IQ/CSRC Study Waveform Sharing Program

Presentation for CSRC members

August 26, 2015

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Brian Smith, iCardiac
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Background

- During the fall of 2013, it was agreed between the IQ-CSRC Steering Committee and the sponsor of the IQ/CSRC study (iCardiac) that ECG waveforms should be made accessible for algorithm testing
  - Will allow other ECG extraction and measurement techniques to be tested on the same waveforms;
  - Waveforms and clinical data in sufficient detail will be shared to allow blinded ECG measurements
  - Analysis will be performed by independent statistician
  - Publication will be encouraged; results should be shared with CSRC's SOC
- Proposal to share the waveforms has been endorsed by IQ-CSRC Steering Committee and the CSRC SOC and Executive Committee

IQ-CSRC Waveform Sharing Program

- The details of the program has been established and agreed upon by the sponsor (iCardiac), the CSRC ECG Data Warehouse Committee and the Telemetric and Holter ECG Warehouse (THEW)
- The program has been established to provide fair and transparent process, which within given limitations mimics standard procedures for ECG studies, e.g. thorough QT studies

- The purpose of today's call is describe the program and the process by which Requesting Core labs will gain access to the waveforms
  - Follow-up TCs can be held as needed with Requesting Core labs to provide further clarification

IQ-CSRC Waveform Sharing Program

Outline of today's phone conference

- Introduction, objective of the waveform sharing program
  - Borje Darpo
- Brief recap of IQ-CSRC study, design and results
  - Borje Darpo
- Statistical analyses
  - Georg Ferber
- THEW warehouse, storing of waveforms
  - Jean-Philippe Couderc
- CSRC ECG Warehouse committee, governance and analysis
  - Cindy Green
- Process for gaining access to waveforms and relevant study data
  - Brian Smith
- Summary
  - Borje Darpo
- Q&A

IQ-CSRC prospective study – Design

- 20 male and female healthy subjects
- 3 treatment periods
- 9 subjects were to receive each drug, 6 on placebo
- Study drugs:
  - ✓ 5 'QT-positive' drugs, well characterized from previous studies
  - ✓ 1 QT negative
  - ✓ Placebo
- Dosing on 2 days:
  - ✓ Day 1: Dose intended to give app. 10 to 12 ms QTc effect
  - ✓ Day 2: Dose intended to give app. 15 to 20 ms effect
  - ✓ 24-hour Holter with ECGs schedule:
    - Day 1: Predose (3 timepoints), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours
    - Day 2: 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours (i.e., 21 timepoints in total).
- Primary analysis: Based on exposure response analysis

Study treatments (1)

Drug	Dose Justification	
	Day 1	Day 2
ZOFRAN (ondansetron HCl)	**52 mg oral**** Dose has not been tested in TQT study. Anticipated effect is 10 to 12 ms. Expected Cmax: 281 ng/mL	**32 mg given by 15 min IV infusion** Based on TQT study results, mean ΔΔQTc= 19.5 ms
QUALAQUIN (quinine sulphate)	**648 mg oral**** In a PK study in HV (n=24) the mean change from baseline QTc at Tmax was 12 ms (from old Qualaquin label). The Cmax on day 1 is about 3.9 µg/mL with an expected increase in QTc of 12 ms based on the PK/PD model.	**648 mg q8h x 4** After the 4th dose (75% of Cmax), the anticipated concentration is 5.1 µg/mL and the anticipated QTc is 19 ms.
ANZEMET (dolasetron)	**100 mg PO**** Target Cmax for hydrodolasetron ~ 278 ng/mL.	**150 mg IV by 15 min infusion** Target Cmax ~ 440 ng/mL

**Dose suggested by FDA

Study treatments (2)

Drug	Dose Justification	
	Day 1	Day 2
Moxifloxacin	**400 mg po**** Mean ΔΔQTc = 10-14 ms Target Cmax ~ 2.95 µg/mL	**800 mg IV given by 60 min IV infusion** Mean ΔΔQTc = ~20 ms
Tikosyn (dofetilide)	**0.125 mg oral** ΔQTc = 10 to 11 ms Target Cmax ~ 0.7 ng/mL	**0.25 mg oral** ΔQTc = 20 ms
Xyzal (levocetirizine) (negative drug)	**5 mg** (therapeutic dose)	**30 mg** Supra-therapeutic dose evaluated in TQT study Target Cmax ~ 1.3 µg/mL
**Dose suggested by FDA		

