What is ADNCA and Why is it Important?

KRISTIN KELLY- Senior Principal CDISC Consultant
MICHAEL CLIFTON – Product Manager, Phoenix
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Kristin Kelly

Senior Principal CDISC Consultant, Pinnacle 21

CERTARA

PINNACLE 21 BY CERTARA

Michael Clifton

Manager, Product Management, Phoenix

Introduction

Introduction

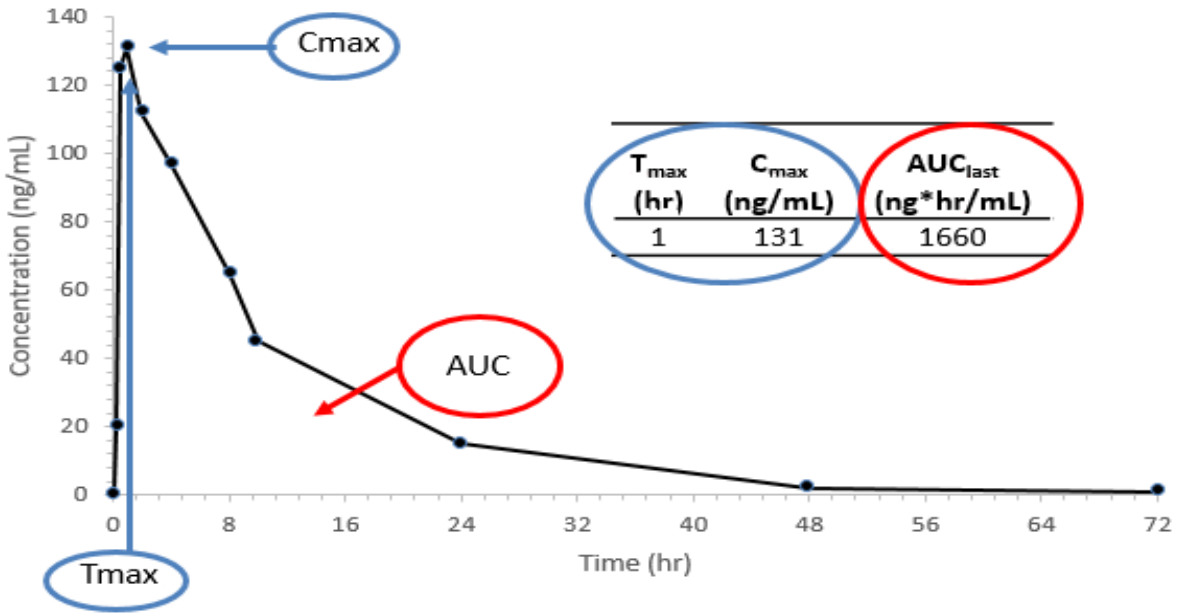
- Pharmacokinetics (PK) is the study of the effect of the body on a drug
  - Analysis of how a drug is absorbed, distributed, metabolized and eventually excreted from the body (ADME)
- Non-compartmental analysis (NCA) is one class of mathematical methods used to calculate PK parameters that describe, characterize and quantify this effect
  - Used to study the level of exposure to a drug based on serial drug concentration data collected from individual subjects
  - Typically performed using software designed to support PK Analysis using drug concentration data as one input, e.g. Phoenix WinNonlin
- The SDTMIG contains two domains to hold this data:
  - Pharmacokinetics Concentrations (PC) - A findings domain that contains concentrations of drugs or metabolites in fluids or tissues as a function of time.
  - Pharmacokinetics Parameters (PP) - A findings domain that contains pharmacokinetic parameters derived from pharmacokinetic concentration-time (PC) data.

Introduction

- CDISC Analysis Data Model Implementation Guide for Non-compartmental Analysis Input Data v1.0 (ADAMIG-NCA) (published in November 2021)
  - Provides the specification for the input dataset for NCA
  - Specifies many of the variables needed for PK parameter calculations as well as general naming conventions that can be used for additional variables
  - The input data format needs to comprehensively associate subject drug concentrations over time with study drug dosing, support the exclusion of specific records and subjects, and provide other supporting information as needed
  - Using this standard format supports submission to regulatory agencies as well as promoting compliance with ADaM standards

Non-Compartmental Analysis (NCA)

- NCA is a time-from-event based analysis that derives multiple parameters from time-concentration profiles for individual subjects



Analysis Dataset for Non-Compartmental Analysis Input Data (ADNCA) Metadata

Analysis Dataset Non-Compartmental Analysis (ADNCA)

- In the ADAMIG-NCA v1.0, the ADaM NCA input dataset is simply referred to as **ADNCA**
  - Not a required naming convention
  - Can have a different name if the convention for naming datasets outlined in the ADaM standards is followed:
    - Must start with 'AD' and cannot be longer than 8 characters: 'ADxxxxxx'
- ADNCA dataset structure is designed to support common NCAs, including analysis with both discrete timepoint measurements (e.g. plasma/serum concentrations) and measurements from collections over time intervals (e.g. urine samples)
  - May be used to create tabular and graphical data representations as needed for PK and PD data review for studies using NCA
  - It is not intended to be used to present graphical or tabular representations of PK parameter results from NCA
  - These data are typically represented in the SDTM Pharmacokinetics Parameters (PP) domain

ADaM Metadata for ADNCA

Dataset Metadata

- The ADNCA dataset is designed to follow the ADaM Basic Data Structure (BDS)
  - BDS datasets contain one or more records per subject, per analysis parameter, per analysis timepoint (more information can be found in the ADaMIG available at: https://www.cdisc.org/standards/foundational/adam)
- Dataset Metadata

Data Structure Name	Data Structure Description	Class of Dataset	Subclass of Dataset	CDISC Notes
ADNCA	Basic Data Structure Non-Compartmental Analysis	BASIC DATA STRUCTURE	NON-COMPARTMENTAL ANALYSIS	Dataset designed to support NCA. Primarily sourced from SDTM.PC and supplemented by information for the EX, EC, or other relevant domains.

