

Preparing PK/PD ADaM Datasets and eCRTs Data Package for FDA Submission

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Covered Topics



Introduction



PK/PD ADaM: ADSL and ADPKPD



Define.xml V2 for FDA



PK/PD Tables, Figures, Listings (TFLs)



Analysis Data Reviewer's Guide



Pinnacle 21 Enterprise Validation



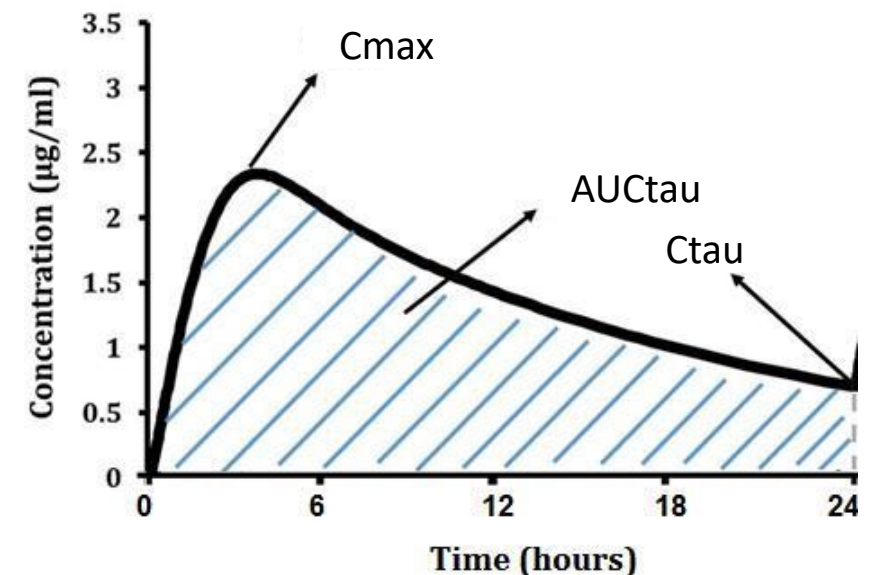
Data Package Folder Structure



Introduction

- The Pharmacokinetics & Pharmacodynamic (PK/PD) analysis studies the relationship between the drug exposure and the efficacy and safety of the drug.
- The PK/PD exposure refers to dose and various measures of integrated drug concentrations in plasma (e.g., AUC_{tau}, C_{max}, C_{tau}).
- Response refers to a direct measure of the pharmacologic effect of the drug, like the efficacy and safety effect of the drug.
- The derived PK/PD datasets (ADSL and ADPKPD) for analysis contain population pharmacokinetics (PopPK) parameters along with safety and efficacy data.

AUC _{tau}	area under the plasma/serum concentration versus time curve over the dosing interval
C _{max}	maximum observed plasma/serum concentration of drug
C _{tau}	observed drug concentration at the end of the dosing interval



Introduction

- Study123 studies the efficacy and safety of Drug A in subjects with ulcerative colitis.
- To assess the pharmacokinetic (PK) characteristics of Drug A is one of the secondary objectives of this Study.
- PK/PD analysis for Drug A and its metabolite will be performed for samples collected from subjects on the active treatment group (Drug A high dose, Drug A low dose).
- The PK parameters, AUCtau, Cmax, and Ctau for Drug A and its metabolite, will be estimated from the Population PK modeling for each subject.
- The PK/PD electronic data package is created according to CDISC standards.



PK/PD ADaM: ADSL and ADPKPD

- PK/PD analysis will have two ADaM datasets: ADSL and ADPKPD.
- ADSL contains variables to support baseline characteristics, PK/PD efficacy endpoints, PK/PD safety endpoints and population PK (PopPK) parameters.
- PopPK parameter variables were generated from NONMEN and copied to PK/PD ADSL.
- PK/PD efficacy and safety variables were created in PK/PD ADSL and copied to ADPKPD.

Active	Dataset	Label	Class	Structure	Input Datasets
Y	ADSL	Subject-Level Analysis Dataset	Subject Level Analysis Dataset	One record per study, per subject	CSR-ES.ADSL, CSR-ES.ADAE, CSR-ES.ADLBCHEM, CSR-ES.ADLBHEMA, CSR-ES.ADEFF, CSR-ES.ADGEBO, NONMEM.POPPK
Y	ADPKPD	Pharmacokinetics/Pharmacodynamics	ADaM Other	One record per study , per subject, per dose group	ADSL

CSR-ES: refers to the clinical study report safety and efficacy analysis we usually do.