Criteria for QT Assessment

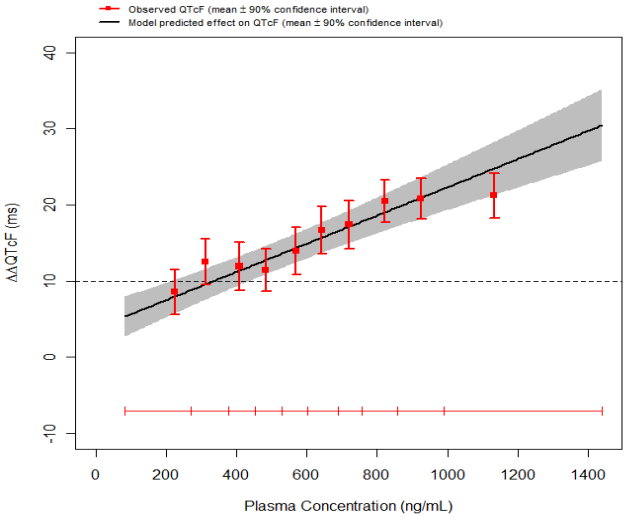
Positive QT assessment

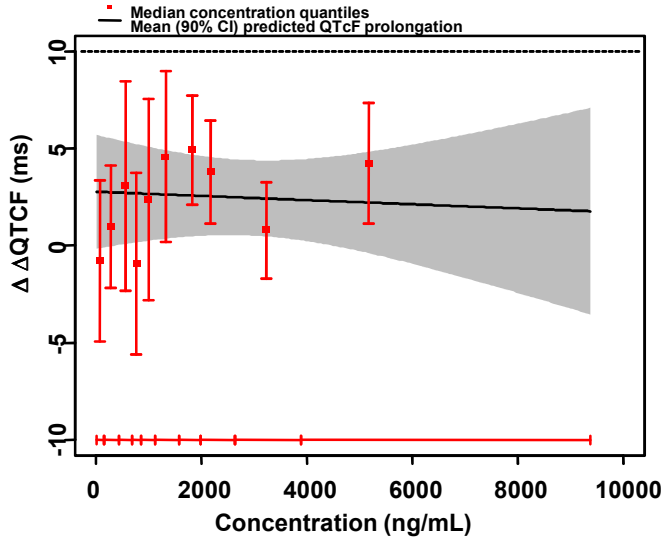
(for the positive drugs <u>in this study</u>):

1. ***The QT effect is detected:***
   The upper bound of the 2-sided 90% confidence interval (CI) of the projected placebo-corrected ΔQTcF is above 10 ms at the observed geometric mean C_{max} of the drug.
2. ***The slope of the ER relationship is statistically significant:***
   The lower bound of the 90% confidence interval for the slope of ΔΔQTcF vs. concentration is above zero.

Negative QT assessment *(to claim that a drug is negative, e.g. levocetirizine)*:

- The upper bound of the confidence interval of the predicted placebo-corrected ΔQTcF at the observed geometric mean C_{max} of the drug is below 10 ms.





Results, evaluable subjects

Number of evaluable subjects

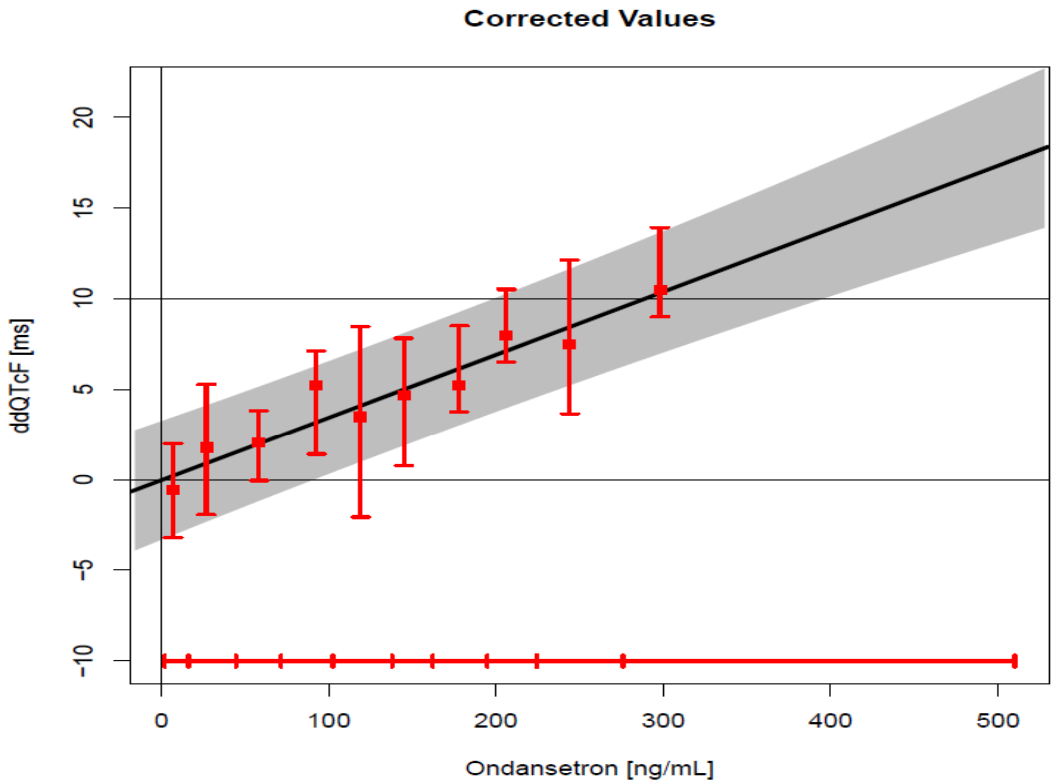
	Day 1	Day 2
Ondansetron	9	9
Quinine	8-9	6
Dolasetron	9	9
Moxifloxacin	9	9
Dofetilide	9	9
Levocetirizine	8	8
Placebo	6	6

