# Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs

## Guidance for Industry

Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

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# Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs

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## 1.0 Introduction

This document provides detailed information and specifications for the content of datasets that should be submitted as part of the sponsor's/applicant's application for drugs required to be assessed in clinical studies for their QT/QTc interval prolongation and proarrhythmic potential. These specifications also provide an opportunity for dialogue between the sponsor/applicant and reviewers to discuss issues with trial design or conduct that may affect the content of the analysis datasets. These specifications were built to support the recommendations provided in the International Council for Harmonisation (ICH) guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (ICH E14) and *Therapeutic Area Data Standards User Guide for QT Studies*[2] (TAUG-QT), and to support the data standards and processes described in the FDA *Study Data Technical Conformance Guide.*[3]

For questions regarding a specific submission, the sponsor/applicant should contact the applicable review division. For questions about a particular data standard implementation issue, contact cder-edata@fda.hhs.gov. For more general recommendations on the use and submission of standardized study data, refer to the *Study Data Technical Conformance Guide*.

[1] This technical specifications document has been prepared by the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2018-D-1216 (available at https://www.regulations.gov/docket?D=FDA-2018-D-1216) (see the instructions for submitting comments in the docket).

[2] https://www.cdisc.org/sites/default/files/members/standard/ta/qt-studies/taug-qtv10.pdf.

[3] https://www.fda.gov/media/88173/download.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended but not required.

This document provides detailed data specifications for the following datasets:

- **Analysis Dataset for Electrocardiogram Tests (ADEG).** This is a one record per subject per parameter per time point dataset that contains a comprehensive set of variables pertaining to the subject and their quantitative measures in the electrocardiogram (ECG) and ECG interpretation statements. This ADEG dataset is based on the Analysis Data Model (ADaM) Basic Data Structure (BDS) and designed to comply with the ADEG dataset described in the TAUG-QT. Additional variables and specific derivations from the standard TAUG-QT ADaM-compliant ADEG dataset are described in Table 1. The intent of the additional variables and specific derivations is to aid in FDA's review process.

- **Pharmacokinetic Concentrations Analysis Dataset (ADPC).** This is a one record per subject per pharmacokinetic (PK) parameter per time point dataset that contains a comprehensive set of variables pertaining to the subject and their quantitative PK measures. This dataset is designed to be a subset of an ADaM-compliant ADPC dataset that allows for concentration-ECG changes analysis (e.g., concentration-QT). Thus, while not all PK samples may have time-matched ECG data, the variables present in both ADEG and ADPC should be coded consistently to allow for proper mapping of time-matched PK and ECG rows. Although this is a subset of ADPC, it also includes additional variables and specific derivations. The additional variables and specific derivations from the standard ADaM-compliant ADPC dataset are described in Table 6. The intent of the additional variables and specific derivations is to aid in FDA's review process.

- **Subject Level Analysis Dataset (ADSL).** This is a one record per subject dataset that contains variables such as subject-level population flags, planned and actual treatments for each period, demographic information, stratification and subgrouping variables, important dates, and so forth. This dataset should be an ADaM-compliant ADSL as desribed in the *ADaM Implementation Guide* (ADaM IG)[4] and discussed in the *Study Data Technical Conformance Guide*.

[4] https://www.cdisc.org/system/files/members/standard/foundational/adam/ADaMIG_v1.1.pdf.

These three datasets should be accompanied by informative metadata in the form of a compliant Define.xml document that describes the source and derivation of the variables.

## 2.0 Overview of the Dataset Specifications

Each section below provides a specification that describes the desired content of the dataset. The variable names and associated metadata are based on current Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM)[5] and ADaM[6] standards where possible. Each specification includes a column that contains information about the variables, such as the expected content, derivation considerations, or assumptions. If any variable is unclear, sponsors/applicants are encouraged to discuss expectations with FDA's QT Interdisciplinary Review Team (IRT) via the applicable review division.

Some variables may not be appropriate for all clinical trials. If a sponsor's/applicant's trial did not collect the data necessary to create a specified variable, then it is acceptable to omit the variable in the datasets. Variables that have been omitted or added should be documented in the Define.xml file and itemized in the Analysis Data Reviewer Guide (ADRG) as a separate table. Sponsors/applicants should also submit programs that were used to create these datasets (see the *Study Data Technical Conformance Guide*).

Consistency in controlled terminology across SDTM and ADaM as well as across ADaM datasets is important to facilitate traceability and support analyses. Using standard controlled terminology (CT) is preferred where applicable (e.g., Medical Dictionary for Regulatory Activities (MedDRA), CDISC-controlled terminology). For variables without standard CT, where appropriate and to the degree possible, sponsor-/applicant-defined controlled terminology should also be consistent across SDTM and ADaM datasets.

Sometimes the ability to efficiently analyze or trace data depends on the use of consistent CT across datasets. For this reason, the specifications identify explicitly certain parameters and variables where consistent controlled terminology across datasets is expected. For example, to support analyses, the sponsor-/applicant-defined controlled terminology for variables such as AVISIT, ATPT, TRTN, and others should be consistent across ADEG and ADPC or, to support traceability between SDTM and ADaM, the value of PARAM in ADEG should be equivalent to the value of the corresponding EGTEST for parameters that are not derived. In all cases, the variable labels and the variable type noted in the specifications should be used.

[5] https://www.cdisc.org/standards/foundational/sdtm.

[6] https://www.cdisc.org/standards/foundational/adam.

## 3.0 Dataset Specifications for Analysis Dataset for Electrocardiogram Tests – ADEG

This dataset is a one record per subject per parameter per analysis period per analysis visit per analysis time point dataset that contains a comprehensive set of variables pertaining to the subject and those variables quantitative measures in the ECG and ECG interpretations. Ideally, all of these variables should be traceable to the submitted tabulations or analysis datasets. Whereas the formation of this dataset duplicates information found in other submitted datasets, the compilation of these variable concepts into one record facilitates FDA's statistical and medical reviews.