  - *Note: The Data Structure Name, Description, and CDISC Notes are intended to provide information to assist data preparers. They are not intended to be metadata submitted in define.xml*

ADaM Metadata for ADNCA

Variable Metadata

- Some standard BDS and Analysis Dataset Subject-level (ADSL) variables that would commonly be used in ADNCA include:

ADSL
- STUDYID
- USUBJID and SUBJID
- SITEID
- AGE or AAGE, and AGEU
- SEX
- RACE
- TRTP and TRTPN
- TRTA and TRTAN
- DOSEP, DOSEA, and DOSEU

BDS
- APERIOD and APERIODC
- AVISIT and AVISITN
- ADT, ATM, and ADTM
- ASTDT, ASTTM, and ASTDTM
- AENDT, AENTM, and AENDTM
- ATPT and ATPTN
- PARAM, PARAMCD, and PARAMN
- AVAL
- DTYPE

ADaM Metadata for NCA

Other Input data for ADNCA

- SDTM Domains
  - Exposure (EX) and/or Exposure as Collected (EC)
    - EXSTDTC, EXENDTC, EXDOSE, EXROUTE, ECOCCUR
  - Pharmacokinetics Concentrations (PC)
    - PCTPT, PCDTC, PCRFTDTC, PCSTRESC, PCSTRESU, PCSPEC, VISITNUM, VISIT
- ADaM Subject-Level Analysis Dataset (ADSL)
  - Common baseline characteristics used in NCA*:
    - BMIBL (body mass index, BMI, at baseline, associated with the time of reference dosing) and BMIBLU (units)
    - HTBL (height at baseline, associated with the time of reference dosing) and HTBLU (units)
    - WTBL (weight at baseline, associated with the time of reference dosing) and WTBLU (units)

*Due to needs of common analysis tools such as Phoenix WNL, units for baseline characteristics are stored in separate variables, rather than as part of the label

ADaM Metadata for NCA

Notable New Standard Variables

- Exclusion Flags

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Core	CDISC Notes
NCAXFL	PK NCA Exclusion Flag	Char	Y	Permissible	Flag for exclusion of a record into a PK NCA calculation (Y = exclusion, Null = inclusion)
NCAXFN	PK NCA Exclusion Flag (N)	Num	1	Permissible	Numeric flag for exclusion of a record into a PK NCA calculation (1 = exclusion, Null = inclusion). NCAXFN can only be included if NCAXFL is also included.
NCAwXRS	Reason w for PK NCA Exclusion	Char		Permissible	This variable is used to explain why the record is not included in the PK NCA.
PKSUMXF	PK Summary Exclusion Flag	Char	Y	Permissible	Flag for exclusion of a record from a PK summary (1 = exclusion, Null = inclusion)
PKSUMXFN	PK Summary Exclusion Flag (N)	Num	1	Permissible	Numeric flag for exclusion of a record from a PK summary (1 = exclusion, Null = inclusion). PKSUMXFN can only be included if PKSUMXFL is also included.

ADaM Metadata for NCA

Notable New Standard Variables

- Dosing and Metabolite Variables

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Core	CDISC Notes
METABFL	Metabolite Flag	Char	Y	Conditional	Flag to designate if observations within a subject are associated with a metabolite. Required if parent drug and metabolites are present in the dataset.
DOSPCTDF	Percent Diff. Nominal vs. Actual Dose	Num		Conditional	Derived variable using a standard percent difference formula: (100*(DOSEA-DOSEP)/(DOSEP)). **DOSPCTDF is required if both DOSEA and DOSEP are populated.**
DOSEFRQ	Dose Frequency	Char	(FREQ)	Conditional	Usually expressed as the number of repeated administrations of DOSE within a specific time period for multiple dose studies.
FANLDTM	First Datetime of Dose for Analyte	Num		Permissible	Date and time of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. If treatment is given over a duration multiple times, this variable will reflect the start date and time of the first dose.
FANLEDTM	First End Datetime of Dose for Analyte	Num		Permissible	End date and time of first exposure to treatment associated with PARAM and ANALYTE for a subject in a study where multiple doses have been given. If treatment is given over a duration multiple times, this variable will reflect the end date and time of the first dose.

ADaM Metadata for NCA

Notable New Standard Variables

- Reference Dates for Dose Variables

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Core	CDISC Notes
PCRFTDT	Reference Date of Dose for Analyte	Num		Required	Date of reference exposure to treatment associated with PARAM and ANALYTE. Based on PC.PCRFTDTC and related to the analyzed profile. If this is a treatment over time, then this is typically the start of the dosing duration.
PCRFTTM	Reference Time of Dose for Analyte	Num		Required	Time of reference exposure to treatment associated with PARAM and ANALYTE. Based on PC.PCRFTDTC and related to the analyzed profile. If this is a treatment over time, then this is typically the start of the dosing duration.
PCRFTDTM	Reference Datetime of Dose	Num		Required	Date and time of reference exposure to treatment associated with PARAM and ANALYTE. Based on PC.PCRFTDTC and related to the analyzed profile. If this is a treatment over time, then this is typically the start of the dosing duration.
PCRFEDTM	Ref. End Datetime of Dose for Analyte	Num		Conditional	The end date and time of the reference exposure to treatment associated with PARAM and ANALYTE. Must be related to the time recorded in PC.PCRFTDTC and to the analyzed profile. If dosing occurs over an interval, this should be populated. If populated, ADOSEDUR and DOSEDURU are required to be filled out.
ADOSEDUR	Actual Duration of Treatment Dose	Num		Conditional	Total treatment duration, as measured in units given in DOSEDURU, derived from PCRFEDTM-PCRFTDTM. This record is generally considered to be associated with an infusion dose and is distinct from TRTDURD, TRTDURM, and TRTDURY, which reference the duration of the entire study rather than the duration of a single treatment event.

