## 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

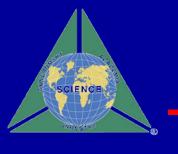
Staff: Syril Pettit

### Mission

H E S I.

#### MISSION:

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



### Participants

H E S I

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 druginduced 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....



- 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.



### 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



- 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.



- 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.



- 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



- 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!