Top Line Results

- All 5 positive drugs met the prespecified criteria , i.e. the study was able to demonstrate a drug-induced QT effect at the dose identified by FDA

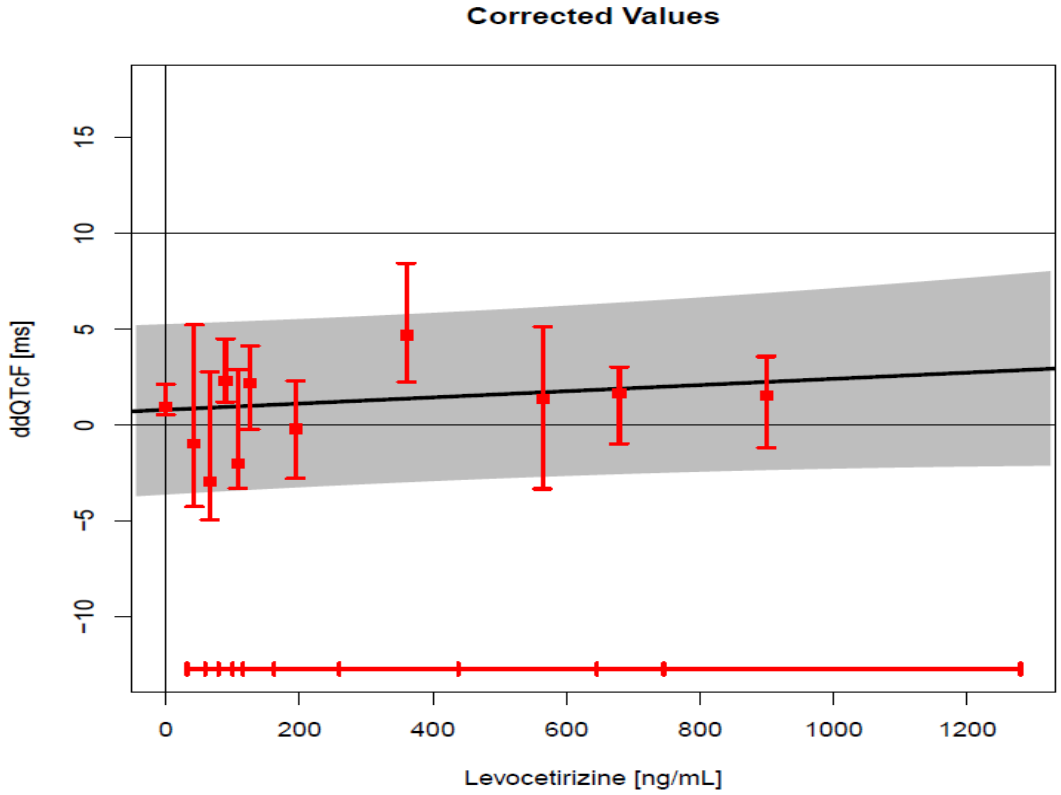
- The negative drug, levocetirizine, also met the criterion, i.e. a QT effect above 10 ms could be excluded

Ondansetron – Exposure response analysis



Slope, mean ms per ng/mL	LB 90% CI	UB 90% CI	Cmax Day 1, ng/mL	Projected QTc effect mean, ms	LB 90% CI	UB 90% CI	*Criteria*
0.035	***0.026****	0.043	284	9.8	6.5	***13.0****	Met