If the ADEG dataset includes heart rate corrected QT (QTc) values obtained with a formula and coefficients derived by the sponsor/applicant or vendor (i.e., QTc values not created from commonly used historical heart rate correction models such as Fridericia's QT correction), the sponsor/applicant should include the heart rate correction-related information in an Analysis Dataset for ECG QTc Model Data (ADQT) as specified in the TAUG-QT. Such ADQT datasets should also be documented in the Define.xml file.

**Table 1: Analysis Variable Metadata for ADEG**

| Variable Name | Variable Label | Type | Code List / Controlled Term | Comments |
|---|---|---|---|---|
| STUDYID | Study Identifier | Char | | |
| USUBJID | Unique Subject Identifier | Char | | |
| TRTSEQP | Planned Sequence of Treatments | Char | | |
| TRTP | Planned Treatment | Char | | |
| TRTPN | Planned Treatment (N) | Num | | The numeric code for TRTP. One-to-one mapping within ADEG to TRTP. The mapping should be the same in ADEG and ADPC. |
| TRTSEQA | Actual Sequence of Treatments | Char | | |
| TRTA | Actual Treatment | Char | | |
| TRTAN | Actual Treatment (N) | Num | | The numeric code for TRTA. One-to-one mapping within ADEG to TRTA. The mapping should be the same in ADEG and ADPC. |
| PARAM | Parameter | Char | EGTEST | For records with a corresponding record in ECG test results (EG) dataset (e.g., for QTcF, "QTcF Interval "). |
| PARAMCD | Parameter Code | Char | | Parameter code with a maximum length of 4 characters. One-to-one correspondence with PARAM. For records with a corresponding record in EG, PARAMCD should be EG.EGTESTCD abbreviated up to 4 characters long. |
| APERIOD | Period | Num | | Populate based on EG.VISITNUM. Note there can be 1 or more visits per period. ADEG.APERIOD and ADPC.APERIOD should be coded consistently so mapping of time-matched measures can be performed. |
| APERIODC | Period (C) | Char | | Character version of APERIOD. One-to-one correspondence with APERIOD. |
| AVISIT | Analysis Visit | Char | | Populate based on EG.VISIT. |
| AVISITN | Analysis Visit (N) | Num | | Numeric version of AVISIT. Since study visits are usually defined by certain time points, defining AVISITN so that it represents the time point associated with the visit can facilitate plotting and interpretation of the values. Alternatively, AVISITN may be a protocol visit number, a cycle number, an analysis visit number, or any other number logically related to AVISIT or useful for sorting that is needed for analysis (see ADaM IG). |
| ATPT | Analysis Time Point | Char | | Populate based on EG.EGTPT. EG.EGTPT and PC.PCTPT should be coded in ADEG.ATPT and ADPC.ATPT in a consistent fashion. |

| Variable Name | Variable Label | Type | Code List / Controlled Term | Comments |
|---|---|---|---|---|
| ATPTN | Analysis Time Point (N) | Num | | ATPTN provides a numeric representation of ATPT. Defining ATPTN so that its values represent the planned time points in a consistent unit (e.g., minutes or hours after dosing) is not required but can facilitate plotting and interpretation of the values. Within the same parameter, there is a one-to-one mapping between ATPT and ATPTN (see ADaM IG). As for ATPT, the coding of ATPTN should be the same for ADEG.ATPTN and ADPC.ATPTN. |
| ATPTREF | Analysis Reference Time Point | Char | | Populate based on EG.EGTPTREF. Description of the fixed reference point referred to by ATPT/ATPTN (e.g., time of dose). For example, "Morning Dose" could be the reference point used. As for ATPT, the coding of ATPTREF should be the same for ADEG and ADPC. |
| ARDTM | Date/Time of Reference | Num | | Date and time of reference. ARDTM provides a date and time representation of ATPTREF. As for ATPTREF, ARDTM should be the same for ADEG and ADPC. Please see Table 2 below as well as the Appendix for examples. |
| AARDTM | Actual Date/Time of Reference | Num | | Actual date and time of reference of ARDTM. |
| ARRLT | Actual Relative Time from Reference TPT | Num | | This is the actual elapsed time (for sample point or start of sampling interval) from reference date and time (ADTM - ARDTM). |
| NRRLT | Nominal Relative Time from Ref TPT | Num | | This is the planned elapsed time (for sample point or start of sampling interval) from reference date and time (ARDTM). |
| RRLTU | Relative Time from Reference TPT Units | Char | UNIT | Units for all elapsed time variables (i.e., *RRLT) from reference time point (ATPTREF). |
| ADTM | Analysis Date and Time | Num | | Populate from EG.EGDTC. |
| ADT | Analysis Date | Num | | Numeric date value from EG.EGDTC. |
| ATM | Analysis Time | Num | | Numeric time value from EG.EGDTC. |
| ADY | Analysis Relative Day | Num | | Populate based on EG.EGDY. |
| AVISDY | Analysis Visit Day | Num | | |
| APERDAY | Analysis Nominal Period Day | Num | | Populate with the numeric relative day within the Period based on AVISITN. For example, "Period 2 Day 1" is APERDAY=1. ADEG.APERDAY and ADPC.APERDAY should be coded consistently so mapping of time-matched measures can be performed. |
| EGREPNUM | ECG Replicate Number | Num | | Populate with EG.REPNUM for non-derived records. Number of ECG replicates within time point. |

