International SAE Consortium, Ltd

An International Industrial Biomedical Consortium Researching the Genetic Basis of Drug Related Serious Adverse Events

Brookings / FDA event on Sentinel Initiative

January 11, 2009
SAEC’s Mission

“The SAEC will identify and validate DNA-variants useful in predicting the risk of drug induced serious adverse events.”
Current SAEC’s Membership [11]

Top 5 SAEs

Abbott Laboratories

EUDRAGENE

Roche

Spanish DILI

Pfizer

Columbia University

Novartis

College of Physicians and Surgeons of New York City

Takeda Pharmaceutical Company Limited

Sanofi Aventis

Spanish DILI

Welcome Trust

CERNER

Western Australia

Wyeth

Economic and Social Research Council

Ely Lilly

GATC

Diligen

United States Department of Veterans Affairs

HMO Research Network

University of Dundee

SANE Consortium

Duke
Key iSAEC Phase 1 Objectives

- Coordinate **international** network[s] for obtaining well phenotyped **cases** and **controls** for SAE PGx research *[SSR and DILI]*
- Using GWAS, explore cross drug/within drug DNA-variants useful in predicting the risk of SSR and DILI
- Create a **publicly available** “knowledge base” of cross drug safety PGx markers for predicting key SAEs
- Manage IP relating to PGx markers useful in predicting SAEs to ensure broad and open access
- Develop a **cross-disciplinary forums** to address clinical and scientific issues related to PGx of SAEs *[e.g. Phenotype Standardization Program]*
- Support the execution of the FDA Critical Path and related international safety PGx regulatory efforts
iSAEC Phase 1 Operational “Dividends”

**Phase 1 Execution**
- DACC development
- SJS characterization & analysis
- DILI network expansion
- DILI characterization & analysis
- Data release(s)
- Phase 2 planning

**Core Investments**
- SSR GWAS, Paper & DR1
- DILI GWAS, Papers (3) & DRs 2 & 3
- TdP GWAS, Paper (1) & DRs 4
- A-E GWAS, Paper (1) & DRs 6
- SAE Cohorts Members Pilots (3)
- DILI & Agranulocytosis Sequencing Pilots
- EMR SAE Case Sourcing Pilots (3)

09/07-6/10
SAEC Web Site

http://www.saeconsortium.org

Examples of severe adverse drug reactions

A number of severe adverse drug reactions are known. These include the conditions which are the initial focus of the Consortium’s efforts:

- **Serious Skin Reactions** (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) - rashes, blisters, severe, mucocutaneous blisters with disorders that are associated with over 200 medicines.
- **Drug Induced Liver Injury (DILI)** - Hepatotoxicity caused by more than 10 different drugs in more than seven different classes, including HAAD, various antibiotics, anticonvulsants, and antivirals.

Letter from the Chairman

November 2007

Dear Colleagues:

Welcome to the website of the International Serious Adverse Event Consortium [SAEC]. We’re delighted you chose to spend a few minutes with us.

We launched the SAEC in August of 2007, as an industrial biomedical consortium, focused on identifying and validating DNA-volants useful in predicting the risk of drug induced, rare serious adverse events [SAEs]. Drug-induced, rare SAEs can be a
"Pathways" to SAE Cases and Controls

**SAE Research → Discovery, Validation and Outcomes**

- **Academic Networks**
  - DILI → EUDRAGENE, DILIGEN, Spain, Scotland
  - SSR → Eudragene, SCAR, GATC, Pharmcos, etc
  - PQT/TDP → Roden, DARE, Montreal Heart
  - AHSR → European Network with MP

- **Pharmaco Safety Cohorts**
  - Global, Cross Industry
  - Key SAEs → Existing & New

- **IHS EMR based research**
  - VA
  - PSP Project
  - HMO Research Network
  - Kaiser
  - European Mkts [Scotland/Nordic/Finland]

- **LS EMR/CDW based research**
  - SAEC [Cerner] Feasibility Project
  - Cerner Patient Recruitment [1,500 → 4,000 hospitals]
  - EMR - CDW mining and enrollment [real time]

**Scalability & Breadth of Safety PGx Research**

SAE Consortium
Phase 1 SSR Discovery Project - June `09

Clinical Cohorts

- GSK Cohorts
  - 73 Cases
  - 140 Controls
- RegiSCAR
  - 400 Cases
- EUDRAGENE
  - 18 Cases

&

Small Collabs

- Japan NI HR
  - ~69
- Small Collabs
  - GATC
    - 19 Cases
  - Italy
    - 20 Cases

Global DACC

- Columbia University

Global SAEC GT Core

- EA, Inc.

- Discovery Cohort \( \rightarrow 81 \)
Phase 1 DILI Discovery Project - as of 06/09

Clinical Cohort Sourcing

- **Diligen**
  - 214 Cases
- **EUDRAGENE**
  - 105 Cases

&

- **Spanish DILI**
  - 53 Cases
- **Scotland**
  - 46 Cases

- **SAEC Members**
  - ~70 Cases
  - ~700 Controls

- **Global DACC**
  - Columbia University
- **Global SAEC GT Core**
  - EA, Inc.

