

ILSI Health and Environmental Sciences Institute (HESI)

Proarrhythmia Models Project Committee

January 2009

Report at HESI Assembly of Members

Chair: Dr. Jean-Pierre Valentin, AstraZeneca
Vice-Chair: Dr. Elena Trepakova, Merck
Staff: Cyril Pettit



H E S I



Mission

MISSION:

To develop a better fundamental understanding of the emerging science, trends, and techniques associated with developing better predictors of drug-induced Torsades de Pointes (TdP).



Participants

Abbott Laboratories

Amgen, Inc.

AstraZeneca

Bayer Health Care

Boehringer-Ingelheim Pharmaceuticals, Inc.

Bristol-Myers Squibb

GlaxoSmithKline

Medivir AB

Merck and Company

Ohio State University

Novartis Pharmaceutical Corporation

Pfizer, Inc.

Procter & Gamble Pharmaceuticals

sanofi-aventis

Schering-Plough Research Institute

U.S. Food and Drug Administration

University of Wisconsin

Spanish Agency on Medicines and Healthcare Products



Stage One Goals

- Quantitative integrated risk assessment (i.e., concentration-response relationship) based on both non-clinical and clinical repolarization assays.
- Establish the sensitivity, specificity and overall predictivity



Stage One Status

- **Define Stage One Goals: *Complete***
- **Establish a database structure: *Complete***
 - Database fields jointly designed by committee/FDA
 - Database structure built and housed at FDA
- **Populate the database**
 - Data internal to FDA (from both HESI member companies and other) currently being uploaded to dbase. ***To be completed by summer '09***
 - Additional data from Phase 1 studies to be contributed by committee member companies – ***To occur during 2009.***
- **Perform data analysis**
 - **Formats for blinded data presentation developed by committee and under consideration by FDA. *Analysis to occur in late 2009.***
- **Publish results**



Proposed Stage Two Goal

- Understand the mechanistic basis for the lack of concordance between non-clinical and clinical repolarization assays for compounds identified in Stage I and determine whether viable non-clinical assays and/or clinical approaches can be put in place to detect them.
- Projected timelines – 2010 - 2011

Technical Publications from prior phase of work in print...

- **International Life Sciences Institute (Health and Environmental Sciences Institute, HESI) initiative on moving towards better predictors of drug-induced torsades de pointes.** A S Bass, B Darpo, A Breidenbach, K Bruse, H S Feldman, D Garnes, T Hammond, W Haverkamp, C January, J Koerner, C Lawrence, D Leishman, D Roden, J P Valentin, M A Vos, Y-Y Zhou, T Karluss and P Sager. *Br J Pharmacol* 154: 1491-1501; doi:10.1038/bjp.2008.279.
 - Publication from work of HESI ProArrhythmia Models Project Committee.
- **Moving towards better predictors of drug-induced torsades de pointes.** A S Bass, B Darpo, J-P Valentin, P Sager and K Thomas. *Br J Pharmacol* 154: 1550-1553; advance online publication, June 23, 2008; doi:10.1038/bjp.2008.215
 - Publication from work of HESI ProArrhythmia Models Project Committee.

Technical Committee on Cardiac Safety

Ramping up....



Cardiac Programs at HESI

- **July 2008:** HESI BOT authorizes formation of HESI **Technical Committee on Cardiac Safety**
 - ProArrhythmia Models Project
 - Cardiac Biomarkers Project

GOAL: Take advantage of common interests, expertise and resources and establish HESI as a center for cardiac programs.



Cardiac Programs at HESI

The Committee officially initiated Jan 1 2009.

- Corporate membership anticipated = 17 companies (some were members of only ProA, only BM, or neither)
- Members of TC may participate in any of the subprojects

IMPACT: Will allow for > engagement on current ProA and BM projects



Cardiac Programs at HESI

- **Some achievements Since July 2008....**
 - Steering Team of Senior Scientists Established
 - Dr. Norman Stockbridge, FDA (*Dir. FDA CardioRenal*)
 - Dr. Gonzalvo Calvo, Spanish Medicines Eval.
 - Dr. Eugene Herman, FDA
 - Dr. Malcolm York, GSK
 - Dr. Jean-Pierre Valentin, AZ
 - Dr. Kendall Wallace, U. Minnesota
 - Dr. Brian Berridge, GSK
 - Dr. Dana Walker, BMS
 - Dr. Mitch Krucoff, MD, Duke U. (liaison to CSRC)
 - Dr. Jon Finkle, MD, GSK (liaison to CSRC)
- Steering Team to help direct new, synergistic HESI programs in cardiac safety for 2009.



Cardiac Programs at HESI

- **Some achievements Since July 2008....**
 - Established partnership with Duke Cardiac Safety Consortium
 - Co-sponsored Cardiac Safety Think Tank Meeting (Bethesda, MD) October 2008, clinical and preclin attendees, senior regulatory FDA, pharma, academia. Joint manuscript in progress.



Cardiac Programs at HESI

- **Some achievements Since July 2008....**
 - January 14, 2009: First joint meeting of Cardiac BM team and ProA team as well as additional interested parties
 - New proposal for symposium and follow-up programs on evaluating functional and structural cardiotoxicity vettted;
 - Workshop anticipated in spring 2009
 - Strong multi-sector, clinical and preclinical interest.
 - Follow-up projects anticipated



Cardiac Programs at HESI

- **In sum:**
 - **Strong membership base established**
 - **Sound and growing scientific portfolio**
 - **Strong platform HESI to integrate both preclinical and clinical science**
 - **Good time to engage as new members!**