



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Date:

Re: Request for Permission to Release Data to the Cardiac Safety Research Consortium

To:

Dear Dr XXXX:

We write to ask for your support in a collaborative effort sponsored by the Cardiac Safety Research Consortium (CSRC), a Critical Path Initiative involving industry, regulatory authorities and academic leaders, to create and analyze a large set of anonymized digital ECG waveforms from human subjects exposed to both placebo and moxifloxacin in selected arms or crossover periods of 'thorough QT/QTc' or similarly designed studies. As detailed below and in Appendix A with this letter, these pooled waveform data sets will be used to constitute a "Cardiac Risk Reference ECG Library" to help develop better, less burdensome, public domain tools for the evaluation of cardiac safety in the development of new medical therapeutics.

As background, on 27 September 2006 the U.S. Food and Drug Administration (FDA) and Duke University (Duke) announced the formation of the CSRC, under the agency's Critical Path Initiative, as a public-private partnership whose focus is the provision of infrastructural support for improved cardiac safety evaluation in the development of new medical therapeutics. Functionally the CSRC is led by combined representation from industry, academics, and regulators, orchestrated through the Duke Clinical Research Institute (DCRI). A brief description of main objectives of this Memorandum of Understanding is attached in Appendix A. To further these objectives, it is the CSRC's intention, as has been presented and discussed in several public meetings, to leverage the collection of some two million digital ECGs in the common waveform XML format in the FDA's "ECG Warehouse" to create the Cardiac Risk Reference ECG Library and facilitate research with deliverables that can lower the burden but improve the quality of safety evaluation of new therapies.

The sources of the data we are requesting are studies that have been submitted to FDA and archived in the FDA's digital ECG Warehouse as a part of new drug evaluations. *We are not asking to include any data related to any of your investigational compounds.* Rather, we are asking you to grant the FDA permission to extract and anonymize only the placebo and moxifloxacin XML ECG waveform files and associated key descriptor variables (see Appendix B) from associated SAS datasets. This anonymized dataset will be provided to the CSRC by the FDA and stored in a password-restricted, secure, auditable environment managed by the DCRI and used only for CSRC-approved research purposes. The format of these anonymized data is detailed in the attached Appendix C. Details of CSRC structure, function and research activity can be found on the CSRC web site: www.cardiac-safety.org



Pooled, anonymized ECG data sets will be used primarily for the evaluation and testing of established ECG algorithms that address drug safety, in particular for the development of improved standards for normal ECG measurements as well as for the development of new algorithms for detection of moxifloxacin vs. placebo effects on the ECG waveform in human subjects, as detailed in Appendix A with this letter. All research applications will be reviewed and approved by the Scientific Oversight Committee (peer review process) of CSRC, per guidelines posted on CSRC's website.

Specific intellectual property related to the development of such new algorithms using the Cardiac Risk Reference ECG Library will be owned by the developers, who are employees of members of CSRC, and will not accrue to either the CSRC or companies donating waveforms to this public-private partnership. In all cases, however, results of CSRC sponsored research using the Cardiac Risk Reference ECG Library will be published or otherwise disseminated in the public domain.

There are three steps involved to engage your support in this Critical Path Initiative:

1. Contacting CSRC Project Lead Kelley Ryan at the DCRI (email: kelley.ryan@duke.edu; telephone 919-668-8681) to notify the CSRC that this effort as something your company would care to support through access to placebo and moxifloxacin data
2. Identifying a point person between your company and the CSRC/FDA for logistical purposes.
3. Sending a letter similar in format to Appendix D example letter to Dr. Norman Stockbridge at the Center for Drug Evaluation, specifying which individual studies in the ECG Warehouse have your company's permission to be included in the pooled Cardiac Risk Reference ECG Library.

It is in the collective interest of academia, industry and federal regulators to facilitate the development of new therapeutics with improved, less burdensome cardiac safety measures, an activity that serves the fundamental focus of the Critical Path Initiatives to improve public health. We sincerely hope you will grant the FDA permission to utilize your placebo and moxifloxacin data in the CSRC Cardiac Risk Reference ECG Library effort.



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If you have any questions about the above, about the CSRC or any related issues, please feel free to contact me directly at 919-286-6860 or email at kruco001@mc.duke.edu.

Sincerely,

Mitchell W. Krucoff, MD, FACC
Principal Investigator
Cardiac Safety Research Consortium
Duke Clinical Research Institute
Duke University Medical Center



APPENDIX A

Highlights of the Memorandum of Understanding between the FDA and Duke relating to the creation of the Cardiac Safety Research Consortium.