Levocetirizine – Exposure response analysis



Slope, mean ms per ng/mL	LB 90% CI	UB 90% CI	Treatment effect (intercept) ms	Cmax Day 2, ng/mL	Predicted QTc effect mean, ms	LB 90% CI	UB 90% CI	*Criterion*
0.0014	***-0.0013***	***0.0041***	0.7	1005	2.1	-2.3	***6.1****	Met

*: QTc effect above 10 ms can be excluded at the geometric mean Cmax on Day 2

Results – primary

Drug	Slope mean (ms per ng/mL)	LB 90% CI	UB 90% CI	Cmax Day 1, mean, (ng/mL)[#]	Predicted ΔΔQTc effect mean, (ms)	LB 90% CI	UB 90% CI
Positive drugs							
Ondansetron	0.033	***0.025***	0.042	284	9.7	6.2	***12.8***
Quinine	0.004	***0.0034***	0.0047	3623	11.6	6.8	***17.1***
Hydro-dolasetron	0.021	***0.013***	0.028	211	7.4	3.0	***11.0***
Moxifloxacin	0.0065	***0.0059***	0.0072	1862	14.5	10.5	***17.7***
Dofetilide*	22.2	***18.9***	25.6	0.42	10.5	6.3	***14.9***
Negative drug							
Levocetirizine	0.0014	***-0.0013***	***0.0041***	1005[#]	2.1	-2.3	***6.1***

CI: Confidence interval; the 90% CI for the predicted QT effect was calculated using a bias-corrected nonparametric bootstrap procedure, which includes variability of Cmax;
Cmax: Geometric mean peak plasma level; LB: Lower bound; UB: Upper bound;
[#]: Cmax on Day 2 for levocetirizine; ΔΔQTcF: Placebo adjusted change from baseline QTcF.
**: For comparative purposes, parameters and predictions for dofetilide derived from a linear model are shown.*
Using an Emax ER model, the predicted mean effect on ΔΔQTcF at Cmax (0.42 ng/mL) was similar: 11.6 ms (90% CI 7.0 to 16.0).

IQ-CSRC prospective study – Publications

1. Darpo B, Sarapa N, Garnett C, Benson C, Dota C, Ferber G, Jarugula V, Johannesen L, Keirns J, Krudys K, Ortemann-Renon C, Riley S, Rogers-Subramaniam D, Stockbridge N. The IQ-CSRC prospective clinical Phase 1 study: "Can early QT assessment using exposure response analysis replace the thorough QT study?". Ann Noninvasive Electrocardiol 2014; 19: 70-81.

2. Darpo B, Benson C, Dota C, Ferber G, Garnett C, Green CL, Jarugula V, Johannesen L, Keirns J, Krudys K, Liu J, Ortemann-Renon C, Riley S, Sarapa N, Smith B, Stoltz RR, Zhou M, Stockbridge N. Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. Clin Pharmacol Ther 2015; 97: 326-35.

3. Darpo B, Garnett C, Keirns J, Stockbridge N. Implications of the IQ-CSRC Prospective Study: Time to Revise ICH E14. Drug Safety 2015; Epub ahead of print; DOI: 10.1007/s40264-015-0325-5.

Sharing of the Waveforms

- Objective is to enable other methods for extraction of ECGs and interval measurements to be tested on the same dataset
- Waveforms are stored by THEW
- Procedure will follow standards for ECG analysis of e.g. TQT studies, i.e. the core labs will be blinded to treatment
- Statistical analysis will be performed by independent statistician (Cindy Green, DCRI)
- Process overseen by CSRC ECG Warehouse Committee

