Cardiovascular Safety in Drug Development: State-of-the-art Assessments

Tutorial: April 13, 2011
Conference: April 14-15, 2011

L'Enfant Plaza Hotel, Washington, DC, USA

PROGRAM CHAIRPERSON

Philip T. Sager, MD, FACC, FAHA
Pharmaceutical Consultant, USA
Chair, Scientific Oversight Committee
Cardiac Safety Research Consortium

SCIENTIFIC PROGRAM COMMITTEE

Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
Office of Drug Evaluation I, Office of New Drugs
CDER, FDA

Peter Kowey, MD, FACC
Chief of Cardiology, Main Line Health System
Professor of Medicine and Clinical Pharmacology
Jefferson Medical College

FEATURED FDA SPEAKERS

Robert J. Temple, MD, CDER
Douglas C. Throckmorton, MD, CDER
Christine E. Garnett, PharmD, CDER
Mary Ross Southworth, PharmD, CDER
Eillis Unger, MD, CDER
Monica L. Fiszman, MD, PhD, CDER
Lars Johannesen, MSc, CDER
Norman Stockbridge, MD, PhD, CDER
Joanne Zhang, PhD, MS, CDER

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Improve Your Safety Analysis During Drug Development and Analyze and Mitigate Potential Risks.

Participate in debate-style presentations and hear commentary and presentations from international industry, academic, and regulatory speakers to help you optimize your cardiovascular safety assessment.

FEATURED TOPICS

- QT issues in drug development
- New approaches to QT analysis
- Phase 3 development when there is a QT signal
- Post-marketing surveillance
- Ischemic events
- Bleeding, blood pressure
- In what situations outcomes studies are necessary

TUTORIAL

April 13, 2011, 1:30-5:00 PM

An Introduction to Clinical Assessment of QT Prolongation in Drug Development

Preregistration is required.

WHO SHOULD ATTEND

- Academic scientists
- Industry management
- Clinical project physicians
- Quality assurance directors
- Preclinical/discovery scientists
- ECG safety data managers
- ECG lab and equipment vendors
- Regulatory specialists
- Clinical project management
- Safety assessment personnel

Co-sponsored by

Cardiac Safety Research Consortium
Duke Clinical Research Institute (DCRI)

FDA

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CONTINUING EDUCATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and the Drug Information Association. PIM is accredited by the ACCME to provide continuing medical education for physicians.

PIM designates this educational activity for a maximum of 13 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Drug Information Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
This program is designated for 16.25 contact hours or 1.625 continuing education units (CEUs).
Type of Activity: Knowledge

Drug Information Association has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 8405 Greensboro Drive, Suite 800, McLean, VA 22102; (703) 506-3275.

Drug Information Association is authorized by IACET to offer 1.6 CEUs for this program.

Continuing Education Credit Allocation:

Tutorial: *An Introduction to Clinical Assessment of QT Prolongation in Drug Development:* 286-000-11-041-L04-P; 3.25 contact hours or .325 CEUs; .3 IACET CEUs

Conference: 13 *AMA PRA Category 1 Credits*™; 286-000-040-L04-P, 13 pharmacy contact hours or 1.3 CEUs; 1.3 IACET CEUs

If you would like to receive a statement of credit, you must attend the program and tutorial, if applicable, sign-in at the DIA registration desk each day of the program, and complete the on-line credit request process through My Transcript at www.diahome.org. Participants will be able to download a statement of credit upon successful submission of the credit request. My Transcript will be available for credit requests on April 29, 2011.

LEARNING OBJECTIVES

At the conclusion of this meeting, participants should be able to:

- Recognize the state-of-the-art approach to performing the thorough QT study, including novel trial designs and understand the potential uses of PK/PD Modeling
- Explain the different approaches to assessing the QT in Development Phase 3 when a QT signal has been identified in Phase 2
- Describe how to evaluate drugs for CV risk
- Define the Benefit:Risk considerations confronting regulators
- Identify major issues in assessing BP changes during drug development
- Recognize the potential safety issues associated with drug-induced BP changes
- Explain the major issues in clinical CV safety evaluation
- Describe new approaches to evaluating post-marketing safety assessment

Unless otherwise disclosed, DIA acknowledges that the statements made by speakers are their own opinion and not necessarily that of the organization they represent, or that of the Drug Information Association.
Speakers and agenda are subject to change without notice.
Recording of any DIA tutorial/workshop information in any type of media, is prohibited without prior written consent from DIA.