ADaM Metadata for NCA

Notable New Standard Variables

- Nominal and Actual Elapsed Time from Dose Variables

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Core	CDISC Notes
NRRLT	Nominal Rel. Time from Ref. Dose	Num		Required	This is the planned elapsed time (for sample point or start of sampling interval) from reference exposure to study treatment.
ARRLT	Actual Rel. Time from Ref. Dose	Num		Required	This is the actual elapsed time (for sample point or start of sampling interval) from reference exposure to study treatment.
MRRLT	Modified Rel. Time from Ref. Dose	Num		Permissible	This variable could be used to modify the ARRLT variable based on analysis needs (e.g., setting negative values to zero or having a mix of nominal and actual time based of TMPCTDF).
RRLTU	Rel. Time from Ref. Dose Unit	Char	(PKUNIT)	Required	This is the unit for all elapsed times from reference dose.

ADaM Metadata for NCA

Notable New Standard Variables

- Concentration Results and Units Variables

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Core	CDISC Notes
AVALU	Analysis Value Unit	Char	(PKUNIT)	Required	Unit for AVAL
PCSTRESC	Character Result/Finding in Std Format	Char		Conditional	Character results/findings in a standard format. The purpose of this column is to capture which records are BLQ or LLOQ in the AVAL column. This column must be a direct copy of PC.PCSTRESC.
PCSTRESU	Standard Units	Char	(PKUNIT)	Conditional	Standardized unit associated with AVAL. Units associated with AVAL are needed for clear NCAs. This column must be a direct copy of PC.PCSTRESU.
PCLLOQ	Lower Limit of Quantitation	Num		Conditional	Indicates the lower limit of quantitation for an assay. Must be a direct copy of PC.PCLLOQ.
ALLOQ	Analysis Lower Limit of Quantitation	Num		Conditional	Indicates the lower limit of quantitation for an assay. Use if PC.PCLLOQ does not support analysis needs.

ADaM Metadata for NCA

Standard BDS Variables with stronger 'Core'

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Core	CDISC Notes
DOSEA	Actual Treatment Dose	Num		Required	DOSEA represents the actual treatment dosage associated with the record. This is the actual numeric amount of the dose used for the NCA analysis and may differ from the EX.EXDOSE.
DOSEU	Treatment Dose Units	Char	(UNIT)	Required	The units for DOSEP and DOSEA. It is permissible to use suffixes such as "P" and "A" to record different units for DOSEP and DOSEA, with labels modified accordingly.
AVISIT	Analysis Visit	Char		Required	The analysis visit description; required if an analysis is done by nominal, assigned or analysis visit. AVISIT may contain the visit names as observed (i.e., from SDTM VISIT), derived visit names, time window names, conceptual descriptions (such as Average, Endpoint, etc.), or a combination of any of these. AVISIT is a derived field and does not have to map to VISIT from the SDTM. AVISIT represents the analysis visit of the record, but it does not mean that the record was analyzed. There are often multiple records for the same subject and parameter that have the same value of AVISIT.

ADNCA Example and CDISC Conformance Rules

ADNCA Example

- This example shows concentration data from both plasma and urine samples for one subject, STD1-56-001, on Day 1

