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Coming soon: ADNCA and the PK submission

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ABSTRACT

This talk will give a preview of the soon to come non-compartmental pharmacokinetic analysis CDISC ADaM standard (ADNCA). ADNCA will be the submission data set that is sent to the PK scientist for calculation of non-compartmental PK parameters. We will present the proposed guidance and give an overview of the steps involved in developing this standard for analysis and submission to the FDA.

The ADNCA data set will adhere closely to the BDS structure. The dataset itself will contain a combination of PK concentration data, its corresponding dosing data, and any additional data necessary to complete the non-compartmental analysis. The inclusion of this extra data is necessary, in part, because of the need to present timing variables related to the concentration event and dosing time. We will discuss the rationale for those timing variables as well as several other variables that are commonly of interest to the PK scientist.

In addition, the ADNCA data standard will support non-compartmental analyses, PK and PD data review, and could be utilized for tabular and graphical presentation of the data. However, ADNCA will not be suitable for population PK modeling analysis and is not intended to be used for presentation of the results of the PK analysis.

The ADNCA standard have been in development for some time and has gone through multiple rounds of revision. The ADaM sub team has delivered a draft to the ADaM leadership team and the two continue to work together.

INTRODUCTION

There is currently a gap in the SDTM and ADaM standards for handling and formatting data to allow for non-compartmental PK parameter calculations. The data that is required for PK parameter software is a combination of several datasets and therefore an SDTM convention like PC would not meet the necessary requirements for this analysis. In addition, the required data structure is more complicated than the currently defined ADaM BDS structure. Therefore, the ADaM leadership team formed a sub team tasked with the creation of a new set of specifications specifically for this situation. The end goal of this sub team was to develop standards that closely follow current ADaM guidance while allowing for flexibility to work with the various types of software packages that are used to analyze PK data and calculate parameters. ADNCA is the end result of this sub teams' effort.

Pharmacokinetics is the study of the effect of the body on a drug. Calculation of pharmacokinetic parameters using a non-compartmental analysis (NCA) approach is a class of mathematical methods for studying the degree of exposure following administration of a drug. NCA is commonly used to analyze drug concentration data by subjects from clinical trials. The derivations result in pharmacokinetic parameters such as Cmax (maximum concentration), Tmax (time at maximum concentration), t1/2 (half-life), and AUC to t (area under the curve to the last time point) that allow the analyst to better understand the distribution of the drug in the body.

Pharmacokinetic parameters are typically calculated using software packages designed to support PK analyses using analysis ready data as the input. The input analysis data needs to comprehensively associate subject drug concentrations with study drug dosing and related time, support the exclusion of specific records and subjects, and provide other information as needed. Parameter calculation is based on the specific dosing regimen, the PK sample collection schedule, and the objective(s) associated with parameter calculations. The parameter calculations will require specific timing variables to relate PK concentration to the actual time from dose.

The flexibility of the BDS structure of the ADNCA will allow the user to incorporate data from multiple sources in order to complete the analysis. For example, if the it was important to segregate the analysis

by sex, the SEX column from the ADSL could be added to the ADNCA dataset. The ability to add these qualifying variables is a unique and necessary feature of the dataset.

Since the analysis data input for non-compartmental parameter calculation is subject to submission to regulatory bodies, it is important to base this dataset on the standardized (SDTM) tabulations data that will be submitted and to comply with ADaM standards.

We will share the proposed approach through examples. The actual IG content will be publically released only after internal ADaM review is completed.

TIMING VARIABLES

Pharmacokinetic Non-Compartmental Analysis is primarily a "time from event" based analysis producing multiple derived parameters. The ADNCA dataset structure is designed to support commonly structured NCAs, including analyses with both discrete time measurements (typical for plasma or serum) and measurements from collections over time (typical for urine). The dataset format is designed to support common NCA analysis needs; additional variables can be added as needed to accommodate more complex derivations.

The ADNCA dataset structure may be used to create multiple tabular and graphical data presentations as they relate to NCA and pharmacokinetic and pharmacodynamics data review, as well as provide a means to assess event collection compliance where the data collected have a structured chronological sequence. Additionally, the ADNCA structure has the potential to be utilized for tabular and graphical data presentation in other pharmacokinetic and pharmacodynamic sparse sampling study designs that do not necessarily require NCA.

ADNCA is comprised of the combination of dose information and concentration results. These data are combined in order to facilitate creation of both nominal and actual timing variables which are necessary to produce accurate PK parameters. The ADNCA dataset will also include timing variables that relate to the most recent dose as well as the very first dose given to the subject. This structure will therefore facilitate the analysis of data from single dose and multiple dose studies.

SDTM cannot be used for the parameter calculations due to the structure of the individual datasets. The analysis needs the timing variables that are compared back to the dosing date and time and those variables need to be in units of hours, days, etc. This ADNCA data set will follow the structure of an ADaM BDS. A new or unique data structure is not needed as the analysis of concentration versus time is not multivariate.