ADSL

PK/PD efficacy and safety variables in study were created in PK/PD ADSL and copied to ADPKPD. PK/PD efficacy and safety endpoints were sourced from the clinical study report safety and efficacy ADaM datasets.

- The PK parameters (AUCtau, Cmax, Ctau) are copied from the POPPK data provided by clinical pharmacology.
- Top five Treatment-Emergent (TE) adverse events (e.g., Headache, etc.).
- Efficacy endpoints (e.g., endoscopy/bleeding/stool (EBS) remission, etc.).

	Study Identifier	Unique Subject Identifier	Age	Sex	Race	Safety Population Flag	Full Analysis Set Population Flag	Planned Treatment for Period 01	Actual Treatment for Period 01	PK/PD Analysis Set Flag
▶ 1	Study123	Study123-12345-10000	55	F	BLACK	Y	Y	Drug A low dose	Drug A low dose	Y
2	Study123	Study123-12345-10001	60	F	WHITE	Y	Y	Drug A low dose	Drug A low dose	Y
3	Study123	Study123-12345-10002	45	F	ASIAN	Y	Y	Drug A high dose	Drug A high dose	Y
4	Study123	Study123-12345-10003	30	M	WHITE	Y	Y	Drug A low dose	Drug A low dose	Y

Drug A AUCtau (h*ng/mL)	Drug A Cmax (ng/mL)	Drug A Ctau (ng/mL)	Metabolite AUCtau (h*ng/mL)	Metabolite Cmax (ng/mL)	Metabolite Ctau (ng/mL)	Nasopharyngitis (Y/N)	Headache (Y/N)	EBS Remission	MCS Remission
1500	500	3	36000	1900	1000	N	N	N	N
1750	370	2	30000	1600	700	N	N	N	N
6000	2200	7	65000	3200	1400	Y	N	N	N
1950	360	5	30000	1500	900	N	N	N	N



ADPKPD

- In ADPKPD, we mainly create the DOSEGRP, ATAUF_S (Drug A AUCtau Subgroups), etc.
- All the PK/PD analyses will be performed on the following 3 populations:
 - *Population 1: All subjects who received Drug A (dosegrp='All Doses')*
 - *Population 2: Only subjects who received Drug A high dose per day (dosegrp='Drug A high dose');*
 - *Population 3: Only subjects who received Drug A low dose per day (dosegrp='Drug A low dose');*
- Population 1 (ie, pooled Drug A high and low dose), subjects will be categorized into 8 octiles based on the distribution of all subjects' PK exposures (atauf_s has value 1,2,...,8).
- Population 2 (ie, Drug A high dose), subjects will be categorized into 4 quartiles based on the distribution of the PK exposures of the subjects who received Drug A high dose(atauf_s has value 1,2,3,4).
- Population 3 (ie, Drug A low dose), subjects will be categorized into 4 quartiles based on the distribution of the PK exposures of the subjects who received Drug A low dose(atauf_s has value 1,2,3,4).



	Study Identifier	Unique Subject Identifier	PK/PD Analysis Set Flag	Drug A AUCtau (h*ng/mL)	Drug A Cmax (ng/mL)	Drug A Ctau (ng/mL)	Metabolite AUCtau (h*ng/mL)	Metabolite Cmax (ng/mL)	Metabolite Ctau (ng/mL)	Nasopharyngitis (Y/N)
▶ 1	Study123	Study123-12345-10000	Y	1500	500	3	36000	1900	1000	N
2	Study123	Study123-12345-10000	Y	1500	500	3	36000	1900	1000	N
3	Study123	Study123-12345-10001	Y	1750	370	2	30000	1600	700	N
4	Study123	Study123-12345-10001	Y	1750	370	2	30000	1600	700	N
5	Study123	Study123-12345-10002	Y	6000	2200	7	65000	3200	1400	Y
6	Study123	Study123-12345-10002	Y	6000	2200	7	65000	3200	1400	Y
7	Study123	Study123-12345-10003	Y	1950	360	5	30000	1500	900	N
8	Study123	Study123-12345-10003	Y	1950	360	5	30000	1500	900	N

EBS Remission is one efficacy endpoint defined in SAP.

Drug A AUCtau of this subject is in the 4th octile of all PK population

Headache (Y/N) is one safety endpoint of adverse event.

