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
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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Justification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZOFRAN (ondansetron HCl)</strong></td>
<td><em>52 mg oral</em></td>
<td><em>32 mg given by 15 min IV infusion</em></td>
</tr>
<tr>
<td></td>
<td>Dose has not been tested in TQT study. Anticipated effect is 10 to 12 ms. Expected Cmax: 281 ng/mL</td>
<td>Based on TQT study results, mean ΔΔQTc= 19.5 ms</td>
</tr>
<tr>
<td><strong>QUALAQUIN (quinine sulphate)</strong></td>
<td><em>648 mg oral</em></td>
<td><em>648 mg q8h x 4</em></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td>After the 4th dose (75% of Cmax), the anticipated concentration is 5.1 µg/mL and the anticipated QTc is 19 ms.</td>
</tr>
<tr>
<td><strong>ANZEMET (dolasetron)</strong></td>
<td><em>100 mg PO</em></td>
<td><em>150 mg IV by 15 min infusion</em></td>
</tr>
<tr>
<td></td>
<td>Target Cmax for hydrodolasetron ~ 278 ng/mL.</td>
<td>Target Cmax ~ 440 ng/mL</td>
</tr>
</tbody>
</table>

**Dose suggested by FDA**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moxifloxacin</strong></td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>400 mg po**</td>
</tr>
<tr>
<td></td>
<td>Mean ΔΔQTc = 10-14 ms</td>
</tr>
<tr>
<td></td>
<td>Target Cmax ~ 2.95 µg/mL</td>
</tr>
<tr>
<td><strong>Tikosyn (dofetilide)</strong></td>
<td>0.125 mg oral</td>
</tr>
<tr>
<td></td>
<td>ΔQTc = 10 to 11 ms</td>
</tr>
<tr>
<td></td>
<td>Target Cmax ~ 0.7 ng/mL</td>
</tr>
<tr>
<td><strong>Xyzal (levocetirizine) (negative drug)</strong></td>
<td>5 mg (therapeutic dose)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose suggested by FDA</strong></td>
<td></td>
</tr>
</tbody>
</table>
**Criteria for QT Assessment**

**Positive QT assessment**
*(for the positive drugs in this study):*

1. **The QT effect is detected:**
   The upper bound of the 2-sided 90% confidence interval (CI) of the projected placebo-corrected ∆QTcF is above 10 ms at the observed geometric mean $C_{\text{max}}$ 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 ∆∆QTcF 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 ∆QTcF at the observed geometric mean $C_{\text{max}}$ of the drug is below 10 ms.
# Results, evaluable subjects

## Number of evaluable subjects

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Quinine</td>
<td>8-9</td>
<td>6</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
• 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

<table>
<thead>
<tr>
<th>Slope, mean ms per ng/mL</th>
<th>LB 90% CI</th>
<th>UB 90% CI</th>
<th>Cmax Day 1, ng/mL</th>
<th>Projected QTc effect mean, ms</th>
<th>LB 90% CI</th>
<th>UB 90% CI</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.035</td>
<td>0.026*</td>
<td>0.043</td>
<td>284</td>
<td>9.8</td>
<td>6.5</td>
<td>13.0**</td>
<td>Met</td>
</tr>
</tbody>
</table>
Levocetirizine – Exposure response analysis

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

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

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

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).


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.
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.
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.

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...
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.

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

Objectives:

- Oversight
  - Provide established governance structure for data access

- Analysis
  - Provide blinded re-analysis for each vendor/core lab
Under FDA’s Critical Path Initiative:

Cardiac Safety Research Consortium (CSRC)

ECG Warehouse

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


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
- 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 \( \Delta QTcF \) ER Model Results
  - ER Robustness Analysis (Day 1 only)
  - ER Robustness Analysis (Parallel Design)
  - \( \Delta \Delta QTcF \) Linear Model Per Time Point Analysis
  - Quantitative Summary of ECG Intervals
  - Quantitative Summary of ECG Intervals CFB(\( \Delta \))

- Figures provided for each re-analysis will include the following for each Drug:
  - \( \Delta \Delta QTcF \) and plasma concentration vs. time point
  - ER predicted effect of \( \Delta \Delta QTcF \) 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-requisites, 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 1\textsuperscript{st} 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 1\textsuperscript{st} round to be released after rollout of 2\textsuperscript{nd} 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

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