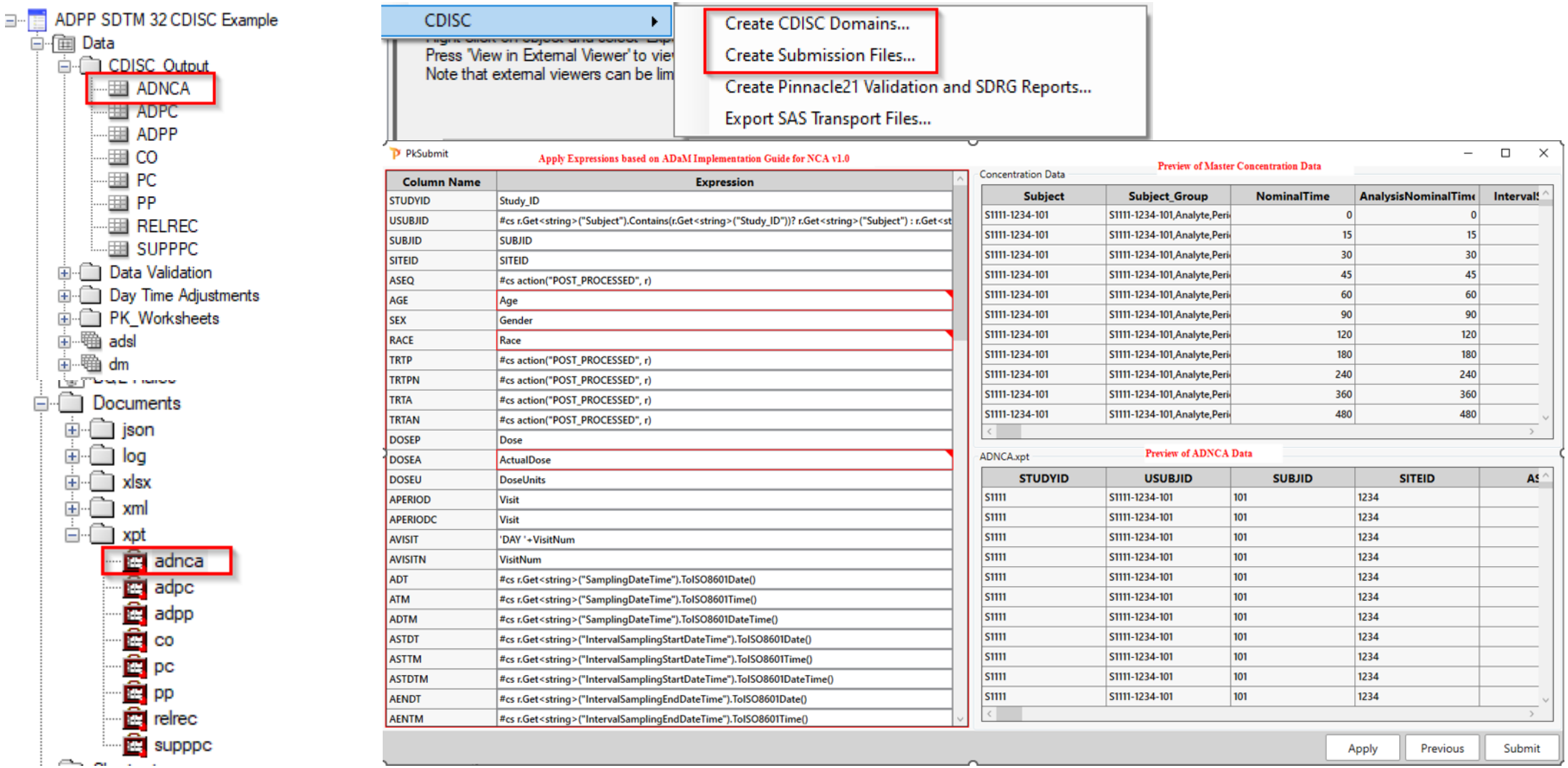
USUBJID	PARAM	PARAMCD	NRRLT	NERRLT	RRLTU	ATPT	AVISIT	PCSPEC	AVAL	PCSTRESU	PCRFTDTM	NCAEXFL	NCAXFN	NCA1XRS
STD1-56-001	Plasma Analyte A (ug/L)	PANALYTA	0		h	Predose	DAY 1	PLASMA	0	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte A (ug/L)	PANALYTA	0.5		h	0.5 H	DAY 1	PLASMA	115	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte A (ug/L)	PANALYTA	2		h	2 H	DAY 1	PLASMA	1320	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte A (ug/L)	PANALYTA	4		h	4 H	DAY 1	PLASMA	1450	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte A (ug/L)	PANALYTA	8		h	8 H	DAY 1	PLASMA		ug/L	2021-12-26T08:00:00	Y	1	Missing AVAL Value
STD1-56-001	Plasma Analyte A (ug/L)	PANALYTA	12		h	12 H	DAY 1	PLASMA	2427	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte A (ug/L)	PANALYTA	24		h	24 H	DAY 1	PLASMA	3621	ug/L	2021-12-26T08:00:00			
STD1-56-001	Urine Analyte A (ug/L)	UANALYTA	-4	0	h	-4 H to Predose	DAY 1	URINE	0	ug/L	2021-12-26T08:00:00			
STD1-56-001	Urine Analyte A (ug/L)	UANALYTA	0	4	h	0 to 4 H	DAY 1	URINE	34.5	ug/L	2021-12-26T08:00:00			
STD1-56-001	Urine Analyte A (ug/L)	UANALYTA	4	8	h	4 to 8 H	DAY 1	URINE	84.2	ug/L	2021-12-26T08:00:00			
STD1-56-001	Urine Analyte A (ug/L)	UANALYTA	8	12	h	8 to 12 H	DAY 1	URINE	65.1	ug/L	2021-12-26T08:00:00			
STD1-56-001	Urine Analyte A (ug/L)	UANALYTA	12	24	h	12 to 24 H	DAY 1	URINE	12.5	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte B (ug/L)	PANALYTB	0		h	Predose	DAY 1	PLASMA	0	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte B (ug/L)	PANALYTB	0.5		h	0.5 H	DAY 1	PLASMA	98.1	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte B (ug/L)	PANALYTB	2		h	2 H	DAY 1	PLASMA	118.3	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte B (ug/L)	PANALYTB	4		h	4 H	DAY 1	PLASMA	120.9	ug/L	2021-12-26T08:00:00			
STD1-56-001	Plasma Analyte B (ug/L)	PANALYTB	8		h	8 H	DAY 1	PLASMA	87.4	ug/L	2021-12-26T08:00:00			