Sharing of the Waveforms – Statistical Analysis

The analysis will follow the primary analysis with some simplifications

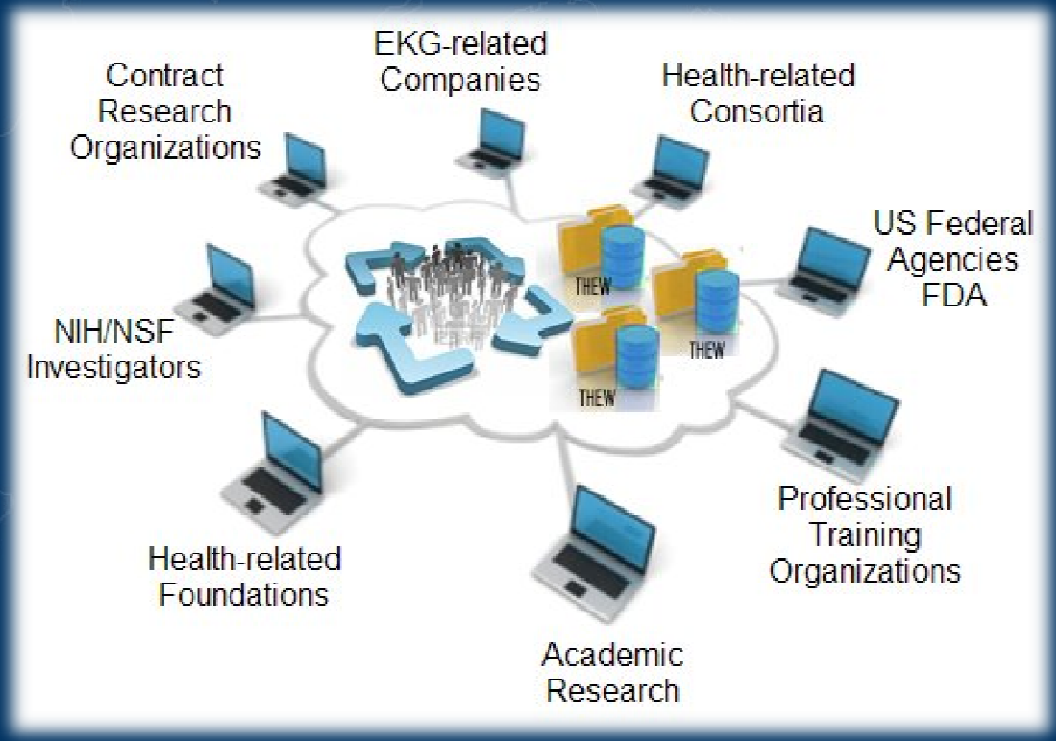
- The tests for appropriateness of the model will be dropped
- Only the linear analysis will be performed
- All timepoints will be used as separate factors (i.e. the concept of "reduced time" will be dropped.

- Robustness analyses
  - Day 1 only
  - Creating a parallel study by excluding active drug arm for subjects also on placebo.

Telemetric and Holter ECG Warehouse

www.THEW-project.org

The objective of the *Telemetric and Holter ECG Warehouse (THEW)* is to provide access to electrocardiographic data to for-profit and not-for-profit organizations for the design and validation of analytic methods and to advance the field of quantitative electrocardiography with a strong focus on cardiac safety.



Mission Statement

National Heart Lung and Blood Institute

TELEMETRIC and HOLTER ECG WAREHOUSE

www.THEW-project.org

U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

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Strategic Partnerships and Intellectual Property

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University of Rochester Telemetric and Holter ECG Warehouse (THEW)

Striving to advance the field of cardiac safety, the THEW initiative is developed under an agreement with FDA for facilitating collaborative discussions between THEW members, and for leveraging resources to implement joint projects among FDA, UR, and other public and private stakeholders. THEW is a publicly accessible data warehouse where scientists from academia, industry, and government can develop and test new computer algorithms related to quantitative electrocardiography. Designed to inform cardiac safety and medical product development, the THEW enables access to unique data and tools to develop automatic ECG analysis

DUA ID#_____

DATA USE AGREEMENT

1. This agreement is between the Telemetric and Holter ECG Warehouse managed by the University of Rochester (THEW), and [Name]_____, [Office]_____, [Center]_____ of the U.S. Food and Drug Administration (FDA) (each a Party or collectively the Parties). The Parties mutually agree to enter into this agreement and to comply with the following specific paragraphs.

2. This agreement addresses the conditions under which THEW will disclose and the FDA will obtain and use the data file(s) specified in section 5. The Parties agree further that any additional instructions or interpretations concerning this agreement or the data specified herein but not specified in this agreement shall not be valid unless issued in writing by the THEW signatory to this agreement shown in section 14.

FDA CORNER : NEW ECG Database

We are pleased to announce a new ECG database available to the THEW members. This new database of standard 12-lead ECGs and corresponding pharmacokinetic data from the U.S. Food and Drug Administration (FDA) sponsored study, "A Double-Blind, Randomized, Placebo-Controlled Single-Dose, Five Period Crossover Study of the Electrocardiographic Effects of Ranolazine, Dofetilide, Verapamil and Quinidine in Healthy Subjects." The FDA conducted this clinical trial to study

THEW and FDA

TELEMETRIC and HOLTER ECG WAREHOUSE

www.THEW-project.org

- The THEW has a fully-operational IT infrastructure for storing and distributing continuous ECG recordings from clinical studies in a secured environment.
- Currently, the THEW contains Holter ECG recordings which are distributed to public and private organizations under specific legal framework.