DAY 1 | WEDNESDAY, APRIL 13, 2011

8:00 AM-5:00 PM TUTORIAL AND MEETING REGISTRATION

1:30-5:00 PM TUTORIAL

An Introduction to Clinical Assessment of QT Prolongation in Drug Development

INSTRUCTOR

Borje Darpo, MD, PhD
Associate Professor of Cardiology
Pharmaceutical Consultant

This workshop serves as an introduction to the area of drug-induced QT prolongation and proarrhythmias. It is intended to provide participants with a background to the topic and is focused on how to clinically assess the 'QT liability' of drugs in development and which expectations regulatory authorities in different regions will have on development programs in this regard.

Learning Objectives

- Discuss the basis for proarrhythmias related to drug-induced prolonged cardiac repolarization
- Recognize basic concepts related to the collection, analysis and interpretation of clinical ECG data, taking into consideration the effect of study design and conduct on these parameters
- Design a program for QT assessment in early as well as late stage clinical trials
- Design, conduct, analyze and interpret data from a 'thorough QT/QTc study'
- Recognize the underlying regulatory thinking in terms of QT prolongation and patient safety
- Discuss emerging new concepts and technologies for QT assessment, such as highly automated measurement methods and concentration effect modeling and their potential role
- Explain the epidemiology of drug-induced proarrhythmias and the role of observational studies in assessing the risk for marketed products

DAY 2 | THURSDAY, APRIL 14, 2011

7:00-8:00 AM MEETING REGISTRATION AND CONTINENTAL BREAKFAST

8:00-8:10 AM WELCOME AND OPENING REMARKS

Philip T. Sager, MD, FACC, FAHA
Pharmaceutical Consultant, USA
Chair, Scientific Oversight Committee
Cardiac Safety Research Consortium

8:10-10:30 AM SESSION 1

CV Safety, Benefits, and Drug Development – What is the Right Balance?

SESSION CHAIRPERSON

Philip T. Sager, MD, FACC, FAHA
Pharmaceutical Consultant, USA
Chair, Scientific Oversight Committee
Cardiac Safety Research Consortium

Plenary Lecture: State-of-the-Art and Regulatory Directions (20 min)

Douglas C. Throckmorton, MD
Deputy Director, Regulatory Programs, Office of the Center Director, CDER, FDA

Is There an Issue at the Current Time Regarding Assessment of Benefit and Risk in Drug Development? (20 min)

Sanjay Kaul, MD, FACC, FAHA
Director, Cardiovascular Diseases Fellowship Training Program, Cedars-Sinai Heart Institute
Professor of Medicine, Cedars-Sinai Medical Center and Geffen School of Medicine at UCLA

Drug Safety and Benefit:Risk- Aligning Payer, Patient, and Clinician Perspectives (20 min)
Robert Giffin, PhD
Senior Research Director
Center for Medical Technology Policy

How Should We Determine Benefit:Risk and How Much Risk is Acceptable? (20 min)
Robert M. Califf, MD
Vice Chancellor for Clinical Research, Duke University Medical Center; Director, Duke Translational Medicine Institute

Panel Discussion: Has the "Benefit" Been Overly De-prioritized Over "Safety" in Determining the Benefit:Risk Ratio with Respect to Public Health? (60 min)
All speakers above and:
Anders Svensson, MD, PhD
Head of Global Clinical Development - Metabolism
F. Hoffmann-La Roche Ltd., Switzerland
Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
Office of Drug Evaluation I, Office of New Drugs, CDER, FDA

10:30-10:45 AM REFRESHMENT BREAK

10:45 AM-2:30 PM SESSION 2

Benefit:Risk Determinations - Approaches and Impact on Drug Development

Session Chairperson
Philip T. Sager, MD, FACC, FAHA
Pharmaceutical Consultant, USA
Chair, Scientific Oversight Committee
Cardiac Safety Research Consortium

Debate - Benefit:Risk Analysis – The Dabigatran Example (25 min)

Bach Nhi Beasley, PharmD
Clinical Reviewer
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I, Office of New Drugs
CDER, FDA
Peter Kowey, MD, FACC
Chief of Cardiology, Main Line Health System
Professor of Medicine and Clinical Pharmacology
Jefferson Medical College

