Safety & Tolerability of Antisense Drugs

INTRODUCTION

Antisense Drugs – Growing Safety Database

- ▲ 2'-MOE chemical class have similar & predictable toxicology profiles in animals – same chemistry for each drug, *different genetic zip code*
  - ➤ 2'-MOE chemistry was selected from many medicinal chemistry modifications for improved safety & potency compared to other antisense chemical classes
- ▲ Predictive safety margin from toxicology doses in animals to therapeutic doses in man
- ▲ Predictable safety in man with thousands of patients dosed to date
- ▲ Effective doses in humans as high as 1,200 mg/wk
- ▲ Many safety issues common to small molecules are not a factor
- ▲ Long-term clinical safety database in patients is growing & supports chronic treatment

The Antisense Advantage: Predictable Safety Profile

Small Molecule Drugs	*Isis' Antisense Drugs*
▲ Each drug is different	▲ Shared chemical structure
➤ Different chemistry	➤ Zip code is only difference
➤ Different side effect profile	▲ Side effect profile common to all class members
▲ Small chemistry changes give big safety changes	▲ Little or no safety effects from *zip* code changes
➤ Toxicity changes are unpredictable	➤ Adverse sequence motifs are designed out
▲ Significant Failure Rate in Early Development	▲ High Success Rate for Early Development Through Phase 1

Bench to Bedside – Defined Process
Major Steps

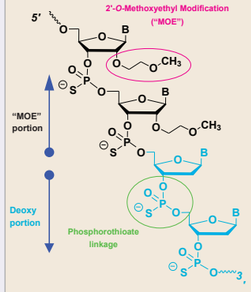
Identify Human Lead → Animal Safety Testing → First in Man – Phase 1 → Phase 2 & 3 Efficacy POC → Drug Marketing Approval

HOW THE ANTISENSE ADVANTAGE PROVIDES CONSISTENT & PREDICTABLE SAFETY PROFILES

The Antisense Advantage: Shared Chemical Structure

MOE | Deoxy | MOE

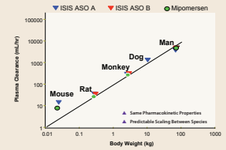
Chimeric structure enables RNase H mechanism



Same Chemistry – Different Genetic Addresses –

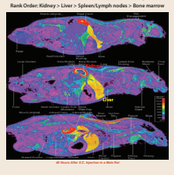
CONSISTENT CHEMISTRY LEADS TO CONSISTENT TISSUE DISTRIBUTION

Pharmacokinetics is Similar Across Sequence & Species



All Second Generation Drugs Have Similar Tissue Distribution = Shared & Predictable Safety Profile

Rank Order: Kidney > Liver > Spleen/Lymph nodes > Bone marrow



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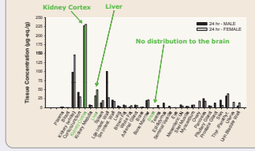


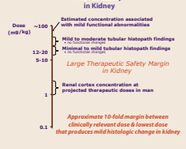
SAME TISSUE DISTRIBUTION PREDICTS SHARED SAFETY PROFILE

Extensive Animal Safety Experience

- ▲ Built on large first-generation experience foundation
- ▲ Second-generation experience proves common profile
  - ➤ 22 ASOs through 13-week toxicology studies in two species (IND-enabling)
  - ➤ Three ASOs through chronic toxicology studies (6 months to1 year) in two species
  - ➤ One ASO through lifetime toxicology in two species
  - ➤ Safety pharmacology, genotoxicology, reproductive toxicology, immunotoxicology all uniformly clean

ANIMAL EXPERIENCE LEADS TO CLINICAL EXPERIENCE

Proven Safety in Kidney



Proven Safety in Kidney: Monkey to Man

- ▲ **Renal effects in animal studies**
  - ➤ Kidney contains highest drug concentrations
    - Accumulation managed clinically by balancing dose & frequency
  - ➤ Histologic changes related to oligonucleotide concentration occur at doses 3 to 10-fold above clinical doses
    - No progression with chronic administration
  - ➤ Kidney concentrations predicted for clinical doses are below critical concentrations
- ▲ **Clinically, no effects for first- or second-generation antisense drugs on:**
  - ➤ Creatinine, BUN & albumin
  - ➤ Specific gravity, urine protein, phosphorus, bicarbonate & uric acid
  - ➤ No increased susceptibility due to pre-existing renal insufficiency, diabetes, age ≥ 65 years, hypertension, renal transplantation or cancer

Extensive Safety Experience: Animals To Man

- ▲ **Unique to Isis & antisense technology**
  - ➤ No other company has this kind of safety experience
  - ➤ Unprecedented among drug platforms

Predictive Safety Profile – Animals to Man

Effect in Animals	Mechanism	Effects in Man
Transient C_____-related aPTT increases	Inhibition of tenase complex	Transient, C_____-related prolongation, IV, not SC
Complement activation (in monkeys)	Inhibition of Factor H	No effects in man
Proinflammatory effects (in rodents, esp. mice)	Release of cytokines or chemokines via toll-like or other receptors in mice	Mild painless erythema at SC injection sites; constitutional symptoms at high doses
Renal tubular cell degeneration at high tox doses (monkey)	Concentration dependent in kidneys; mechanism not known	No renal effects in man

No Effects Observed in Clinical Studies

Animal Studies Predict Lack of Effects

- ▲ **No adverse effect in these organ systems**
  - ➤ Bone marrow
  - ➤ Skeletal muscle
  - ➤ CNS
  - ➤ Mitochondrial
  - ➤ Heart
  - ➤ Gastrointestinal
  - ➤ Lung
  - ➤ Not antigenic
- ▲ **No displacement of lipophilic drugs from plasma proteins**
- ▲ **No cytochrome P450 interactions**
- ▲ **No genotoxicity (altered genetics)**
- ▲ **No teratogenicity (birth defects)**
- ▲ **No carcinogenicity**