| Variable Name | Variable Label | Type | Code List / Controlled Term | Comments |
|---|---|---|---|---|
| AVAL | Analysis Value | Num | | Populate with EG.EGSTRESN for non-derived records. Also create derived records for the average of the individual replicate values for ECG measurements collected at each nominal time point (e.g., average of triplicates). |
| AVALC | Analysis Value (C) | Char | | Populate with EG.EGSTRESC. |
| AVALU | Units of Analysis Value | Char | UNIT | Populate with EG.EGSTRESU. |
| DTYPE | Derivation Type | Char | DTYPE | Type of derivation (e.g., DTYPE="AVERAGE" for records containing the average of the replicate values for each time point). |
| ABLFL | Baseline Record Flag | Char | Y | Character indicator to identify the baseline record for each subject, parameter, and baseline type (BASETYPE) combination. |
| AEGBLFL | Flag for Records used to Derive the Baseline | Char | Y | If record was used to derive the baseline, then AEGBLFL="Y" else AEGBLFL is null. |
| BASE | Baseline Value | Num | | The subject's baseline analysis value for a parameter and baseline definition (i.e. BASETYPE). BASE contains the value of AVAL copied from a record within the parameter on which ABLFL eq "Y" and same BASETYPE. Note that a baseline record may be derived (e.g., it may be an average) in which case DTYPE should be populated on the baseline record. |
| CHG | Change from Baseline | Num | | If ABLFL ne "Y" and DTYPE eq "AVERAGE" then CHG=AVAL – BASE. |
| BASETYPE | Baseline Type | Char | | Encodes the key that allows for identifying baseline rows that correspond to each DTYPE eq "AVERAGE" and ABLFL ne "Y". |
| ACOMPFL | Comparator Record Flag | Char | Y | If record is part of the comparator treatment (e.g., placebo) then ACOMPFL="Y" else ACOMPFL is null. |
| COMP | Comparator Value | Num | | If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMP=AVAL; else COMP value is based on the corresponding COMPTYPE (see BASETYPE). |
| COMPBASE | Baseline Value of the Comparator | Num | | If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMPBASE=BASE else COMPBASE value is based on the corresponding COMPTYPE. |
| COMPCHG | Change from Baseline in the Comparator | Num | | If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMPCHG=CHG else COMPCHG value is based on the corresponding COMPTYPE. |
| CCOMPCHG | Comparator corrected change from BL | Num | | If DTYPE ne "AVERAGE" then null else if ACOMPFL ne "Y" then CCOMPCHG=CHG – COMPCHG else null. |
| COMPTYPE | Comparator Type | Char | | Encodes the key that allows for identifying comparator treatment (e.g., placebo) rows used to compute the comparator and baseline corrected changes (i.e., double deltas) from |

| Variable Name | Variable Label | Type | Code List / Controlled Term | Comments |
|---|---|---|---|---|
| | | | | each DTYPE eq ”AVERAGE” and ACOMPFL ne “Y”. This is similar to BASETYPE above. |
| ECGPCFL | ECG Matching PK Flag | Char | | Populate with “Y” if there is a matching nominal PK sample time point for the nominal ECG time point (i.e., if there are time-matched PK measures in ADPC for this ECG). |
| EGSEQ | Sequence Number | Num | | Populate with EG.EGSEQ. Missing for derived records. |
| EGLEAD | Lead Location Used for Measurement | Char | EGLEAD | Populate with EG.EGLEAD. |
| EGREFID | ECG Reference ID | Char | | Populate with EG.EGREFID. Missing for derived records. |
| CRITy | Analysis Criterion y | Char | | A text string identifying a pre-specified criterion within a parameter, for example QTcF ≥ 500. Required if CRITyFL exists (see ADaM IG). |
| CRITyFL | Criterion y Evaluation Result Flag | Char | Y | Character flag variable indicating whether the criterion defined in CRITy was met by the data on record. See CRITy for more information regarding how to use CRITy and CRITyFL to indicate whether a criterion is met (see ADaM IG). |
| IUTANLFL | Intersection Union Test Analysis Flag | Char | Y | Character flag variable set to “Y” if the record is used in the intersection union test (i.e., by-time) analysis or null otherwise. |
| CATANLFL | Categorical Analysis Flag | Char | Y | Character flag variable set to “Y” if the record is used in the categorical analysis or null otherwise. |
| CQTANLFL | Concentration QT Analysis Flag | Char | Y | Character flag variable set to “Y” if the record is used in the concentration-QT analysis or null otherwise. |
| ANL01 | Analysis 01 | Char | | A text string describing the analysis number 01, which is reserved for the primary analysis (e.g., assessment of investigational drug treatment QT effects). |
| ANL01FL | Analysis Flag 01 | Char | Y | Selection variable to identify the exact set of records used in the analysis number 01 corresponding to ANL01. |
| ANL02 | Analysis 02 | Char | | A text string describing the analysis flag number 02, which is reserved for the assay sensitivity analysis (e.g., assessment of positive control QT effects). |
| ANL02FL | Analysis Flag 02 | Char | Y | Selection variable to identify the exact set of records used in the analysis number 02 corresponding to ANL02. |
| ANLzz | Analysis zz | Char | | A text string describing the analysis flag number zz. Note that zz ≥ 03 because ANL01 and ANL02 are reserved for investigational drug and assay sensitivity analyses, respectively. |

| Variable Name | Variable Label | Type | Code List / Controlled Term | Comments |
|---|---|---|---|---|
| ANLzzFL | Analysis Flag zz | Char | Y | Selection variable to identify the exact set of records used in the analysis number zz (e.g., any analysis that was not investigational drug or assay sensitivity). Note that zz ≥ 03 is because ANL01FL and ANL02FL are reserved for investigational drug and assay sensitivity analyses, respectively. |

### 3.1 Examples

The examples below are reduced examples and only contain a few time points per period per period day for one or a limited number of subjects and DTYPE eq “AVERAGE” for illustration purposes.

Two reduced examples are provided below for time-matched (Table 2) and pre-dose (Table 3) baseline definitions in order to illustrate the recommended approach to encode time information, ABLFL, and AEGBLFL. ARDTM is a numerical value representing the date and time. To facilitate readability, the value of this variable is displayed as a date and time string.