EXAMPLE 1: DIFFERENCE BETWEEN AVISIT IN ADNCA AND 'DAY' VARIABLES IN SDTM

The AVISIT variable in ADNCA is useful for PK analysis in many situations, for example, it is used as a key variable to extract the concentration-time profiles for different days in multiple day studies.

When deriving the AVISIT and AVISITN variables from tabulated variables in SDTM domains, the following examples shows how the AVISIT variable is different from the PCDY variable in the PC domain of SDTM. Similar considerations will apply to VISIT variables in SDTM domains.

The PCDY variable indicates the study day of when the sample was taken. This variable is one of the timing variables for the specific observations in the records of the PC domain dataset. The example below shows that for the samples taken 24 and 36 hours after dosing, the PCDY variable correctly indicates that this is day "2" and "3" of the study, respectively.

However, with respect to the concentration-time profile for PK analysis, the AVISIT variable needs to indicate that these samples are part of the profile that is related to the day 1 dose. Therefore, the AVISIT variable should have a value of "DAY 1" and corresponding AVISITN has the value of "1".

Table 1

PCRFTDTC	PCDY	PCTPT
2011-12-26T08:00	1	PREDOSE
2011-12-26T08:00	1	30MIN
2011-12-26T08:00	1	1H
2011-12-26T08:00	1	2H
2011-12-26T08:00	1	4H
2011-12-26T08:00	1	8H
2011-12-26T08:00	1	12H
2011-12-26T08:00	2	24H
2011-12-26T08:00	2	36H
2011-12-26T08:00	3	48H
PCDY Variable in PC Domain		

TRTRDTM	AVISIT	AVISITN
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
2011-12-26T08:00:00	DAY 1	1
AVISIT, AVISITN Variables in ADNCA		

Table 1: Example of Difference between AVISIT in ADNCA and 'day' variables in SDTM

Note that TRTRDTM is a numerical value representing the date and time. To make the table readable, the value of this variable is displayed as a date and time string.

EXAMPLE 2: TIMING AND VALUES FOR MULTIPLE ORAL DOSING

This example shows the nominal and relative times for a multiple oral dosing trial.

Note that the modified relative time from reference dose (MRRELTM) was added for analysis purposes: the negative ARRELTM on row 1 and row 8 is assigned zero, as PK software like Phoenix® WNL will only include observations starting from dosing, and not prior to dosing for parameter estimation.

Table 2

AVISIT	ATPT	ADTM	TRTRDTM	NFRELTM	AFRELTM	NRRELTM	ARRELTM	MRRELTM	FRELTMU	RRELTMU	AVAL
DAY 1	Predose	13AUG15:08:30	13AUG15:09:00	0.00	-0.50	0.00	-0.50	0.00	HR	HR	0
DAY 3	0.5 H	15AUG15:09:30	15AUG15:09:00	48.50	48.50	0.50	0.50	0.50	HR	HR	5.168
DAY 3	1 H	15AUG15:10:00	15AUG15:09:00	49.00	49.00	1.00	1.00	1.00	HR	HR	18.020
DAY 3	2 H	15AUG15:11:03	15AUG15:09:00	50.00	50.05	2.00	2.05	2.05	HR	HR	31.580
DAY 3	4 H	15AUG15:13:00	15AUG15:09:00	52.00	52.00	4.00	4.00	4.00	HR	HR	18.500
DAY 3	6 H	15AUG15:15:00	15AUG15:09:00	54.00	54.00	6.00	6.00	6.00	HR	HR	16.700
DAY 3	24 H	16AUG15:08:53	15AUG15:09:00	72.00	71.88	24.00	23.88	23.88	HR	HR	0.656
DAY 9	Predose	21AUG15:08:53	21AUG15:09:00	192.00	191.88	0.00	-0.12	0.00	HR	HR	1.544
DAY 9	0.5 H	21AUG15:09:30	21AUG15:09:00	192.50	192.50	0.50	0.50	0.50	HR	HR	2.216
DAY 9	1 H	21AUG15:10:02	21AUG15:09:00	193.00	193.03	1.00	1.03	1.03	HR	HR	6.008
DAY 9	2 H	21AUG15:11:10	21AUG15:09:00	194.00	194.17	2.00	2.17	2.17	HR	HR	32.400
DAY 9	4 H	21AUG15:13:00	21AUG15:09:00	196.00	196.00	4.00	4.00	4.00	HR	HR	22.940
DAY 9	6 H	21AUG15:15:00	21AUG15:09:00	198.00	198.00	6.00	6.00	6.00	HR	HR	23.540
DAY 9	24 H	22AUG15:08:53	21AUG15:09:00	216.00	215.88	24.00	23.88	23.88	HR	HR	1.724

Table 2: Example of Timing and Values for Multiple Oral Dosing

FLAGS

Flags are necessary to allow the data to communicate with the PK scientist and other data consumers. The scientist uses the flags on either a subject level or a record level. Allowing for subject level flags is a unique and necessary addition to ADNCA, as these flags often need to be programmed after the data is analyzed and pre-determined exclusion rules may not be applicable. ADNCA will allow for the inclusion of flags expected by the PK scientists for parameter calculations.