CLINICAL EXPERIENCE LEADS TO EXTENSIVE SAFETY EXPERIENCE

Clinical Safety Experience is Extensive – *Thousands of Patients Dosed*

- ▲ **Large first-generation experience foundation (8 Isis drugs, 3,800 antisense-treated subjects)**
- ▲ **Second-generation experience**
  - ➤ 20 antisense drugs to clinic
  - ➤ >2,800 subjects treated with antisense drugs
  - ➤ 79 clinical studies
  - ➤ 12 treatment populations (healthy, rheumatoid arthritis, diabetes, hypercholesterolemia, cancer, etc.)
  - ➤ IV/SC doses as high as 1,200 mg/wk (17 mg/kg/wk)
    - ~ 200 mg/wk is typical development dose for non-cancer indications – excellent therapeutic index
  - ➤ Growing treatment duration experience *
    - > 500 treated ≥ 12 weeks
    - > 280 treated ≥ 6 months
    - > 120 treated ≥ 1 year

*(*as of 13 April 2011)*

Antisense Drugs Well Tolerated in Diverse Patient Populations

- ▲ Hypercholesterolemia
- ▲ Type 2 Diabetes
- ▲ Rheumatoid Arthritis
- ▲ Multiple Sclerosis
- ▲ Asthma
- ▲ Macular Edema
- ▲ Cancer

Antisense Drugs Well Tolerated in a Number of Diverse Administration Routes

- ▲ IV/SC
- ▲ Intravitreal
- ▲ Intradermal
- ▲ Intrathecal
- ▲ Aerosol
- ▲ Enema
- ▲ Oral

SAFETY PLATFORM EXPERIENCE LEADS TO FILINGS

KIDNEY

No Antisense Treatment Effect on Kidney Function *(as measured by serum creatinine levels)* in Man

Pooled Clinical Creatinine Results For 5 IV/SC Administered Antisense Drugs Standard Treatment Dose: 200 mg/wk

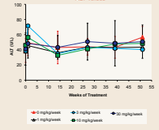
LIVER

Proven Safety in Liver No Class Effect in Primates: Monkey to Man

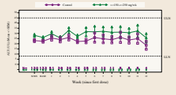
- ▲ **Preclinical**
  - ➤ Mild (2- to 3-fold) ALT & AST increases in mice that are secondary to pro-inflammatory effects (immune cell infiltrates in liver)
  - ➤ No first- or second-generation ASO class effect on ALT & AST in monkeys – predicts man
- ▲ **Clinical**
  - ➤ No first- or second-generation ASO class effect on liver enzymes (ALT or AST)
    - Elevations observed with some populations related to pharmacology
    - No antisense drug related hepatotoxicity

No Increase in Liver Enzymes in Chronic Monkey Study at High Doses

ALT Values



No Antisense Treatment Effect on ALT Levels in Man

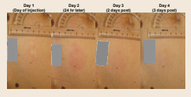


Pooled Clinical Experience From 4 Antisense Drugs Standard Treatment Dose: 200 mg/wk

ISR

Most Common Side Effect: Local Skin Responses at Subcutaneous Injection Sites

Typical Injection Site Reaction (ISR) is Transient Erythema (Redness) Only



150 mg injected into lower left abdomen on Day 1

- ▲ **Drugs injected by the subcutaneous route often exhibit localized ISRs**
  - ➤ Antisense drugs are no different, although less severe than those seen for protein/peptide biologics (e.g. Enbrel, Kineret)
- ▲ **Second-generation antisense drugs**
  - ➤ Typical doses: 100 - 200 mg/injection
  - ➤ Typical ISR is mild erythema (dose-dependent frequency, severity & duration)
  - ➤ Variable inter-injection & inter-subject occurrence
    - Approx. 40% of injections at 200 mg dose
    - Median duration 1 week
- ▲ **ISRs possibly due to mild local proinflammatory effect**
  - ➤ Systemic proinflammatory effects (constitutional symptoms) mainly limited to high dose iv infusion in cancer studies

Methods that Potentially Reduce the Incidence & Severity of Injection Site Reactions

- ▲ **Provide instruction on administration techniques**
  - ➤ Vary site of injection week to week
  - ➤ Method of injection
- ▲ **Include pre-treatment & post-treatment options**
  - ➤ Use of cold compress prior to or following treatment
  - ➤ Use of warm compress after treatment
  - ➤ Patient position during treatment
  - ➤ Application of topical steroids after treatment
- ▲ **Offer alternative dosing schedules**
  - ➤ More frequent doses with less drug/volume per treatment

ISR

SUMMARY

Successful Safety Submissions Worldwide

Antisense Drugs Show Consistently Good Safety & Tolerability in the Clinic

- ▲ Clinical safety established with multiple second-generation ASOs in several disease populations including type 2 diabetes, hypercholesterolemia, cancer & inflammatory disease
  - ➤ Class/chemistry effects predominate, therefore toxicity profile is generally predictable from sequence to sequence
- ▲ No clinically significant class effects observed on hepatic, renal or cardiac function
- ▲ Most common Adverse Events (AE) in clinical studies is transient, painless injection site erythema (not progressive, not associated with lymphadenopathy or any other systemic effects)
- ▲ Modest, but growing experience in patients with hepatic & renal impairment suggests no new classes of AEs
- ▲ Modest, but growing experience in longer-term treatment of patients (>6 months) suggests no new classes of AEs
- ▲ No evidence of drug-drug interactions
- ▲ Numerous additional potential safety issues excluded