional disability

Soon demonstrate proof-of-concept & provide information opening up a wide range of disease

Targeting Apolipoprotein C-III For Triglyceride Management

ApoC-III Antisense Drug Results in Dose-Dependent Reduction

C57BL/6 Plasma TG

Blinded, randomized, placebo-controlled, dose-response study in patients with elevated apoC-III & triglycerides

Hepatic-derived coagulation factors

- Factor XI
- Apolipoprotein CIII (APO-CIII)

Target: Apolipoprotein C-III (APO-CIII)

Source: Decision Resources

Due to its Applications in Both Arterial & Venous Thrombosis

ISIS-FXIRx Has Potentially Broad Market Opportunities

Warfarin

Associated with significant mortality & morbidity

Anti-platelet market to decrease to $8.2 billion due to decreasing the potential for adverse events

Rx will be used for prevention of CV disease

AF patients have a five-fold risk of stroke

Combination Therapy

Once per week or less frequent dosing

Orphan indications

Genetically validated & safe target in humans

Diverse & growing program

Novel mechanisms of action & areas

Multiple drug opportunities

Summary