



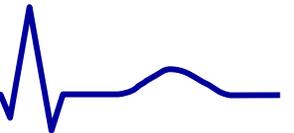
CSRC White Papers

An update – Oct. 2009

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Current Status

3 - published papers

7 - white papers in progress

3 - new initiatives in planning phase

All involving academia, industry and regulators

Published papers



Assessing proarrhythmic potential of drugs when optimal studies are infeasible.

Rock EP et al. Am Heart J. 2009;157(5):827-36

New precompetitive paradigms: focus on cardiac safety. EDITORIAL

Finkle J, et al. Am Heart J. 2009;157(5):825-6

Current challenges in the evaluation of cardiac safety during drug development: translational medicine meets the Critical Path Initiative.

Piccini JP et al. Am Heart J. 2009;158(3):317-26

White Papers in Progress

- Atrial Fibrillation Ablation Thinktank Proceedings Paper
- Evaluation of Ventricular Arrhythmias in Early Stage Development
- QT Evaluation of Biologics and Large Molecules
- Use of Cardiac Troponin Measurement During Drug Development
- Evaluation of Electrocardiographic Cardiac Safety in Drugs with Autonomic Effects
- Developing Drugs with Preclinical or Early Clinical Cardiovascular Safety Signals: Review of Marketed Compounds that had Signals for Cardiotoxicity
- Points to Consider for Thorough Blood Pressure Evaluations



Other initiatives planned

- PK/PD Analysis for QT Evaluation
 - Luana Koplowitz (lpk@dfpharma.com)
- Evaluation of Non-QT Electrocardiographic Safety e.g. Sinus Node, AV Conduction, QRS effects, etc
- Pediatric Cardiac Safety
 - Matt Killeen

White Papers in Progress

- **Working Title**
 - **Planning the Safety of Atrial Fibrillation Ablation Registry Initiative (SAFARI) As a Collaborative Pan-Stakeholder Critical Path Registry Model: A *Cardiac Safety Research Consortium ‘Incubator’ Think Tank***
- **Leader**
 - Sana M. Al-Khatib (alkha001@MC.DUKE.EDU)
- **Current Status**
 - Being finalized for submission to the AHJ
- **Expected publication date**
 - in 2-3 months
- **Key messages/objectives**
 - Consensus on the utility of such registry, benefits include:
 - Understand AF ablation clinical practices
 - Collect information on patterns, efficacy and safety of both the AF ablation procedure as well as drug use before and after AF ablation
 - Compare effects in ‘routine’ clinical settings to those observed in clinical trials
 - Hypotheses generation, and to inform sample size calculations for future randomized clinical trials.

White Papers in Progress

- **Working Title**
 - **Evaluation of Ventricular Arrhythmias in Early Clinical Pharmacology Trials and Potential Consequences for Later Development (working title)**
- **Leader**
 - Sherene Min (sherene.s.min@gsk.com)
- **Current Status**
 - Near final draft undergoing CSRC membership/regulatory review
- **Expected publication date**
 - 1st half 2010
- **Key messages/objectives**
 - Evaluation of ventricular arrhythmias documented in early clinical pharmacology trials, and their potential consequences for later clinical drug development.
 - Implications of intensive ECG monitoring in the detection of ventricular arrhythmias and clinical implications for drug development
 - Summary of the current thinking and consensus opinions for addressing this issues.

White Papers in Progress

- **Working Title**
 - ECG Assessment for Therapeutic Proteins
- **Leader**
 - Ignacio Rodriguez (ignacio.rodriguez.ir1@roche.com)
- **Current Status**
 - Finalized Draft – Webinar Nov 3rd
- **Expected publication date:**
 - 1Q 2010
- **Key messages/objectives**
 - Summary of reasonable approaches to evaluate QT effects in development programs of therapeutic proteins
 - Appropriate ECG monitoring is expected for all compounds in development, including therapeutic proteins
 - Recommendations for ECG monitoring in the different phases of development
 - Large targeted molecules (e.g. mAbs, fusion proteins), with no secondary effects on cardiac function, are usually not expected to have TQT studies

White Papers in Progress

- **Working Title**
 - Troponin Measurements during clinical trials - Points to consider for monitoring and management of potential cardiotoxicity.
- **Leaders**
 - Kristin Newby (newby001@dcric.duke.edu) and Rick Becker (richard.becker@duke.edu)
- **Current Status**
 - First draft completed
- **Expected publication date:**
 - 2Q 2010
- **Key messages/objectives**
 - Determine the role of troponin for assessing potential cardiotoxicity in all phases of drug development
 - Present practical approaches to use serum troponin as a biomarker for detecting potential cardiotoxicity in clinical studies. With recommendations on how to monitor cTn in clinical development, and how to interpret potential signals

White Papers in Progress

- **Working Title**
 - QT/QTc Evaluation for Drugs with Autonomic Effects
- **Leader**
 - Christine Garnett (Christine.Garnett@fda.hhs.gov)
- **Current Status**
 - First draft complete
- **Expected publication date**
 - 6/2010
- **Key messages/objectives**
 - Summary of reasonable approaches to evaluate the QT or QTc interval for therapies that have HR and/or autonomic effects.
 - Some methods include: individualized QT/RR correction, PK-PD modeling, Holter bin analysis, dynamic beat-to-beat analysis, and QT assessment during constant heart rate (i.e., pacing).
 - At present, there is not enough information to select one as the optimal method. Therefore, the group chose to describe methods that can improve this assessment and encourage further research in the area.

White Papers in Progress

- **Working Title**
 - **Developing Drugs with Preclinical or Early Clinical Cardiovascular Safety Signals: Review of Marketed Compounds that had Signals for Cardiotoxicity**
- **Leader**
 - Adel Nada (adel.nada@abbott.com)
- **Current Status**
 - Data collection, and draft status.
- **Expected publication date**
 - Within 12 months.
- **Key messages/objectives**
 - Describe how early non-clinical and clinical non-QT CV safety endpoints (such as AV block, valvulopathy, myocardial ischemia, and decreased ventricular contractility) impact marketed, or once marketed, compounds.
 - Describe relevant thresholds of regulatory concern as related to these endpoints.
 - Describe and recommend future directions relevant to the profiling and management of these endpoints.

White Papers in Progress

- **Working Title**
 - **Blood Pressure as a Cardiac Safety Endpoint – Evaluation and Design Framework**
- **Leader**
 - Jeff Heilbraun (jheilbraun@medifacts.com)
- **Current Status**
 - First draft
- **Expected publication date**
 - TBD
- **Key messages/objectives**
 - Provide background on regulatory interest - defining the reason as a cardiac safety consideration
 - Insight into BP methodologies
 - Therapeutic indications - examples & considerations
 - BP trial design and paradigm

Comments

- Time required to complete the paper
- Conflicts
- Goodwill
- Consensus
 - “good to have” but “no need to have”
- Present areas of controversy and areas where further research is needed
- No guidance documents or regulatory requirements
- Great forum for knowledge sharing!

Thank you