EXAMPLE 3: EXCLUSION FLAGS

This section shows examples for the use of the exclusion flags PKEFL for subject-level exclusions and PKREFL for record-level exclusions. The examples show exclusions for reasons that are mainly triggered by sampling considerations. Other reasons, for example records excluded due to a dosing issue, caused by some violation of dosing requirements, would be recorded accordingly.

The first table below shows two examples for record-level exclusions.

The record for subject CPW-s001 at nominal time 2 hours is excluded because no concentration value is available. The record should still be included in the dataset for traceability reasons and to support consistent reporting.

The records for subject CPW-s003 after the dose at time 0 hours are all excluded because the subject vomited too soon after the dose administration (PKEFL set to “Y” and REXSUBJ set to “Vomiting” for all records for this profile). Note that because this is flag indicates record-level exclusion, other observations about this subject would still be included in the analysis.

Table 4

USUBJID	ARRELTM	NRRELTM	RRELTMU	AVAL	PCSTRESU	VOMITFL	VRELTM	PKEFL	REXSUBJ	PKERFL	REXRE
CPW-s001	0	0	h	0	ug/L	Y	0.75				
CPW-s001	0.33333	0.25	h	19.4	ug/L	Y	0.75				
CPW-s001	0.5	0.5	h	118.8	ug/L	Y	0.75				
CPW-s001	1	1	h	115	ug/L	Y	0.75				
CPW-s001	2	2	h		ug/L	Y	0.75			Y	Missing AVAL Value
CPW-s001	4	4	h	91.2	ug/L	Y	0.75				
CPW-s001	8	8	h	67.6	ug/L	Y	0.75				
CPW-s003	0	0	h	0	ug/L	Y	0.083333		Y	Y	Vomiting
CPW-s003	0.4	0.25	h	19.8	ug/L	Y	0.083333		Y	Y	Vomiting
CPW-s003	0.75	0.5	h	126	ug/L	Y	0.083333		Y	Y	Vomiting
CPW-s003	1.33333	1	h	131.25	ug/L	Y	0.083333		Y	Y	Vomiting
CPW-s003	2	2	h	114	ug/L	Y	0.083333		Y	Y	Vomiting
CPW-s003	4	4	h	97.85	ug/L	Y	0.083333		Y	Y	Vomiting
CPW-s003	7	8	h	68.25	ug/L	Y	0.083333		Y	Y	Vomiting

Table 3: Example of Record Level Exclusions

The following table shows an example for subject-level exclusion but also includes some record-level exclusions.

- The record for subject CPW-s011 at nominal time 0.25 hours is excluded because the sample was taken too late.
- The record for subject CPW-s011 on AVISIT 2 is excluded because it is an intermediate control sample and there are not enough data for any PK analysis.
- All records for subject CPW-s013 are excluded (PKEFL = "Y") because there are not enough data for PK analysis for day 1 (REXSUBJ = "Incomp. Day 1 Samples") and it was decided not to analyze any of the data for this subject.

Table 5

USUBJID	TRTAN	ARRELTM	NRRELTM	RRELTMU	AVISITN	AVAL	PCSTRESU	PKEFL	REXSUBJ	PKERFL	REXRE
CPW-s011	1	0	0	h	1	0	ug/L				
CPW-s011	1	0.4	0.25	h	1	80.3	ug/L			Y	Late Sample
CPW-s011	1	0.5	0.5	h	1	118.8	ug/L				
CPW-s011	1	1	1	h	1	115	ug/L				
CPW-s011	1	2	2	h	1	132	ug/L				
CPW-s011	1	4	4	h	1	91.2	ug/L				
CPW-s011	1	8	8	h	1	67.6	ug/L				
CPW-s011	1	-0.5	-0.5	h	2	128.7	ug/L			Y	Interm. Control Sample
CPW-s013	1	0	0	h	1	0	ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples
CPW-s013	1	0.25	0.25	h	1	19.8	ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples
CPW-s013	1	0.5	0.5	h	1		ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples
CPW-s013	1	1	1	h	1		ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples
CPW-s013	1	2	2	h	1		ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples
CPW-s013	1	4	4	h	1		ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples
CPW-s013	1	7	8	h	1		ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples
CPW-s013	1	-0.5	-0.5	h	2	75.075	ug/L	Y	Incomp. Day 1 Samples	Y	Incomp. Day 1 Samples

Table 4: Example of Subject Level Exclusion

CONCLUSION

ADNCA is the result of the ADaM sub team tasked with creating a standard for analysis data used to support calculation of PK parameters. What we proposed needs to comply with ADaM standards as well as work with various software packages for PK analysis. ADNCA is still a work in progress. The sub team is working closely with the ADaM leadership to finalize this submission standard. Please stand by and await this standard to complete ADaM review and eventually make it to public review.

REFERENCES

Xie, Y., Chai, P., Kirby S., Wang N. 2011 "Pharmacokinetic Data Submission in the CDISC Environment." American Association of Pharmaceutical Scientists

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