Mathematical Approaches to Modeling Benefit:Risk (20 min)
John F.P. Bridges, PhD
Assistant Professor, Department of Health Policy & Management, John Hopkins Bloomberg School of Public Health

Is an Individual Signal Noise or a Public Health Issue? How Do We Decide? Which Sources Should We Be Most and Least Confident In? (15 min each)
Ralph C. Schimmer MD, PhD, MBA
Global Head Drug Safety Sciences - Metabolism and Cardiovascular
F. Hoffmann-La Roche Ltd., Switzerland
Mary Ross Southworth, PharmD
Deputy Director for Safety, Office of New Drugs
CDER, FDA

12:20-1:20 PM LUNCHEON

1:20-2:30 PM SESSION 2 (CONTINUED)

Session Chairperson
Peter Kowey, MD, FACC
Chief of Cardiology, Main Line Health System
Professor of Medicine and Clinical Pharmacology
Jefferson Medical College

Mini Symposium: Impact of Safety Issues on Early-stage Drug Development (8 min each)

Jeff Leiden, MD, PhD
Managing Director
Clarus Ventures
Orville G. Kolterman, MD
Senior Vice President, Medical Affairs
Amylin Pharmaceuticals, Inc.
Jonathan C. Fox, MD, PhD
Vice President, Clinical Therapeutic Area, Cardiovascular and Gastrointestinal Diseases
AstraZeneca Pharmaceuticals
Peter Kowey, MD, FACC
Chief of Cardiology, Main Line Health System
Professor of Medicine and Clinical Pharmacology
Jefferson Medical College
Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular & Renal Products
Office of Drug Evaluation I, Office of New Drugs, CDER, FDA

Panel Discussion (30 min)
All speakers above and:
Philip T. Sager, MD, FACC, FAHA

2:30-3:30 PM SESSION 3

Abstract Presentations

Session Chairperson
Peter Kowey, MD, FACC
Chief of Cardiology, Main Line Health System
Professor of Medicine and Clinical Pharmacology
Jefferson Medical College

Postural Changes As Positive Control For TQT Studies: Eliminating the Moxifloxacin Group (15 min)
Bill Wheeler, MD, FACC
Therapeutic Area Lead-Cardiovascular
Celerion, Inc.

Can Food Serve As a Non-pharmacological Control in Thorough Cardiac Safety Studies? (15 min)
Jorg Taubel MD, FFPM
Chief Executive Officer
Richmond Pharmacology Ltd.

QT Assessment When There is a Heart Rate Increase (15 min)
Arne Ring, PhD
Head of the Statistics and Modeling Group, Diabetes Trials Unit, University of Oxford

Validity of Heart Rate QT Corrections (15 min)
Marek Malik, MD, PhD
Professor of Cardiac Electrophysiology
St. Paul's Cardiac Electrophysiology

3:30-3:50 PM REFRESHMENT BREAK

3:50-5:50 PM SESSION 4

CV Safety - Blood Pressure

SESSION CHAIRPERSON

Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
Office of Drug Evaluation I, Office of New Drugs, CDER, FDA

How the QT Experience Can be Leveraged to Rationally Approach Other Safety Concerns (15 min)

Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
Office of Drug Evaluation I, Office of New Drugs
CDER, FDA

BP Assessment in Preclinical Studies and the Correlation to Clinical Trials - What is the Predictive Value (15 min)

Peter Hoffmann, MD, PhD and Haisong Ju
Novartis
Preclinical Safety
Translational Cardiovascular Advisory Team

Drug-Induced Changes in BP and Variability - What is the Scope of the Problem in Drug Development, Examples, and How Do We Model the Risk? (20 min)

Michael A. Weber, MD
Professor of Medicine
State University of New York

Debate: Is a "Thorough BP" Assessment Required for All Drugs or Only Those with Preclinical Signals? (10 min each)

CON Argument

David E. Gutstein, MD
Director, Clinical Pharmacology, Merck Research Laboratories
Chair, Merck Cardiovascular Safety Board
Clinical Associate Professor, New York University School of Medicine

PRO Argument

Domenic Sica, MD
Professor of Medicine
Medical College of VA

FDA Commentary

Ellis Unger, MD
Deputy Director, Office of Drug Evaluation I
Office of New Drugs
CDER, FDA

Panel Discussion: Do We Need to Do an Outcome Study if There is a BP Signal? (40 min)

All speakers above and:

Eric L. Michelson, MD
Senior Director Clinical Research
AstraZeneca

Ignacio Rodriguez, MD
Director, Drug Safety Risk Management
Hoffman- La Roche, Inc.