**Table 2: Reduced ADEG Example Illustrating Time Encoding**

| USUBJID | TRTA | TRTSEQA | ABLFL | AEGBLFL | APERIOD | APERDAY | ATPT | ATPTN | ATPTREF | ARDTM | NRRLT | RRLTU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1002 | Placebo | Placebo - Moxi | Y | Y | 1 | -1 | 0.5 h | 1 | Morning dose | 2018-05-20T08:00:00 | 0.5 | Hours |
| 1002 | Placebo | Placebo - Moxi | Y | Y | 1 | -1 | 1 h | 2 | Morning dose | 2018-05-20T08:00:00 | 1 | Hours |
| 1002 | Placebo | Placebo - Moxi | Y | Y | 1 | -1 | 4 h | 3 | Morning dose | 2018-05-20T08:00:00 | 4 | Hours |
| 1002 | Placebo | Placebo - Moxi | | | 1 | 1 | 0.5 h | 1 | Morning dose | 2018-05-21T08:00:00 | 0.5 | Hours |
| 1002 | Placebo | Placebo - Moxi | | | 1 | 1 | 1 h | 2 | Morning dose | 2018-05-21T08:00:00 | 1 | Hours |
| 1002 | Placebo | Placebo - Moxi | | | 1 | 1 | 4 h | 3 | Morning dose | 2018-05-21T08:00:00 | 4 | Hours |
| 1002 | Moxi | Placebo - Moxi | Y | Y | 2 | -1 | 0.5 h | 1 | Morning dose | 2018-05-27T08:00:00 | 0.5 | Hours |
| 1002 | Moxi | Placebo - Moxi | Y | Y | 2 | -1 | 1 h | 2 | Morning dose | 2018-05-27T08:00:00 | 1 | Hours |
| 1002 | Moxi | Placebo - Moxi | Y | Y | 2 | -1 | 4 h | 3 | Morning dose | 2018-05-27T08:00:00 | 4 | Hours |
| 1002 | Moxi | Placebo - Moxi | | | 2 | 1 | 0.5 h | 1 | Morning dose | 2018-05-28T08:00:00 | 0.5 | Hours |
| 1002 | Moxi | Placebo - Moxi | | | 2 | 1 | 1 h | 2 | Morning dose | 2018-05-28T08:00:00 | 1 | Hours |
| 1002 | Moxi | Placebo - Moxi | | | 2 | 1 | 4 h | 3 | Morning dose | 2018-05-28T08:00:00 | 4 | Hours |

**Table 3: Reduced AEDG Example Illustrating Multiple Predose Time Points Used for Baseline**

| USUBJID | TRTA | ABLFL | AEGBLFL | AVAL | APERIOD | APERDAY | ATPT | ATPTN | ATPTREF | ARDTM | NRRLT | RRLTU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1002 | Placebo | | Y | 381.133 | 1 | 1 | -1 h | 1 | Morning dose | 2018-05-21T08:00:00 | -1 | Hours |
| 1002 | Placebo | | Y | 380.066 | 1 | 1 | -0.5 h | 2 | Morning dose | 2018-05-21T08:00:00 | -0.5 | Hours |
| 1002 | Placebo | | Y | 380.632 | 1 | 1 | 0 h | 3 | Morning dose | 2018-05-21T08:00:00 | 0 | Hours |
| 1002 | Placebo | Y | | 380.610 | 1 | 1 | Baseline | 4 | Morning dose | 2018-05-21T08:00:00 | 0 | Hours |
| 1002 | Placebo | | | 378.179 | 1 | 1 | 0.5 h | 5 | Morning dose | 2018-05-21T08:00:00 | 0.5 | Hours |
| 1002 | Placebo | | | 376.497 | 1 | 1 | 1 h | 6 | Morning dose | 2018-05-21T08:00:00 | 1 | Hours |
| 1002 | Placebo | | | 366.803 | 1 | 1 | 4 h | 7 | Morning dose | 2018-05-21T08:00:00 | 4 | Hours |
| 1002 | Moxi | | Y | 395.322 | 2 | 1 | -1 h | 1 | Morning dose | 2018-05-28T08:00:00 | -1 | Hours |
| 1002 | Moxi | | Y | 393.478 | 2 | 1 | -0.5 h | 2 | Morning dose | 2018-05-28T08:00:00 | -0.5 | Hours |
| 1002 | Moxi | | Y | 392.465 | 2 | 1 | 0 h | 3 | Morning dose | 2018-05-28T08:00:00 | 0 | Hours |
| 1002 | Moxi | Y | | 393.755 | 2 | 1 | Baseline | 4 | Morning dose | 2018-05-28T08:00:00 | 0 | Hours |
| 1002 | Moxi | | | 400.421 | 2 | 1 | 0.5 h | 5 | Morning dose | 2018-05-28T08:00:00 | 0.5 | Hours |
| 1002 | Moxi | | | 383.874 | 2 | 1 | 1 h | 6 | Morning dose | 2018-05-28T08:00:00 | 1 | Hours |
| 1002 | Moxi | | | 378.260 | 2 | 1 | 4 h | 7 | Morning dose | 2018-05-28T08:00:00 | 4 | Hours |

Another reduced example is provided in Table 4 to illustrate the use of BASETYPE. The table only shows rows with DTYPE eq "AVERAGE", which contain the average value of AVAL of the parameters measured in the individual ECG waveforms grouped by USUBJID, APERIOD, APERDAY, NRRLT, and PARAMCD. In this example, the study had a full time-matched baseline day (Day -1). Thus, BASETYPE has the time-matched key for each subject and time point. AVAL values from the rows with ABLFL eq "Y" get propagated (arrows) to the BASE column of the rows with the same BASETYPE for each subject. BASE is then used to compute the change from baseline of each row as CHG = AVAL – BASE. For example, subject 1002 had a QTcF of 375.000 msec at NRRLT 1h at baseline (i.e., 1 hour after DAY -1 Morning dose). Therefore, the change from baseline on Day 14 at NRRLT 1h in this example is CHG = AVAL – BASE = 375.667 – 375.000 = 0.667 msec.