Database	SUI*	Leads	Sampling	ECGs	Ind.	Size	Unit
Acute Myocardial Infarction	E-HOL-03-0160-001	3	200 Hz	160	93	15.2	GB
Coronary Artery Disease	E-HOL-03-0271-002	3	200 Hz	271	271	26.2	GB
Healthy	E-HOL-03-0202-003	3	200 Hz	202	202	19.2	GB
Thorough QT study #1	E-HOL-03-0102-005	3	200 Hz	102	34	4.5	GB
Thorough QT study #2	E-HOL-12-0140-008	12	1,000 Hz	140	70	267	GB
Torsades de Pointes (TdPs)	E-OTH-12-0006-009	12	180 Hz	6	6	1.3	GB
Sotalol IV and History of TdPs	E-OTH-12-0068-010	12	1,000 Hz	68	34	244	MB
AF and cardioversion	E-OTH-12-0073-011	12	1,000 Hz	73	73	1.7	GB
Chest Pain (IMMEDIATE LR ECG)	E-HOL-12-1172-012	12	180 Hz	1172	1154	338	GB
Genotyped Long QT syndrome	E-HOL-03-0480-013	2 or 3	200 Hz	480	307	43.2	GB
Chest Pain (IMMEDIATE HR ECG)	E-HOL-12-0171-014	12	1,000 Hz	171	171	296	GB
Exercise testing and perfusion imaging	E-OTH-12-0927-015	12	1,000 Hz	927	927	23	GB
ESRD patients during and after hemodialysis	E-HOL-12-0051-016	12	1000 Hz	51	51	187	GB
FDA1-quinidine, verapamil, ranolazine, dofetilide	E-OTH-12-5232-020	12	1000 Hz	22	22	1.7	GB
Collaborative studies (require the submission of a research proposal to an ad-hoc THEW committee)							
DEFINITE Study (NorthWestern Univ.)	E-HOL-03-0401-017	3	500 Hz	401	236	110	GB
Occluded Artery Trial (Stony Brooke Univ.)	E-OTH-03-0802-018	3	500 Hz	802	223	6	GB
Quinidine (AZCERT)	E-OTH-12-2365-019	12	500 Hz	2423	24	17	MB
TOTALS						**3.17**	**TB**

AMI: Acute Myocardial Infarction Patients; CAD: Coronary Artery Patients; TdPs: torsades de pointes; Afib.: atrial fibrillation; LQTS:Long QT syndrome; Pts : patients.

- 3,150 Holter recordings
- 10K standard 12-lead ECGs
- Data from 3,800 individuals
- Single file format (ISHNE for ECG waveforms and annotation information)