CDISC Conformance Rules for ADNCA

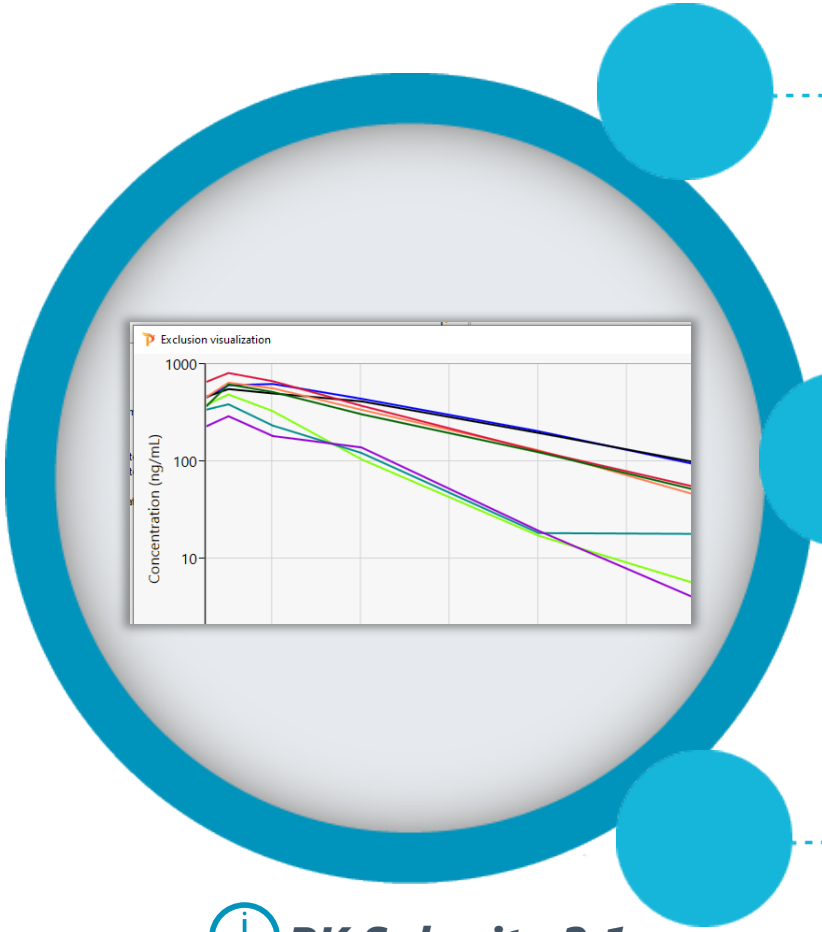
- CDISC conformance rules specific to ADNCA
  - Published in ADaM Conformance Rules v5.0
  - 84 rules under 'NON-COMPARTMENTAL ANALYSIS' subclass
    - Rules to check for presence of 'Required' variables
    - Others check values for flag variables, e.g. Value is not Y or null
    - Rules that check for conditional and paired variables
      - Example: COHORTN is present and COHORT is not present
  - Available in P21 Enterprise engine 2405.0 (released August 2024)

ADNCA Dataset Creation and PK Parameter Results in Phoenix

Creation of CDISC ADNCA dataset



PK Submit Overview



PK Submit v2.1

Generation of ADNCA CDSIC domain

Higher efficiency in NCA through automation

- Single automated workflow
- Automated decisions and recommendations

Intuitive options to simplify the process

- Guided walkthrough of key decisions
- Convenient tools for common actions

Streamline processes in regulatory submissions

- Audit logs to track changes and exceptions
- Integrates with Pinnacle 21 Community

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PK Submit Overview

1

Data Preparation

- Map to Data Model
- Merge Data
- Data Validation Checks

2

Data Modification

- Set Analysis Profiles
- Apply BLQ Rules
- Sample Duplication
- Visual and Conditional Exclusions

3

Finalize PK Data

- AUCtau for Single Dose
- Slope Selector
- Ratios
- Conditional Exclusions

4

CDISC Creation and Validation

- Create PK-Related CDISC Domains, including ADNCA
- Generate Submission Files
- Validate using Pinnacle21 Community

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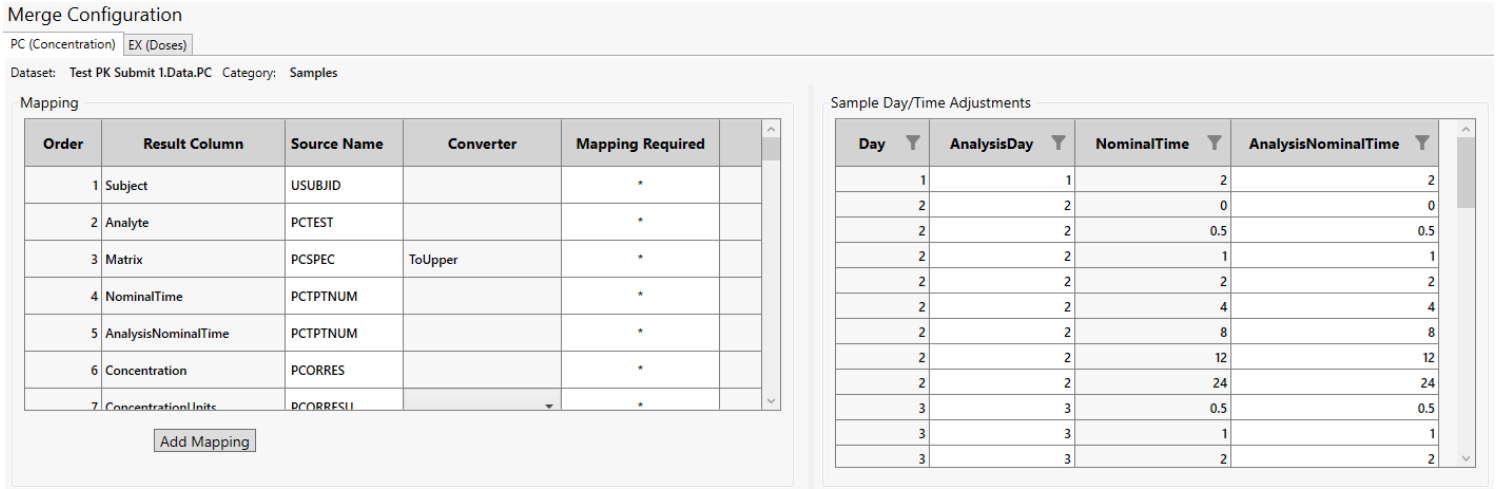
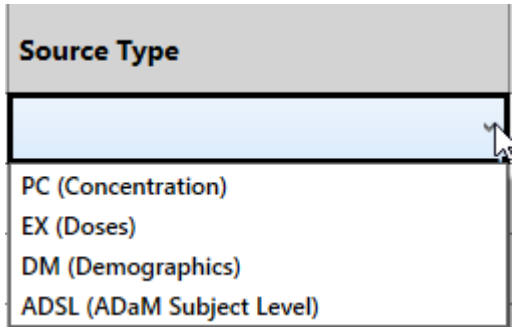
PK Submit: Data Prep Overview