Headache (Y/N)	EBS Remission	MCS Remission	Dose Group	Drug A AUCtau Subgroup	Drug A Cmax Subgroup	Drug A Ctau Subgroup	Metabolite AUCtau Subgroup	Metabolite Cmax Subgroup	Metabolite Ctau Subgroup
N	N	N	All Doses	4	4	3	5	5	4
N	N	N	Drug A low dose	1	1	1	1	1	1
N	N	N	All Doses	8	8	8	8	8	8
N	N	N	Drug A low dose	4	4	4	4	4	4
N	N	N	All Doses	4	5	4	4	4	4
N	N	N	Drug A high dose	1	1	1	1	1	1
N	N	N	All Doses	7	7	5	6	7	6
N	N	N	Drug A low dose	3	3	2	2	3	2

Define.xml v2 FDA

ADaM-IG 1.1

- Reviewers Guide

▶ Analysis Datasets

▶ Controlled Terminology

▶ Analysis Derivations

▶ Comments

Date of Define-XML document generation: 2020-08-04T11:02:24Z

Define-XML version: 2.0.0

Stylesheet version: 2016-07-08

Standard	ADaM-IG 1.1
Study Name	Study123
Study Description	Phase 2 Study to Evaluate the Efficacy and Safety of Drug A in Subjects with Active Ulcerative Colitis
Protocol Name	Study123
Metadata Name	Study123 Data Definitions
Metadata Description	Phase 2 Study to Evaluate the Efficacy and Safety of Drug A in Subjects with Active Ulcerative Colitis

Analysis Datasets for Study Study123 (ADaM-IG 1.1)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
ADSL	Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET	One record per study, per subject	Analysis	STUDYID, USUBJID	adsl.xpt	Analysis Reviewers Guide [page=13]
ADPKPD	Pharmacokinetics/Pharmacodynamics	ADAM OTHER	One record per study, per subject, per dose group	Analysis	STUDYID, USUBJID, DOSEGRP	adpkpd.xpt	Analysis Reviewers Guide [page=14]

Go to the [top](#) of the Define-XML document

ADSL (Subject-Level Analysis Dataset) - SUBJECT LEVEL ANALYSIS DATASET

[Location: [adsl.xpt](#)]

Variable	Label	Key	Type	Length or Display Format	Controlled Terms or Format	Source / Derivation / Comment
STUDYID	Study Identifier	1	text	14		Predecessor: CSR-ES.ADSL.STUDYID
USUBJID	Unique Subject Identifier	2	text	26		Predecessor: CSR-ES.ADSL.USUBJID



PK/PD Tables, Figures, Listings (TFLs)

Some examples of the **efficacy** tables are below.

- 1) Summary Statistics of AUCtau by Octile Subgroups for population 1 and Quartile Subgroups for population 2 & 3.
- 2) Proportion of Subjects Achieving MCS Remission by AUCtau Octile Subgroup for Population 1 and Quartile Subgroup for population 2 & 3.
- 3) Comparison of AUCtau by with or without Achieving MCS Remission

Some examples of the **safety** tables are below.

- 1) Proportion of Subjects with Selected Treatment-Emergent Adverse Event (TEAE) by AUCtau or Cmax Octile Subgroups for population 1
- 2) Proportion of Subjects with Selected TEAE by AUCtau or Cmax Quartile Subgroups for population 2 & 3
- 3) Proportion of Subjects with Selected Grade 3 or 4 TE Lab Abnormalities by AUCtau or Cmax Octile Subgroups
- 4) Summary Statistics of AUCtau or Cmax by Selected Grade 3 or 4 TE Lab Abnormalities



Analysis Data Reviewer's Guide (ADRG)

ADRG is a required piece for the ADaM electronic data package. The PK/PD ADRG is created following the PHUSE ADRG template. Since different source datasets were used to create the PK/PD ADaM datasets, ADRG **Section 1.4 Source Data Used for Analysis Dataset Creation** explains in detail how we created the PK/PD ADSL and ADPKPD from the source NONMEM.POPPK and CSR efficacy and safety ADaM datasets. For FDA submission, the ADRG is saved as adrg.pdf.

The ADRG in .pdf format should satisfy certain pdf properties according to the Portable Document Format (PDF) Specifications from the FDA (September 2016 v4.1). For example, File Options of Compatibility is selected to 'Acrobat 5.0 (PDF 1.4)' and File Option of Optimize for fast web view is checked.