THEW Content

TELEMETRIC and HOLTER ECG WAREHOUSE

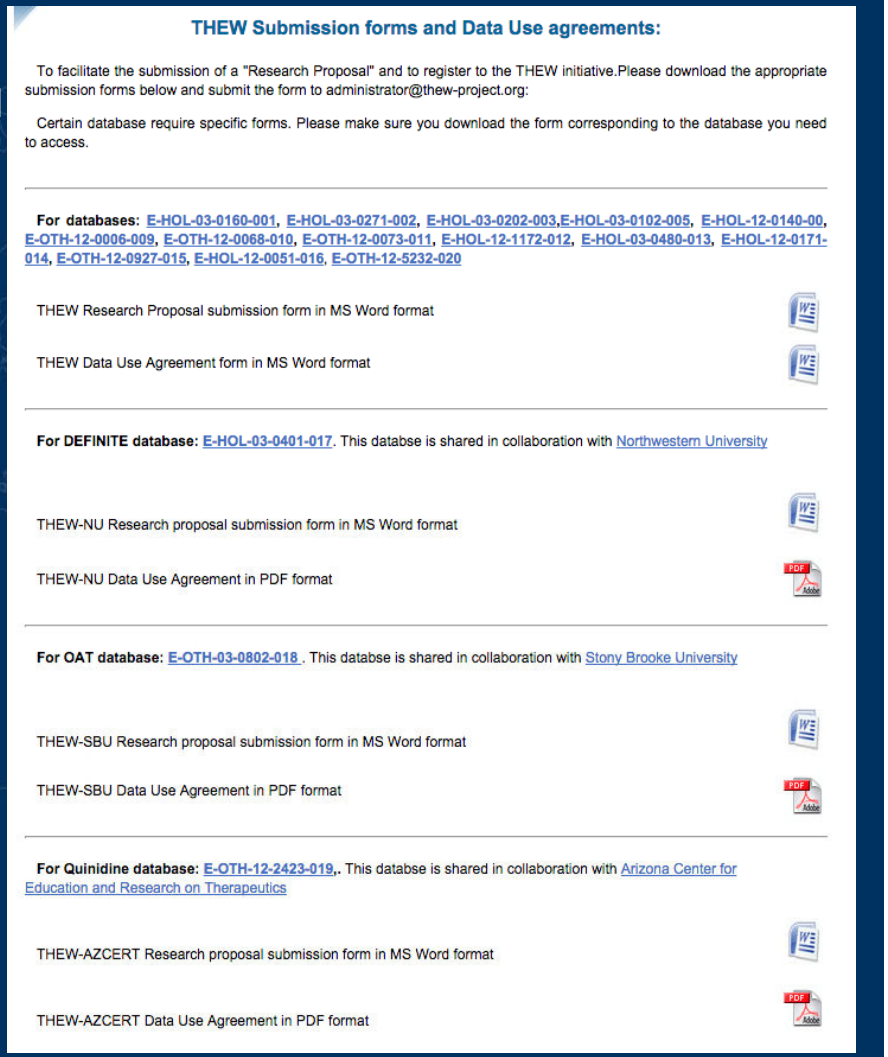
www.THEW-project.org

- The THEW database are shared and distributed based on specific Data Sharing Agreements (DSA) and Data Use Agreement (DUA).
- The type of sharing mechanism is selected by the data owner:

1- Open database
submission to the THEW Scientific Committee

2- Collaborative studies
submission to specific ad-hoc Committees

IQ-CSRC dataset
will be shared using this mechanism



THEW Submission forms and Data Use agreements:

To facilitate the submission of a "Research Proposal" and to register to the THEW initiative.Please download the appropriate submission forms below and submit the form to administrator@thew-project.org:

Certain database require specific forms. Please make sure you download the form corresponding to the database you need to access.

For databases: E-HOL-03-0160-001, E-HOL-03-0271-002, E-HOL-03-0202-003,E-HOL-03-0102-005, E-HOL-12-0140-00, E-OTH-12-0006-009, E-OTH-12-0068-010, E-OTH-12-0073-011, E-HOL-12-1172-012, E-HOL-03-0480-013, E-HOL-12-0171-014, E-OTH-12-0927-015, E-HOL-12-0051-016, E-OTH-12-5232-020

THEW Research Proposal submission form in MS Word format

THEW Data Use Agreement form in MS Word format

For DEFINITE database: E-HOL-03-0401-017. This databse is shared in collaboration with Northwestern University

THEW-NU Research proposal submission form in MS Word format

THEW-NU Data Use Agreement in PDF format

For OAT database: E-OTH-03-0802-018 . This databse is shared in collaboration with Stony Brooke University

THEW-SBU Research proposal submission form in MS Word format

THEW-SBU Data Use Agreement in PDF format

For Quinidine database: E-OTH-12-2423-019,. This databse is shared in collaboration with Arizona Center for Education and Research on Therapeutics

THEW-AZCERT Research proposal submission form in MS Word format

THEW-AZCERT Data Use Agreement in PDF format

THEW Data Sharing Mechanisms

CSRC ECG Data Warehouse

Objectives:

- Oversight
  - Provide established governance structure for data access
- Analysis
  - Provide blinded re-analysis for each vendor/core lab

Current CSRC ECG Data Warehouse

Under FDA's Critical Path Initiative:

Cardiac Safety Research Consortium (CSRC)
MOU Duke – FDA (2006)

ECG Warehouse
FDA–Mortara (2004)

- Access to Non-Drug and Moxifloxacin ECGs Released by Sponsor
- 19 TQT Studies Released to Date
- >500 Congenital Long QT ECGs
- Available for Research Projects Approved by SOC

Publications

- Kligfield P, Green C, et. al. The Cardiac Safety Research Consortium electrocardiogram warehouse: thorough QT database specifications and principles of use for algorithm development and testing. Am Heart J 2010 Dec;160(6):1023-28.
- Green CL, Kligfield P, et. al. Detection of QT prolongation using a novel electrocardiographic analysis algorithm applying intelligent automation: Prospective blinded evaluation using the Cardiac Safety Research Consortium electrocardiographic database. Am Heart J 2012 Mar;163(3):365-71.
- Kligfield P, Badilini F, et. al. Comparison of automated measurements of electrocardiographic intervals and durations by computer-based algorithms of digital electrocardiographs. Am Heart J 2014;167(2):150-59.