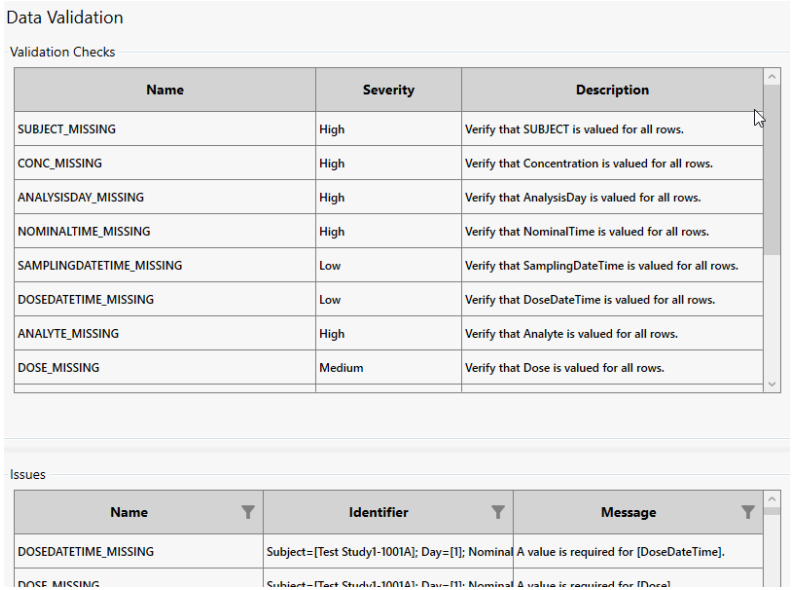
1

Data Preparation

- Map to Data Model
- Merge Data
- Data Validation Checks







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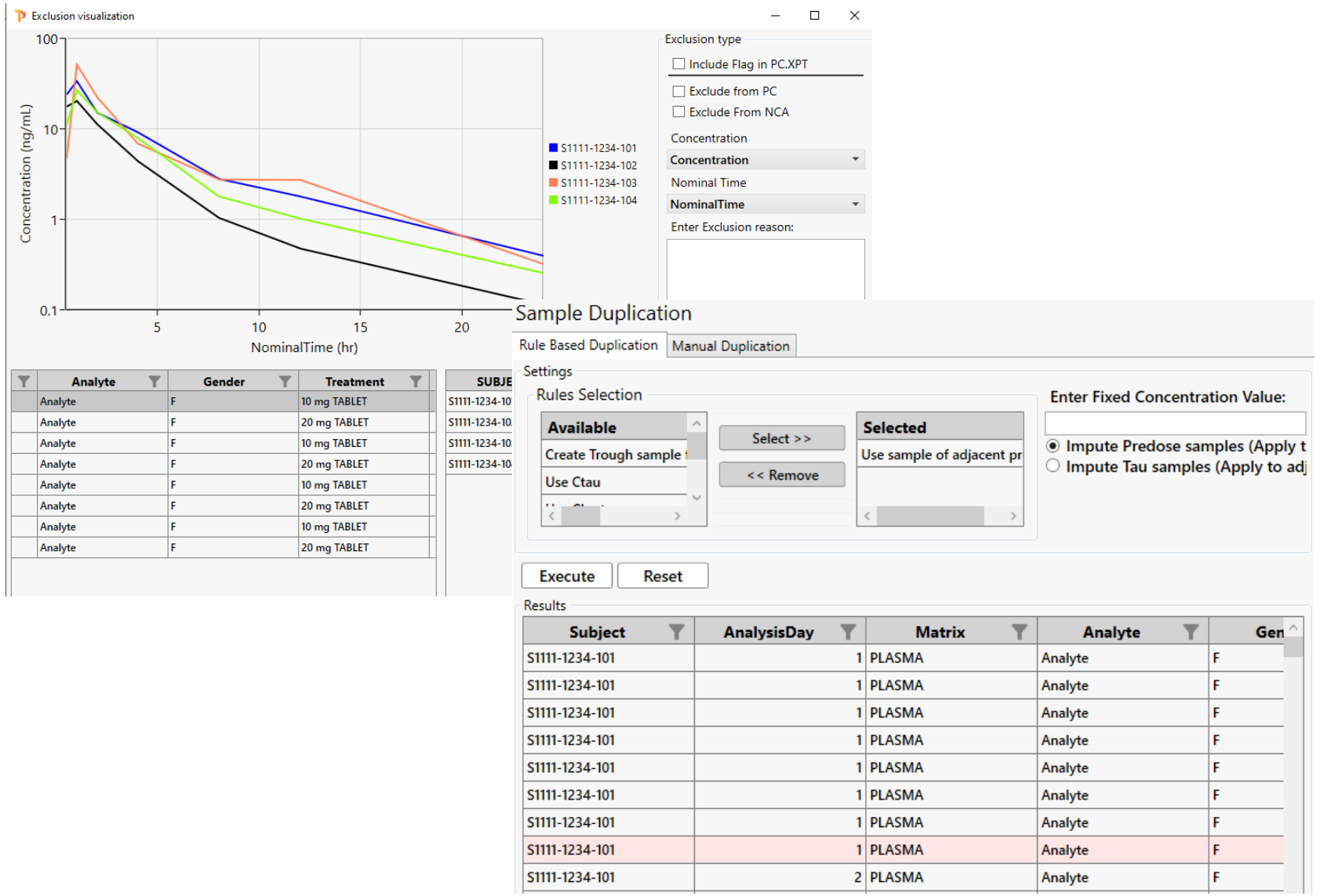
PK Submit: Analysis Overview