**Table 4: Reduced ADEG Illustrating Use of BASETYPE in a Subset of Data From a Study With Full Time-Matched Baseline Day**

| USUBJID | APERIOD | APERDAY | ATPTREF | NRRLT | RRLTU | AVAL | EGSTRESU | ABLFL | BASE | CHG | BASETYPE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1002 | 1 | -1 | Morning dose | 0.5 | Hours | 372.333 | msec | Y | 372.333 | | Baseline Day 0.5 h |
| 1002 | 1 | -1 | Morning dose | 1 | Hours | 375.000 | msec | Y | 375.000 | | Baseline Day 1 h |
| 1002 | 1 | -1 | Morning dose | 4 | Hours | 372.667 | msec | Y | 372.667 | | Baseline Day 4 h |
| 1002 | 1 | 14 | Morning dose | 0.5 | Hours | 374.000 | msec | | 372.333 | 1.667 | Baseline Day 0.5 h |
| 1002 | 1 | 14 | Morning dose | 1 | Hours | 375.667 | msec | | 375.000 | 0.667 | Baseline Day 1 h |
| 1002 | 1 | 14 | Morning dose | 4 | Hours | 371.000 | msec | | 372.667 | -1.667 | Baseline Day 4 h |
| 1003 | 1 | -1 | Morning dose | 0.5 | Hours | 402.333 | msec | Y | 402.333 | | Baseline Day 0.5 h |
| 1003 | 1 | -1 | Morning dose | 1 | Hours | 401.333 | msec | Y | 401.333 | | Baseline Day 1 h |
| 1003 | 1 | -1 | Morning dose | 4 | Hours | 406.667 | msec | Y | 406.667 | | Baseline Day 4 h |
| 1003 | 1 | 14 | Morning dose | 0.5 | Hours | 393.667 | msec | | 402.333 | -8.667 | Baseline Day 0.5 h |
| 1003 | 1 | 14 | Morning dose | 1 | Hours | 397.333 | msec | | 401.333 | -4.000 | Baseline Day 1 h |
| 1003 | 1 | 14 | Morning dose | 4 | Hours | 396.667 | msec | | 406.667 | -10.000 | Baseline Day 4 h |

Lastly, Table 5 illustrates the use of COMPTYPE in a parallel study from one subject from the active treatment arm (ACOMPFL eq "") and the 6 subjects from the placebo arm (ACOMPFL eq "Y"). Table 5 shows QTcF data from DTYPE eq "AVERAGE" rows. The cells with thicker borders highlight the COMPTYPE matched rows. The COMP values are computed as the average of AVAL values of placebo data (ACOMPFL eq "Y") grouped by COMPTYPE. COMPBASE and COMPCHG values are computed in a similar fashion using the values from BASE and CHG columns, respectively. Finally, the comparator change from baseline (i.e., double delta) is computed as CCOMPCHG = CHG – COMPCHG. Note that for crossover designs, where each subject is his or her own control, USUBJID should be included in COMPTYPE. For example, COMPTYPE = "1001, placebo at 0.5 h" for USUBJID eq "1001".

**Table 5: Reduced ADEG Illustrating Use of COMPTYPE in a Subset of Data From a Parallel Study**

| USUBJID | TRTA | NRRLT | AVAL | BASE | CHG | ACOMPFL | COMP | COMPBASE | COMPCHG | CCOMPCHG | COMPTYPE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1001 | Drug | 0.5 | 390.333 | 390.333 | 0.000 | | 388.889 | 391.111 | -2.222 | 2.222 | Placebo group at 0.5 h |
| 1001 | Drug | 1 | 388.333 | 393.333 | -5.000 | | 390.111 | 393.389 | -3.278 | -1.722 | Placebo group at 1 h |
| 1001 | Drug | 4 | 387.333 | 381.000 | 6.333 | | 388.222 | 389.556 | -1.333 | 7.667 | Placebo group at 4 h |
| 1002 | Placebo | 0.5 | 374.000 | 372.333 | 1.667 | Y | 388.889 | 391.111 | -2.222 | | Placebo group at 0.5 h |
| 1002 | Placebo | 1 | 375.667 | 375.000 | 0.667 | Y | 390.111 | 393.389 | -3.278 | | Placebo group at 1 h |
| 1002 | Placebo | 4 | 371.000 | 372.667 | -1.667 | Y | 388.222 | 389.556 | -1.333 | | Placebo group at 4 h |
| 1003 | Placebo | 0.5 | 393.667 | 402.333 | -8.667 | Y | 388.889 | 391.111 | -2.222 | | Placebo group at 0.5 h |
| 1003 | Placebo | 1 | 397.333 | 401.333 | -4.000 | Y | 390.111 | 393.389 | -3.278 | | Placebo group at 1 h |
| 1003 | Placebo | 4 | 396.667 | 406.667 | -10.000 | Y | 388.222 | 389.556 | -1.333 | | Placebo group at 4 h |
| 1005 | Placebo | 0.5 | 401.667 | 392.333 | 9.333 | Y | 388.889 | 391.111 | -2.222 | | Placebo group at 0.5 h |
| 1005 | Placebo | 1 | 398.333 | 392.667 | 5.667 | Y | 390.111 | 393.389 | -3.278 | | Placebo group at 1 h |
| 1005 | Placebo | 4 | 399.333 | 390.333 | 9.000 | Y | 388.222 | 389.556 | -1.333 | | Placebo group at 4 h |
| 1007 | Placebo | 0.5 | 378.000 | 383.000 | -5.000 | Y | 388.889 | 391.111 | -2.222 | | Placebo group at 0.5 h |
| 1007 | Placebo | 1 | 377.667 | 390.000 | -12.333 | Y | 390.111 | 393.389 | -3.278 | | Placebo group at 1 h |
| 1007 | Placebo | 4 | 381.000 | 387.000 | -6.000 | Y | 388.222 | 389.556 | -1.333 | | Placebo group at 4 h |
| 1008 | Placebo | 0.5 | 398.667 | 410.333 | -11.667 | Y | 388.889 | 391.111 | -2.222 | | Placebo group at 0.5 h |
| 1008 | Placebo | 1 | 401.333 | 412.333 | -11.000 | Y | 390.111 | 393.389 | -3.278 | | Placebo group at 1 h |
| 1008 | Placebo | 4 | 396.000 | 399.667 | -3.667 | Y | 388.222 | 389.556 | -1.333 | | Placebo group at 4 h |
| 1010 | Placebo | 0.5 | 387.333 | 386.333 | 1.000 | Y | 388.889 | 391.111 | -2.222 | | Placebo group at 0.5 h |
| 1010 | Placebo | 1 | 390.333 | 389.000 | 1.333 | Y | 390.111 | 393.389 | -3.278 | | Placebo group at 1 h |
| 1010 | Placebo | 4 | 385.333 | 381.000 | 4.333 | Y | 388.222 | 389.556 | -1.333 | | Placebo group at 4 h |