5:50 PM END OF DAY 1

6:00-7:00 PM NETWORKING RECEPTION

DAY 3 | FRIDAY, APRIL 15, 2011

7:00-8:00 AM MEETING REGISTRATION AND CONTINENTAL BREAKFAST

8:00-10:25 AM SESSION 5

QT Issues in Drug Development

SESSION CHAIRPERSON

Peter Kowey, MD, FACC
Chief of Cardiology, Main Line Health System
Professor of Medicine and Clinical Pharmacology
Jefferson Medical College

IRT Experiences – Novel Approaches and Identified Issues/ Learnings – What Are the Best Practices? (20 min)

Joanne Zhang, PhD, MS
Mathemetical Statistician, Office of Translational Sciences, OB, CDER, FDA

How to Develop a Drug During Phase 3 When There is a QT Signal (20 min)

Jay W. Mason, MD
Professor of Medicine, University of Utah
CMO, Spaulding Clinical Research

Labeling Implications and Practices When There is a QT Signal – What Goes into the Decision Making (15 min)

Monica L. Fiszman, MD, PhD
Clinical Reviewer
Office of New Drugs, Division of Cardiovascular and Renal Products
CDER, FDA

Update on the ICH Q&A Process - Issues Under Discussion (15 min)

Charles Benson, MD, PhD
Medical Fellow
Eli Lilly and Company

Statistical Approaches to Determining Assay Sensitivity Without an Active Control (20 min)

Lars Johannesen, MSc
ORISE Research fellow
Division of Pharmacometrics
Office of Clinical Pharmacology
CDER, FDA

Christine E. Garnett, PharmD
Pharmacometrics Reviewer, Office of Clinical Pharmacology
CDER, FDA

Mini Symposium: Characterizing the QT Effects in Early Phase Studies to Permit Replacement of the TQT Study: How Do We Achieve This Goal? (12 min each)

Assay Sensitivity and ECG Quality

Borje Darpo, MD, PhD
Associate Professor of Cardiology
Pharmaceutical Consultant

Concentration QTc Analysis of Phase 1 Data and Concordance With TQT Study

Timothy J. Carrothers, ScD
Senior Scientist
Pharsight Consulting Services

Regulatory Perspective

Christine E. Garnett, PharmD
Pharmacometrics Reviewer, Office of Clinical Pharmacology
CDER, FDA

Panel Discussion (30 min)

All speakers above

10:25-10:45 AM REFRESHMENT BREAK

10:45-11:30 AM SESSION 6

Abstract Presentations

Session Chairperson

Philip T. Sager, MD, FACC, FAHA
Pharmaceutical Consultant, USA
Chair, Scientific Oversight Committee
Cardiac Safety Research Consortium

T-Wave Morphology Abnormalities in Benign, Potent and Arrhythmogenic Ikr Inhibition (15 min)

Jean-Philippe Couderc, PhD
Associate Professor of Medicine/Electrical and Computer Engineering
Director of the Center for Quantitative Electrocardiography and Cardiac Safety
University of Rochester Medical Center Rochester

Talk given by Lars Johannesen, MSc

Computerized Extraction of Electrocardiograms from Continuous 12-Lead Holter Recordings Reduces Measurement Variability in a Thorough QT Study (15 min)

Samuel George, MD
Senior Medical Advisor
NewCardio, Inc.