Comparison between CSR Safety and Efficacy ADRG and PK/PD ADRG Section 1.3

Left: CSR Safety and Efficacy ADRG

Right: PK/PD ADRG

CSR-ES ADRG 1.3

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
ADaM	2.1
ADaM IG	1.1
SDTM	1.4
SDTM IG	3.2
Controlled Terminology	NCI SDTM 2018-12-21, NCI ADaM 2018-12-21
Data Definitions	Define 2.0.0
Medications Dictionary	WHODrug BMAR19
Medical Events Dictionary	MedDRA 22.1
Toxicity Grading Dictionary	CTCAE v4.03
Other	ADaM Structure for Occurrence Data (OCCDS) Version 1.0

PK/PD ADRG 1.3

Standard or Dictionary	Versions Used
<u>ADaM</u>	2.1
<u>ADaM IG</u>	1.1
SDTM	1.4
SDTM IG	3.2
Controlled Terminology	NCISDTM 2018-12-21, <u>NCIADaM</u> 2018-12-21
Data Definitions	Define 2.0.0
Medications Dictionary	<u>WHODrug</u> BMAR19
Medical Events Dictionary	MedDRA 22.1
Toxicity Grading Dictionary	CTCAE v4.03



Analysis Data Reviewer's Guide

In analysis data reviewer's guide section 5.2 Analysis Dataset, the below table specifies the functional categories for each analysis dataset.

- PK/PD ADSL: Demographic and baseline characters, efficacy and safety endpoints.
- PK/PD ADPKPD: Efficacy, safety endpoints from PK/PD ADSL, PK/PD related analysis variables.

<u>Dataset</u> Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
<u>ADSL</u> Subject-Level Analysis Dataset	Subject Level Analysis Dataset	X	X	X			One record per study, per subject
<u>ADPKPD</u> Pharmacokinetics/ Pharmacodynamics	ADaM Other	X	X		X		One record per study, per subject, per dose group



Pinnacle 21 Enterprise Validation

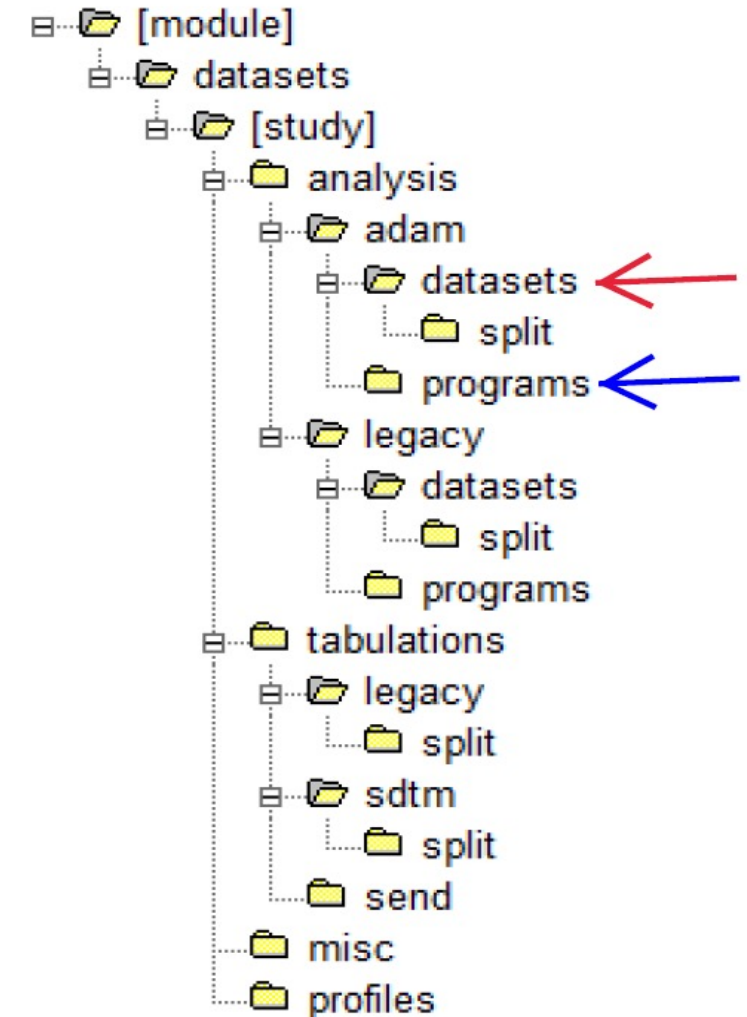
Pinnacle 21 Enterprise (P21E) is used to validate the PK/PD ADaM data package. Except for the PopPK parameters, the variables derived in the PK/PD ADaM datasets use information from the clinical study report safety and efficacy ADaM datasets, so the Standard, SDTM CT, ADaM CT, MedDRA and validation engine will be the same as the CSR.ES ADaMIG package. For PK/PD, the P21E ADaMIG package is like below.