## 4.0 Dataset Specifications for Pharmacokinetic Concentrations Analysis Dataset – ADPC

This is a one record per subject per PK parameter per analysis period per analysis visit per analysis time point dataset that contains a comprehensive set of variables pertaining to the subject and their quantitative pharmacokinetic measures. This dataset is designed to be a subset of an ADaM-compliant ADPC dataset that allows for concentration-ECG changes analysis (e.g., concentration-QT). Thus, while not all PK samples may have time-matched ECG data, the variables present in both ADEG and ADPC should be coded consistently to allow for proper mapping of time-matched PK and ECG rows. Ideally, these variables should be traceable to the submitted tabulations and/or analysis datasets. Whereas the formation of this dataset duplicates information found in other submitted datasets, the compilation of these variable concepts into one record facilitates FDA's statistical and medical reviews.

**Table 6: Analysis Variable Metadata for ADPC**

| Variable Name | Variable Label | Type | Code List / Controlled Term | Comments |
|---|---|---|---|---|
| STUDYID | Study Identifier | Char | | |
| USUBJID | Unique Subject Identifier | Char | | |
| TRTSEQP | Planned Sequence of Treatments | Char | | |
| TRTP | Planned Treatment | Char | | |
| TRTPN | Planned Treatment (N) | Num | | The numeric code for TRTP. One-to-one mapping within ADEG to TRTP. The mapping should be the same in ADEG and ADPC. |
| TRTSEQA | Actual Sequence of Treatments | Char | | |
| TRTA | Actual Treatment | Char | | |
| TRTAN | Actual Treatment (N) | Num | | The numeric code for TRTA. One-to-one mapping within ADEG to TRTA. The mapping should be the same in ADEG and ADPC. |
| APERIOD | Period | Char | | Populate based on PC.VISITNUM. Note there can be 1 or more visits per period. ADEG.APERIOD and ADPC.APERIOD should be coded consistently so mapping of time-matched measures can be performed. |
| APERIODC | Period (C) | Num | | Character version of APERIOD. One-to-one correspondence with APERIOD. |
| AVISIT | Analysis Visit | Char | | Populate based on PC.VISIT. |
| AVISITN | Analysis Visit (N) | Num | | Numeric version of AVISIT. Since study visits are usually defined by certain time points, defining AVISITN so that it represents the time point associated with the visit can facilitate plotting and interpretation of the values. Alternatively, AVISITN may be a protocol visit number, a cycle number, an analysis visit number, or any other number logically related to AVISIT or useful for sorting that is needed for analysis (see ADaM IG). |

| Variable Name | Variable Label | Type | Code List / Controlled Term | Comments |
|---|---|---|---|---|
| ATPT | Analysis Time Point | Char | | Populate based on PC.PCTPT. EG.EGTPT and PC.PCTPT should be coded in ADEG.ATPT and ADPC.ATPT in a consistent fashion so mapping of time-matched measures can be performed. |
| ATPTN | Analysis Time Point (N) | Num | | ATPTN provides a numeric representation of ATPT. Defining ATPTN so that its values represent the planned time points in a consistent unit (e.g., minutes or hours after dosing) is not required but can facilitate plotting and interpretation of the values. There should be a one-to-one mapping between ATPT and ATPTN (see ADaM IG). As for ATPT, the coding of ATPTN should be the same for ADEG.ATPTN and ADPC.ATPTN. |
| ATPTREF | Analysis Reference Time Point | Char | | Populate based on PC.PCTPTREF. Description of the fixed reference point referred to by ATPT/ATPTN (e.g., time of dose). As for ATPT, the coding of ATPTREF should be the same for ADEG and ADPC. |
| ARDTM | Date/Time of Reference | Num | | Date and time of reference. ARDTM provides a date and time representation of ATPTREF. As for ATPTREF, ARDTM should be the same for ADEG and ADPC. |
| AARDTM | Actual Date/Time of Reference | Num | | Actual date and time of reference of ARDTM. |
| ARRLT | Actual Relative Time from Reference TPT | Num | | This is the actual elapsed time (for sample point or start of sampling interval) from reference date and time (ADTM - ARDTM). |
| NRRLT | Nominal Relative Time from Reference TPT | Num | | This is the planned elapsed time (for sample point or start of sampling interval) from reference date and time (ARDTM). |
| RRLTU | Relative Time from Reference TPT Units | Char | UNIT | Units for all elapsed time variables (i.e., -RRLT) from reference time point (ATPTREF). |
| ADTM | Analysis Date and Time | Num | | Populate from PC.PCDTC. |
| ADT | Analysis Date | Num | | Numeric date value from PC.PCDTC. |
| ATM | Analysis Time | Num | | Numeric time value from PC.PCDTC. |
| ADY | Analysis Relative Day | Num | | Populated based on PC.PCDY. |
| AVISDY | Analysis Visit Day | Num | | |
| APERDAY | Analysis Nominal Period Day | Num | | Populate with the numeric relative day within the Period based on AVISITN. [For example, "Period 2, Day 1" is APERDAY=1]. ADEG.APERDAY and ADPC.APERDAY should be coded consistently so mapping of time-matched measures can be performed. |
| PARAM | Analyte Name | Char | | Analyte name from PC.PCTEST. |
| PARAMCD | Parameter Code | Char | | Analyte code with a maximum length of 4 characters. Analyte code from PC.PCTESTCD should be abbreviated up to 4 characters long. One-to-one correspondence with PCTEST. |
| AVAL | Analysis Value | Num | | Populate based on PC.PCSTRESN. |
| AVALU | Units of Analysis Value | Char | PKUNIT | Populate based on PC.PCSTRESU. |
| LLOQFL | Lower Limit of Quantification Flag | Char | Y | If record value was below the lower limit of quantification, then LLOQFL ="Y" else LLOQFL is null. |
| PCSEQ | Sequence Number | Num | | Populate based on PC.PCSEQ. |

### 4.1 Examples

A key point in the ADEG and ADPC definitions is that time information for time points with both ECG and PK samples (i.e., ECGPCFL eq "Y") should be consistent. Additionally, the format allows for time point without both ECG and PK samples collected. A reduced example is presented below to illustrate these points. In Table 7, the row for 12 hours after the morning dose in ADEG has ECG data that has no PK sample data-associated ADPC in Table 8. Similarly, the PK sample collected 14 hours after the morning dose in ADPC has no ECG data associated in ADEG. Please note that this a reduced example for illustration purposes and only contains a few time points per period day for one subject.