CSRC Governance Structure

- The Scientific Oversight Committee (SOC) evaluates proposals for CSRC ECG data use
  - Foster collaboration and fair access
  - Should be a trivial process for algorithm researchers
- Contact CSRC to receive a proposal form
  - cardiacsafety@dm.duke.edu
  - http://cardiac-safety.org/projects/
  - Available to answer any questions
  - CSRC will notify THEW of proposal approval

Data Analysis

- Measurements resulting from researcher's algorithm are sent to the CSRC ECG Warehouse statistician for assimilation and re-analysis
  - CSV format is suggested
- A statistical analysis is done in accordance with the approved re-analysis plan (SAP)
  - Based on the primary IQ-CSRC analysis plan
  - Results compared to original study results
- A nominal fee is charged to cover costs associated with the re-analysis of data
  - Payment should be received before results disclosed
- Publication or some type of dissemination of performance is encouraged

Statistical Output

- Tables provided for each re-analysis will include the following sorted by Drug and Time Point:
  - Primary ΔQTcF ER Model Results
  - ER Robustness Analysis (Day 1 only)
  - ER Robustness Analysis (Parallel Design)
  - ΔΔQTcF Linear Model Per Time Point Analysis
  - Quantitative Summary of ECG Intervals
  - Quantitative Summary of ECG Intervals CFB(Δ)
- Figures provided for each re-analysis will include the following for each Drug:
  - ΔΔQTcF and plasma concentration vs. time point
  - ER predicted effect of ΔΔQTcF vs. plasma concentration

Sharing of the Waveforms –Procedure

- All Participating Core Labs will be requested to:
  - Submit proposal to the CSRC Scientific Oversight Committee for participation in the program
  - Review and sign the Waveform Sharing Program Agreement
  - Review and sign the THEW Data Use Agreement
  - Make a payment to the THEW for $5000 for support and access to the waveforms
  - Make a payment to DCRI for $5000 for statistical review and reporting

Sharing of the Waveforms - Procedure

- All Core Labs that have completed all pre-requirements, will receive access to the following at agreed upon dates:
  - Raw ISHNE and Annotation Files from all enrolled subjects
    - Total of ~115 24-Hour Holter Recordings
  - Study Protocol
  - Relevant subject demographics and dosing time as it relates to the ISHNE data
  - Support from THEW for access to the data
  - Support from iCardiac's PM for any study related questions
  - A separate online meeting will be given to participating core labs to go over more in-depth operational details

Sharing of the Waveforms - Timelines

The following timelines will apply:

- Access to the data will be given on two (2) separate rounds at pre-defined dates within the next 3-6 months to participating Core Labs
  - Target date for 1st round: Early October
- Core Labs will have 6 weeks from receipt of data those dates to submit timepoint level data for all measurements (QT, QTcF, RR, PR and QRS) to DCRI for analysis
  - If results not submitted in 6 weeks, data will not be analyzed and Core Lab will not be allowed to participate in program.
- Results will be made available to the Core Lab and Waveform Governance Committee at a pre-defined date from DCRI.
- Results will not be released until all Core Labs have finished analysis.
  - Results from 1st round to be released after rollout of 2nd round

Sharing of Results

- All Requesting Core labs will receive their results on the same date
- Results will be shared with CSRC Scientific Oversight Committee
  - Requesting Core labs agree that results thereby will be regarded as publicly accessible
- A joint publication is proposed but participation will not be mandated
  - Participation from interested Requesting Core labs, CSRC ECG Warehouse committee, Dr Ferber, and iCardiac
  - Cindy Green will lead the publication effort

Thank you!

Questions?

Back-up Slides

Results – sensitivity analyses

Drug	Slope, mean (ms per ng/mL)	LB 90% CI	UB 90% CI	Cmax Day 1, (ng/mL)[#]	Predicted ΔΔQTc effect mean, (ms)	LB 90% CI	UB 90% CI
Ondansetron							
Day 1 only	0.032	***0.022***	0.043	284	9.5	7.2	***13.5***
Parallel design	0.042	***0.031***	0.052	259	10.2	6.8	***13.5***
Quinine							
Day 1 only	0.004	***0.0031***	0.0051	3623	9.8	6.7	***17.3***
Parallel design	0.0034	***0.0027***	0.0041	3643	9.5	4.8	***14.5***
Hydrodolasetron							
Day 1 only	0.016	***0.0008***	0.032	211	6.8	3.4	***11.6***
Parallel design	0.020	***0.012***	0.029	205	7.3	2.7	***11.5***
Moxifloxacin							
Day 1 only	0.0045	***0.0025***	0.0065	1862	11.7	10.6	***17.9***
Parallel design	0.0065	***0.0058***	0.0072	1708	13.3	9.6	***17.0***
Dofetilide*							
Day 1 only	28.7	***20.6***	36.7	0.42	11.3	6.1	***14.6***
Parallel design	25.0	***20.9***	29.0	0.40	8.9	5.1	***13.9***
Levocetirizine							
Day 2 only	0.00042	*-0.0032*	*0.0041*	1005[#]	2.0	-2.6	***6.0***