Name ↕	Standard ↕	SDTM CT ↕	ADAM CT ↕	SEND CT ↕	MedDRA ↕	WHODD ↕	LOINC ↕	SNOMED ↕	Compatibility ↕	Last Updated ▾
ADaMIG	ADaM-IG 1.1	2018-12-21	2018-12-21		22.1				FDA 2010.1	2021-04-14 07:55:34



PK/PD Data Package Folder Structure

- PK/PD data package was submitted as a separate study under the module 5/datasets eCTD folder.
- PK/PD ADaM datasets, adrg.pdf, define.xml and the stylesheet define2-0-0.xsl are put in the **/datasets** folder .
- All SAS programs for analysis datasets and safety and efficacy summary tables and figures are put in the **/programs** folder.



module5\datasets\pkpd\analysis\adam\datasets

- PK/PD ADaM datasets in xpt format (adsl.xpt, adpkpd.xpt)
- Analysis Data Reviewer's Guide (adrg.pdf)
- define.xml and the stylesheet define2-0-0.xsl

› module5 › datasets › pkpd › analysis › adam › datasets

Name	Date modified	Type	Size
 adpkpd.xpt	7/22/2020 3:28 PM	SAS Xport Transpo...	1,731 KB
 adrg.pdf	3/16/2021 8:15 AM	Adobe Acrobat D...	626 KB
 adsl.xpt	7/22/2020 3:28 PM	SAS Xport Transpo...	1,153 KB
 define.xml	8/4/2020 11:02 AM	XML Document	183 KB
 define2-0-0.xsl	8/4/2020 11:02 AM	XSL Stylesheet	155 KB



module5\datasets\pkpd\analysis\adam\programs

Format: .txt files for all programs, included init.txt.

- 2 ADaM programs (a-adsl.txt, a-adpkpd.txt)
- 1 format program: taskfmt.txt
- 1 init.txt
- 1 local macro: summary.txt
- 26 table and figure programs in .txt format

module5 > datasets > pkpd > analysis > adam > programs				
Name	Date modified	Type	Size	
a-adpkpd.txt	7/22/2020 3:23 PM	Text Document	9 KB	
a-adsl.txt	7/22/2020 3:23 PM	Text Document	31 KB	
g-aelab-pk.txt	7/22/2020 3:23 PM	Text Document	16 KB	
g-aelab-pk-dose.txt	7/22/2020 3:23 PM	Text Document	18 KB	
g-eff-i.txt	7/22/2020 3:23 PM	Text Document	12 KB	
g-eff-i-dose.txt	7/22/2020 3:23 PM	Text Document	13 KB	
g-eff-m.txt	7/22/2020 3:23 PM	Text Document	12 KB	
g-eff-m-dose.txt	7/22/2020 3:23 PM	Text Document	12 KB	
g-pkcomp-eff-i.txt	7/22/2020 3:23 PM	Text Document	9 KB	
g-pkcomp-eff-m.txt	7/22/2020 3:23 PM	Text Document	6 KB	
g-pksum-aelab.txt	7/22/2020 3:23 PM	Text Document	12 KB	
g-pksum-aeoi.txt	7/22/2020 3:23 PM	Text Document	10 KB	
g-pksum-saedeath.txt	7/22/2020 3:23 PM	Text Document	8 KB	
init.txt	7/22/2020 3:23 PM	Text Document	9 KB	
summary.txt	7/22/2020 3:23 PM	Text Document	2 KB	
t-aelab-pk.txt	7/22/2020 3:23 PM	Text Document	18 KB	
t-aelab-pk-i-dose.txt	7/22/2020 3:23 PM	Text Document	18 KB	
t-aelab-pk-m-dose.txt	7/22/2020 3:23 PM	Text Document	17 KB	
taskfmt.txt	7/22/2020 3:23 PM	Text Document	5 KB	

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**Thank you
for your
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