WGGT to date
- Discovery Cases ➔ ~500
- Population Controls ➔ ~700
- WTCCC Controls ➔ ~4800

SAE Consortium
Pharmacos Sourced SAE Cohorts

- Agranulocytosis Pharmaco 1 Cohort
- DILI Pharmaco 5 Potential Cohorts
- PQI/TDP Pharmaco 1 Cohort
- SSR Pharmaco 1 Cohort
- Angio-Edema Pharmaco 1 Cohort
- Control Cohorts (2)
- AHSS Pharma Cohorts (TBD)

SAE Consortium
Sourcing SAE cases via Providers & EMRs
Phase 1 Feasibility Project

- 2009-10 Feasibility Projects
- Focus: Using EMR and associated research systems to determine the feasibility of yielding high quality SAE cases.
- SAE targets/3/collaboration [of joint interest]
  - Cerner → Hepatotoxicity, TdP/ PQT, and SSR
  - HMORN → Hepatotoxicity, EWG, and SSR
  - VA → Hepatotoxicity and Rhabdo/Myopathy
- Standardized phenotype translated into EMR data ontology - feasibility of (retrospective) case detection in CDW
- Determine how many potential cases and key clinical data gaps

EMR SAE Case Sourcing

- Cerner Health Facts [15.5 million pts.]
- HMORN 16 million pts.
- VA Health System [7 million pts.]

SAE Consortium
HMORN Sourced SAE Cohorts (Pilot)
SAE PSP Project Phase 1 - EMR ID of SAE Cases

- ADR research challenges → lack of phenotype standards and “coding” into EMR data ontologies
- PSP 1 Focus: Immunologic Related SAEs (SSR, DILI & AHHS) and TdP/PQT
- 2009-10 Project → Munir Pirmohamed, Chairman; Julian Arbuckle, Project Consultant
- EWG Steering Committee → Munir Pirmohamed (Liverpool), Ann Daly (Newcastle), Paul Watkins (UNC), Guru Aithal (Nottingham), Dan Roden (Nashville) & Dr. Elijah Behr (London)
- Organizing committee → Arthur Holden (SAEC), Michael Dunn (WT), Munir Pirmohamed (Clinical Chairman), and ShaAvhree Buckman (FDA)
- Expert Working Committees (3) → AHHS/SSR, DILI, and TdP/PQT
- Q4'09 - Member CRF inputs solicited; representative involvement in 2010 consensus conference
- Pooled funding → SAEC project management and working group meetings, WT 2010 consensus conference, and FDA scientific writing consultants for proceedings write-up

1. Draft phenotype definitions (staff)
2. Formation & EWGs initial meetings/drafts
3. PSP Consensus Conference (UK)
4. Scientific Write Up & Publication

Q3`09 Q4`09 Q1`10 Q3`10

SAE Consortia

FDA

Wellcome Trust
Key Points from SAEC’s Phase 1

1. Genomic technology and the scope of the SAEC’s collaborative networks are helping to enable basic genomic research on drug induced SAEs ... a significant public health and drug industry/FDA challenge ... faster and more efficiently.

2. Robust statistical inference is possible from relatively small SAE cohorts [e.g. DILI research] and larger, well constructed control cohorts

3. DNA variants may be useful in predicting and mitigating SAE risk for some drugs in some patients → certainly supportive of safety PGx studies as part of clinical development or post market surveillance studies

4. There are important genetic effects at root of many SAEs, but many of these effects will likely be drug and ethnicity specific, and vary in terms of their predictability and clinical utility

5. At the same time, we are finding genetic risk alleles [e.g. HLA B*5701] that predispose certain individuals to drug induced SAEs [e.g. SSR, Acute hypersensitivity reaction, or DILI] across multiple drugs.
SAEC Evolutionary Perspective

Phase 1
SAE Research Feasibility & PGx Infrastructure
- DILI GWAS
- SSR GWAS
- Other GWASs
- Limited Rx/ethnicities

- SAEC GWAS/Clinical Database I
  - Publications (~5)
  - IP filings (5 -- ~200+ markers)

2007-2009
SAEC Era

Phase 2
SAE Research Feasibility & PGx Infrastructure
- Immunologic based SAEs
- AHSS, DILI, & SSR
- Causal Drugs → Targeted & member recommended
- Technology → Web-based/EMR based ID & enrollment
- GWAS & Sequencing Pilot(s)

- SAEC GWAS/Clinical Database II
  - SAE Healthcare Partnerships
  - Publications (~TBD)
  - IP filings (10 -- ~300+ markers)

2010-2012

“LT Assets”
Enhanced Pharmaco SAE Research Partners, Data & Capabilities

SAE Research /PV Channels (HMORN, EMRs, SAE CRO?)

SAE Clinical /Genetic Database (Wellcome Trust)

ADR/SAE Academic Partners (Sanger, Columbia, Duke, etc.)

ADR/SAE IP Cache (~300+ SAE Markers)

2012+
Post SAEC

Enhanced Pharmaco SAE Research Partners, Data & Capabilities

SAE Consortium
EMR based drug safety PGx science

- “Standardization” of phenotype
- “Functional/ compatible” ontology/ies
- Drug and ethnic diversity
- High quality phenotyping \(\rightarrow\) real time
- Adequate case & control numbers (e.g. 50 cases X drug X ethnicity/3X control)
- Supporting genomics skills and infrastructure
- Committed partners, with “results orientation”
The SAEC Has Established an Ideal Collaborative Framework for SAE Research

- Global orientation to deal with ethnic diversity
- Driving standardized phenotyping across SAE/ADRs
- Strong research design skills via Scientific Management Committee
- Strong network development skills → adequate size cohorts & optimal controls [from academia, providers and companies]
- Strong genomics “core”
- Excellent Data Analysis & Coordinating Center [@ Columbia] with state-of-the-art analysis pipeline and public website for data release
- Efficient IP pipeline to ensure all discovered markers are placed unencumbered into the public domain
- Strong, focused management
- Strong integration → industry, academia, providers & regulators