**Table 7: ADEG Example**

| TRTA | TRTSEQA | APERIOD | APERDAY | ECGPCFL | ATPT | ATPTN | ATPTREF | ARDTM | NRRLT | RRLTU |
|---|---|---|---|---|---|---|---|---|---|---|
| Moxi | Moxi -Placebo | 1 | 1 | Y | 0.5 h | 1 | Morning dose | 2018-05-21T08:00:00 | 0.5 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | Y | 1 h | 2 | Morning dose | 2018-05-21T08:00:00 | 1 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | Y | 4 h | 3 | Morning dose | 2018-05-21T08:00:00 | 4 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | | 12 h | 4 | Morning dose | 2018-05-21T08:00:00 | 12 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | Y | 16 h | 6 | Morning dose | 2018-05-21T08:00:00 | 16 | Hours |

**Table 8: ADPC Example**

| TRTA | TRTSEQA | APERIOD | APERDAY | ATPT | ATPTN | ATPTREF | ARDTM | NRRLT | RRLTU |
|---|---|---|---|---|---|---|---|---|---|
| Moxi | Moxi -Placebo | 1 | 1 | 0.5 h | 1 | Morning dose | 2018-05-21T08:00:00 | 0.5 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | 1 h | 2 | Morning dose | 2018-05-21T08:00:00 | 1 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | 4 h | 3 | Morning dose | 2018-05-21T08:00:00 | 4 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | 14 h | 5 | Morning dose | 2018-05-21T08:00:00 | 14 | Hours |
| Moxi | Moxi -Placebo | 1 | 1 | 16 h | 6 | Morning dose | 2018-05-21T08:00:00 | 16 | Hours |

## 5.0 Appendix: Coding Datasets From Parallel With Nested Crossover Study Design

This appendix contains recommendations about how to code data from a randomized placebo-controlled parallel design QT study with a nested crossover arm for the positive control (Figure 1) in ADEG and ADPC datasets.

**Figure 1: Example of Parallel Study With Nested Crossover Design**[7]

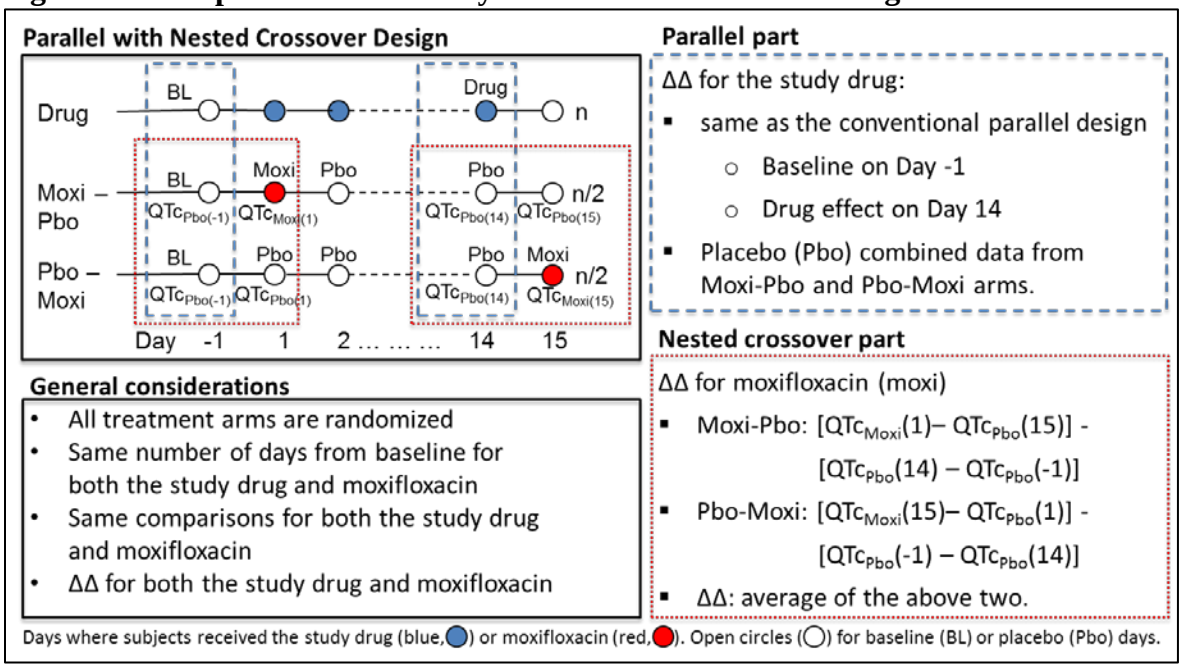


Figure 1 describes a randomized, placebo- (Pbo) controlled, parallel design study with a nested crossover design. Briefly, the two-part study uses time-matched baseline and moxifloxacin (Moxi) as the positive control:

1. A parallel part where the drug and placebo are administered for 14 days and the effect of the drug is evaluated on Day 14 (dashed blue boxes); and
2. A nested crossover part where the Pbo/Moxi treatment group is divided into two arms (Moxi-Pbo, and Pbo-Moxi), with half of the subjects in each (dotted red boxes). In the Moxi-Pbo arm, the positive control (Moxi) is given on Day 1, followed by placebo to Day 15. In the Pbo-Moxi arm, placebo is given on Day 1 to Day 14 and positive control (Moxi) on Day 15.