2

Data Modification

- Set Analysis Profiles
- Apply BLQ Rules
- Sample Duplication
- Visual and Conditional Exclusions

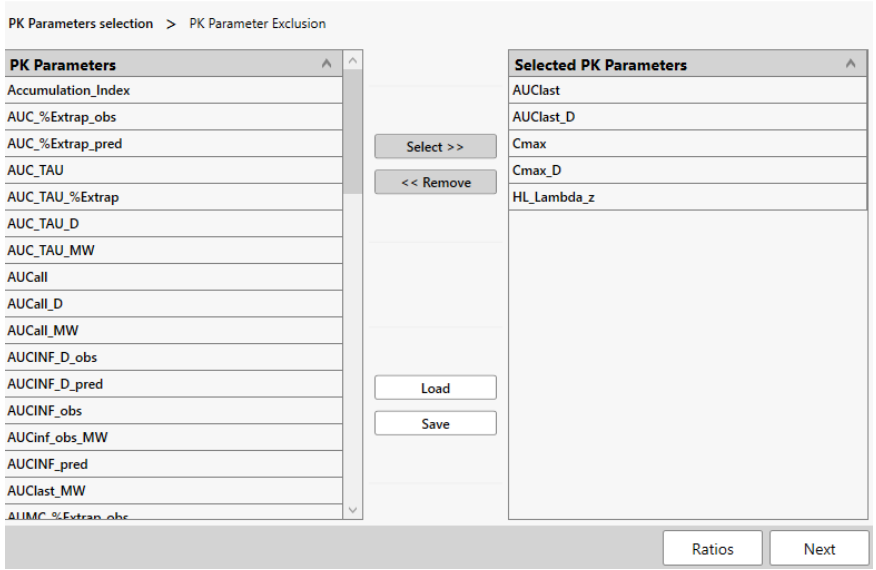


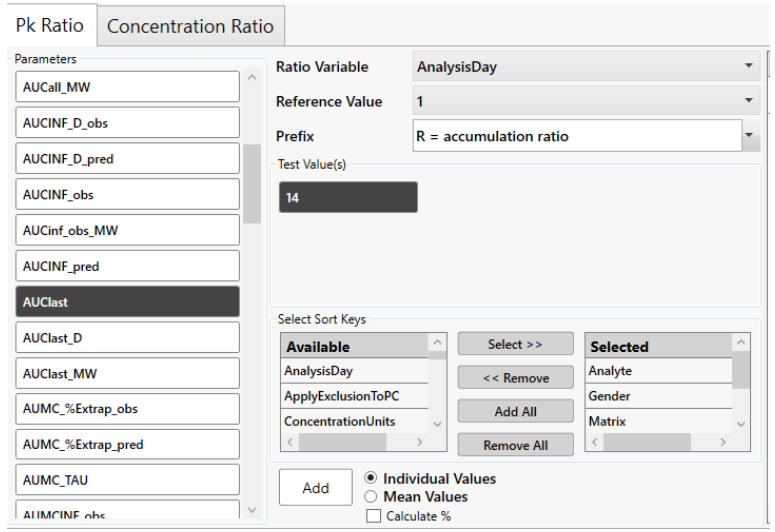
PK Submit: PK Parameters Overview

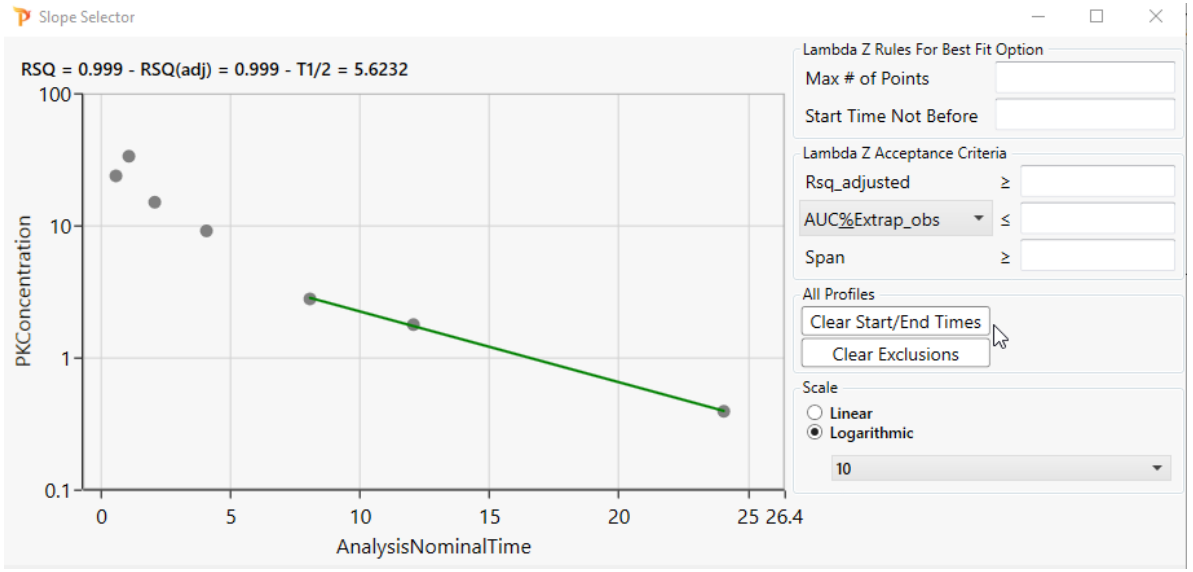
3

Finalize PK Data

- AUCtau for Single Dose
- Slope Selector
- Ratios
- Conditional Exclusions







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PK Submit: CDISC Overview (ADNCA Creation)

4

CDISC Creation and Validation

- Create PK-Related CDISC Domains, including ADNCA
- Generate Submission Files
- Validate using Pinnacle21 Community

CDISC domains and ADaM datasets generated by PK Submit:

- PC
- PP
- CO
- POOLDEF
- RELREC
- SUPPPC
- ADPC
- ADPP
- ADNCA

PkSubmit — Apply Expressions based on ADaM Implementation Guide for NCA v1.0

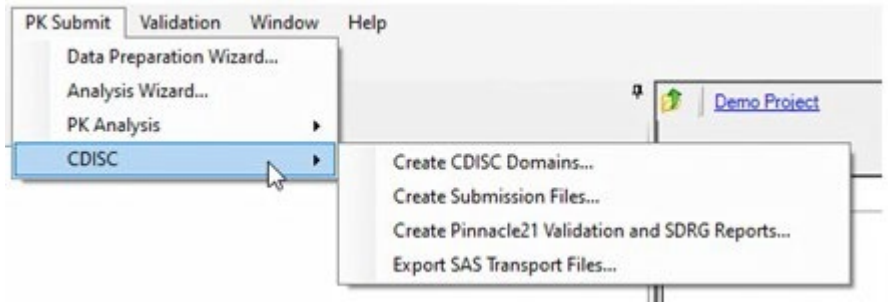
Column Name	Expression
STUDYID	Study_ID
USUBJID	#cs r.Get<string>("Subject").Contains(r.Get<string>("Study_ID"))? r.Get<string>("Subject") : r.Get<st
SUBJID	SUBJID
SITEID	SITEID
ASEQ	#cs action("POST_PROCESSED", r)
AGE	Age
SEX	Gender
RACE	Race
TRTP	#cs action("POST_PROCESSED", r)
TRTPN	#cs action("POST_PROCESSED", r)
TRTA	#cs action("POST_PROCESSED", r)
TRTAN	#cs action("POST_PROCESSED", r)
DOSEP	Dose
DOSEA	ActualDose
DOSEU	DoseUnits
APERIOD	Visit
APERIODC	Visit
AVISIT	'DAY '+VisitNum
AVISITN	VisitNum