Under the Memorandum of Understanding between the FDA and Duke, the CSRC's initial areas of scientific activities will include, but will not be limited to, the following:

1. To compile an ECG waveform library from clinical trials that could be used for identifying early predictors of cardiac risk (Cardiac Risk Reference ECG Library);
2. To utilize the Cardiac Risk Reference ECG Library to evaluate new ECG biomarkers of cardiac risk;
3. To utilize the Cardiac Risk Reference ECG Library to advance ECG measurement tools and measurement standards relevant to current regulatory requirements for new therapy evaluation;
4. To facilitate implementation of such measurement tools and standards for clinical decision-making and medical product development in the interest of public health; and
5. To encourage the development of educational tools and public dissemination of these research results widely available to researchers, clinicians, industry, regulatory authorities and patients.



APPENDIX B

Anonymised Data Structure Details

This anonymized dataset will be used by the CSRC to perform research including testing ECG analysis algorithms and developing new biomarkers for risk assessment. Actual subject IDs will be stripped from the data as will true dates, sponsor identification, site, and core lab information. Unique identifiers (UIDs) will be assigned. The technology used to generate the UIDs will not allow the determination of how the UID was generated. Below is an example of selected variables in the SAS dataset.

subjid	regimen	baseline	hour	uid	gender	age
1	PLACEBO	B	2	E66220C2-E2F3-4B89-9142-B36029E74213	Female	46

The UID will provide a link to the annotated ECG waveform in the ECG warehouse. Once this dataset/library is created, we believe that it will be an important asset for the CSRC..



APPENDIX C

Data Specifications for analysis dataset from ECG Warehouse (Revised 19APR2007)

The data will be analyzed by study, using the QT and other intervals that were submitted by the sponsor, and also using the Veritas algorithm (an arbitrary automated algorithm and not necessarily a “gold standard”). If a sponsor submitted both manual and machine readings to the Warehouse for the same study, each will be analyzed separately.

Variables to include in the SAS datasets:

Study and Design Descriptions:

Study Identifier

- arbitrarily numbered (1, 2, ...)

Study Design

- Parallel
- Crossover
- Other (titration, etc.)

Population

- healthy volunteers
- patients – provide therapeutic area (the therapeutic area should be the same as the primary division that the IND/NDA is under for the study in question)

Dosing type

- oral
- intravenous
- intramuscular
- sublingual
- other

Dosing Regimen

- single dose
- multiple dose

Study Day

Actual Time of ECG

Nominal time of ECG post dose (pre-dose ECG is time 0)

Replicate number (see note below)

Scheduled or unscheduled ECG (see note below)

Treatment (baseline, placebo, moxifloxacin)

Period and sequence in a crossover study (see note below)

Definition of baseline (1=pre-dose, 2=time-matched)

Subject-specific Information: (all patient identifying information will be stripped with the exception of):

- Age



- Sex
- Race
- Ethnicity (as reported by sponsor)

ECG Information:

- ECG lab ID number (arbitrary, non-identifiable)
- Type of ECG acquisition device (standard resting 12-lead, 12-lead continuous)
- ECG, 12-lead Holter, etc., brand and model)
- ECG parameters
 - QT
 - VR (calculate from RR if not provided)
 - RR (calculate from VR if not provided)
 - QTcF
 - QTcB
 - QTcS (from Sagie *et al.*, in the Framingham study)
 - QTcH (Hodges' correction)
 - QTcI (individual correction by subject)
 - QTcP (population correction by study)
 - PR
 - QRS
- Individual changes from baseline in the above variables
- Method of Interval Measurement
- completely manual (each interval measured)
 - Lead used, if provided
- completely automated
 - name of software that performs interval measurements, if not produced by the recording device
- semi-automated or computer-assisted
 - name of software that performs interval measurements, if applicable



APPENDIX D

Sample letter to Dr. Norman Stockbridge at the Center for Drug Evaluation authorizing the transfer to CSRC.

Company letterhead

Date

Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
HFD-110
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Contribution of Data to Cardiac Safety Research Consortium
<Insert IND or NDA#, Study Identifiers>

Dear Dr. Stockbridge:

We are aware of the creation of a Critical Path Initiative by the U.S. Food and Drug Administration (FDA) and Duke University (Duke) in September 2006. FDA and Duke created a public-private partnership, the Cardiac Safety Research Consortium (CSRC), that focuses on research into cardiac safety of medical products and consists of industry, academics, and regulators.

We write to respond to a letter dated [INSERT DATE] from Dr. Krucoff on behalf of the CSRC requesting the extraction of certain of our company's datasets from the FDA ECG Warehouse (the XML files of the annotated ECG waveforms) and key variables from the associated SAS datasets (see Appendix A) for placebo and positive control arms of studies which our company has already submitted. Our understanding is that with our authorization for extraction of the data, these datasets will be anonymized by FDA and used by the CSRC to perform research, including testing ECG analysis algorithms and developing new biomarkers for risk assessment as outlined in Appendix B.

The purpose of this letter is to authorize FDA to extract [insert sponsor's name's] datasets as described above and to incorporate those anonymized datasets from our company's clinical trials into a CSRC database that will be used by CSRC as outlined in Appendix B. The specific studies we are releasing to CSRC are enumerated in an attachment to this letter.

Very truly yours,
<Insert name>