In the example described in Figure 1, each study part has the same number of subjects. For example, if the parallel part has 40 subjects, then the nested crossover part should include 40

[7] Adapted from Zhang J, Moxifloxacin Can be Given Within the Placebo Cohort During a Parallel-Designed Thorough QT Study - FDA Perspective. DIA Cardiovascular Safety, QT, and Arrhythmia in Drug Development, Bethesda, Maryland, 2009.

subjects (20 subjects per arm). This study design therefore provides an example of coding both parallel and crossover studies. Note that this design results in different baseline definitions for each study part (right panels in Figure 1). In Figure 1, all placebo data from Day 14 are used together with baseline data from Day -1 when used in the parallel part and in the Moxi-Pbo arm of the nested crossover part. However, in the Pbo-Moxi arm of the nested crossover part, the data from Day 14 are coded as baseline and the data from Day -1 data are coded as placebo. Note also that, in the Pbo-Moxi arm, the data from Day 1 are coded as baseline in the nested crossover part but not used in the parallel part. Data from a parallel study with a nested crossover design can be coded in one ADEG and one ADPC dataset. The ADPC dataset can be coded following the specifications in the main body of this document. Recommendations for coding the ADEG dataset are provided below.

For the parallel part in the example presented in Figure 1, Day -1 contains the baseline data and drug effects in QT corrected for placebo are assessed on Day 14. Thus, all Day -1 rows will have ABLFL set to "Y" and Day 14 rows will have ANL01FL set to "Y" as well as IUTANLFL and/or CQTANLFL set to "Y", as appropriate. In addition, rows from Moxi-Pbo and Pbo-Moxi arms on Day 14 will have ACOMPFL set to "Y" because the placebo is the comparator in this example. While subjects in the nested crossover part received moxifloxacin on Day 1 and Day 15, only placebo data will be included in the analysis of the parallel part because only rows from Day 14 have ANL01FL set to "Y". Note that Day -1 rows have ABLFL set to "Y" but ANL01FL set to null.

For the nested crossover part, only data from the Moxi-Pbo and Pbo-Moxi arms are used. For the Moxi-Pbo arm, the baseline data come from Day 15 and Day -1 for the moxifloxacin day (Day 1) and placebo day (Day 14), respectively (Figure 1). To facilitate analysis, the nested crossover data needs to be coded like a cross-over study with two periods. Thus, Day -1 and Day 15 will have ABLFL set to "Y", Day 1 and Day 14 will have ANL02FL set to "Y", and IUTANLFL and/or CQTANLFL will be set to "Y", as appropriate. Additionally, Days 1 and 14 will be coded as Day 1 and Days -1 and 15 as -1 and period will be set to 1 for the moxifloxacin day (and baseline) and 2 for the placebo day (and baseline). Lastly, Day 14 will have ACOMPFL set to "Y" because this day has the placebo data for this arm. For the Pbo-Moxi arm, the baseline data come from Day 1 and Day 14 for the moxifloxacin day (Day 15) and placebo day (Day -1), respectively. Thus, Day 1 and Day 14 will have ABLFL set to "Y", Day -1 and Day 15 will have ANL02FL set to "Y", and IUTANLFL and/or CQTANLFL will be set to "Y", as appropriate. Similar to the other arm, the Days 15 and -1 will be coded as Day 1 and Days 1 and 14 as Day -1 and the placebo day (and baseline) will be coded as period 1 and moxifloxacin day (and baseline) as period 2. Finally, Day -1 will have ACOMPFL set to "Y" because this day has the placebo data for this arm.

In both parts, IUTANLFL and CQTANLFL are populated as described above but also take into account whether the analysis of QT effects is to be performed either using by time analysis (IUTANLFL) or using concentration-QT modeling (CQTANLFL), or both.

**Table 9: Summary of Flags Per Part and Treatment Arm in ADEG for a Parallel Study With Nested Crossover Design**

| Part | Arm | Study day | | | |
|---|---|---|---|---|---|
| | | Day -1 | Day 1 | Day 14 | Day 15 |
| Parallel | Drug | ABLFL | | TRTx = "Drug"<br>IUTANLFL<br>CQTANLFL<br>ANL01FL | |
| | Moxi-Pbo | ABLFL | | TRTx = "Placebo"<br>ACOMPFL<br>IUTANLFL<br>CQTANLFL<br>ANL01FL | |
| | Pbo-Moxi | ABLFL | | TRTx = "Placebo"<br>ACOMPFL<br>IUTANLFL<br>CQTANLFL<br>ANL01FL | |
| Nested Crossover | Moxi-Pbo | ABLFL[2] | TRTx = "Moxi"<br>IUTANLFL<br>CQTANLFL<br>ANL02FL[1] | TRTx = "Placebo"<br>ACOMPFL<br>IUTANLFL<br>CQTANLFL<br>ANL02FL[2] | ABLFL[1] |
| | Pbo-Moxi | TRTx = "Placebo"<br>ACOMPFL<br>IUTANLFL<br>CQTANLFL<br>ANL02FL[2] | ABLFL[1] | ABLFL[2] | TRTx = "Moxi"<br>IUTANLFL<br>CQTANLFL<br>ANL02FL[1] |

[1]: Represented in data as Period 1, Day -1 (ABLFL eq "Y") and Day 1 (ABLFL eq ""); [2]: Represented in data as Period 2, Day -1 (ABLFL eq "Y") and Day 1 (ABLFL eq "")

Placebo data should be coded consistently in TRTx as "Placebo" when building an ADEG dataset. Table 9 summarizes which flags should be populated with "Y" for each part and treatment arm in the ADEG dataset. Presence of xxFL in a cell in Table 9 indicates that the FL column is set to "Y": otherwise it is not defined. While it may seem that there could be duplicated rows when implementing this approach, the BASETYPE variable will maintain uniqueness of rows from the nested crossover part that have multiple baseline definitions.