ADT	#cs r.Get<string>("SamplingDateTime").ToISO8601Date()
ATM	#cs r.Get<string>("SamplingDateTime").ToISO8601Time()
ADTM	#cs r.Get<string>("SamplingDateTime").ToISO8601DateTime()
ASTDT	#cs r.Get<string>("IntervalSamplingStartDateTime").ToISO8601Date()
ASTTM	#cs r.Get<string>("IntervalSamplingStartDateTime").ToISO8601Time()
ASTDTM	#cs r.Get<string>("IntervalSamplingStartDateTime").ToISO8601DateTime()
AENDT	#cs r.Get<string>("IntervalSamplingEndDateTime").ToISO8601Date()
AENTM	#cs r.Get<string>("IntervalSamplingEndDateTime").ToISO8601Time()

Concentration Data — Preview of Master Concentration Data

Subject	Subject_Group	NominalTime	AnalysisNominalTime	Interval
S1111-1234-101	S1111-1234-101,Analyte,Peri	0	0	
S1111-1234-101	S1111-1234-101,Analyte,Peri	15	15	
S1111-1234-101	S1111-1234-101,Analyte,Peri	30	30	
S1111-1234-101	S1111-1234-101,Analyte,Peri	45	45	
S1111-1234-101	S1111-1234-101,Analyte,Peri	60	60	
S1111-1234-101	S1111-1234-101,Analyte,Peri	90	90	
S1111-1234-101	S1111-1234-101,Analyte,Peri	120	120	
S1111-1234-101	S1111-1234-101,Analyte,Peri	180	180	
S1111-1234-101	S1111-1234-101,Analyte,Peri	240	240	
S1111-1234-101	S1111-1234-101,Analyte,Peri	360	360	
S1111-1234-101	S1111-1234-101,Analyte,Peri	480	480	

ADNCA.xpt — Preview of ADNCA Data

STUDYID	USUBJID	SUBJID	SITEID	AS
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	
S1111	S1111-1234-101	101	1234	



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