Discriminating Changes in QT/QTc Interval Due to Moxifloxacin or Vardenafil Using Dynamic Beat-to-Beat Electrocardiogram Analyses (15 min)

Anthony Fossa, PhD
Vice President/Consultant, Cardiovascular Safety
iCardiac Technologies

11:30 AM-12:55 PM SESSION 7

CV Safety Data Evaluation, and Long-term Safety Assessment

Session Chairperson

Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
Office of Drug Evaluation I, Office of New Drugs, CDER, FDA

Plenary Lecture: The Future of CV Safety and Drug Development (apprx. 30 min)

Robert Temple, MD
Deputy Center Director for Clinical Science
CDER, FDA

Cardiac Safety Research Consortium - Impact and Ongoing Efforts to Impact Safety (20 min)

Mitchell W. Krucoff, MD, FACC
Professor of Medicine/Cardiology; Director, Cardiovascular Devices Unit; Director, eECG Core Lab
Duke University Medical Center/Duke Clinical Research Institute

Novel Approaches, Scientific Improvements, and Uses of Post-marketing Data (20 min)

Darren Toh, ScD
Department of Population Medicine
Harvard Medical School / Harvard Pilgrim Health Care Institute

12:55-1:00 PM CLOSING REMARKS

Philip T. Sager, MD, FACC, FAHA
Pharmaceutical Consultant, USA
Chair, Scientific Oversight Committee
Cardiac Safety Research Consortium

1:00 PM MEETING ADJOURNED

REGISTRATION FORM
Register online or fax this page to +1.215.442.6199

DIA is a financially independent nonprofit, global, multidisciplinary association that provides a neutral forum for sharing information that optimizes the development and lifecycle management of biopharmaceutical and related products.

Cardiovascular Safety in Drug Development: State-of-the-art Assessments

Event #11009

- **Tutorial: April 13, 2011**
- **Conference: April 14-15, 2011**

L'Enfant Plaza Hotel, Washington, DC, USA

Registration Fees

Registration fee includes refreshment breaks, luncheons, and reception (if applicable), and will be accepted by mail, fax, or online.

Industry Fee US $1005 ❑

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Tutorial April 13, 2011, 1:30-5:00 pm

An Introduction to Clinical Assessment of QT Prolongation in Drug Development US $405 ❑

PAYMENT OPTIONS:

Register online at www.diahome.org or check payment method.

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❑ **CHECK** drawn on a US bank payable to and mailed along with this form to: Drug Information Association Inc, P.O. Box 95000-1240, Philadelphia, PA 19195-1240, USA. Please include a copy of this registration form to facilitate identification of attendee.

❑ **BANK TRANSFER** When DIA completes your registration, an email will be sent to the address on the registration form with instructions on how to complete the Bank Transfer. Payment should be made in US dollars. Your name and company, as well as the Event I.D. # must be included on the transfer document to ensure payment to your account.

Participants with Disabilities: *DIA event facilities and overnight accommodations are accessible to persons with disabilities. Services will be made available to sensory-impaired persons attending the event if requested at least 15 days prior to event. Contact the DIA office to indicate your needs.*

TRAVEL AND HOTEL The most convenient airports are Reagan National or Washington Dulles International and attendees should make airline reservations as early as possible. The L'Enfant Plaza Hotel is holding a block of rooms at the reduced rate below until March 23, 2011, for the DIA event attendees. Room availability at this rate is guaranteed only until this date or until the block is filled.

Single $199 **Double $199**

Attendees must make their own hotel reservations. Contact the L'Enfant Plaza Hotel by telephone at +1.800.635.5065 or fax at +1.202.646.5060 and mention the DIA event. The hotel is located at 480 L'Enfant Plaza, SW, Washington, DC 20024, USA.

CANCELLATION POLICY: On or before APRIL 6, 2010
Administrative fee that will be withheld from refund amount:
Member or Nonmember = $200
Government or Academia or Nonprofit (Member or Nonmember) = $100
Tutorial (if applicable) = $50

Cancellations must be in writing and be received by the cancellation date above. Registrants who do not cancel by that date and do not attend will be responsible for the full registration fee paid. Registrants are responsible for cancelling their own hotel and airline reservations. You may transfer your registration to a colleague at any time but membership is not transferable. Please notify DIA of any such substitutions as soon as possible. Substitute registrants will be responsible for nonmember fee, if applicable.

DIA reserves the right to alter the venue, if necessary. If an event is cancelled, DIA is not responsible for any airfare, hotel or other costs incurred by registrants.

Participants with Disabilities: DIA event facilities and overnight accommodations are accessible to persons with disabilities. Services will be made available to sensory-impaired persons attending the event if requested at least 15 days prior to event. Contact the DIA office to indicate your needs.

EVENT INFORMATION

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Fax **+1.215.442.6199,** email **Benjamin.Zaitz@diahome.org**

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