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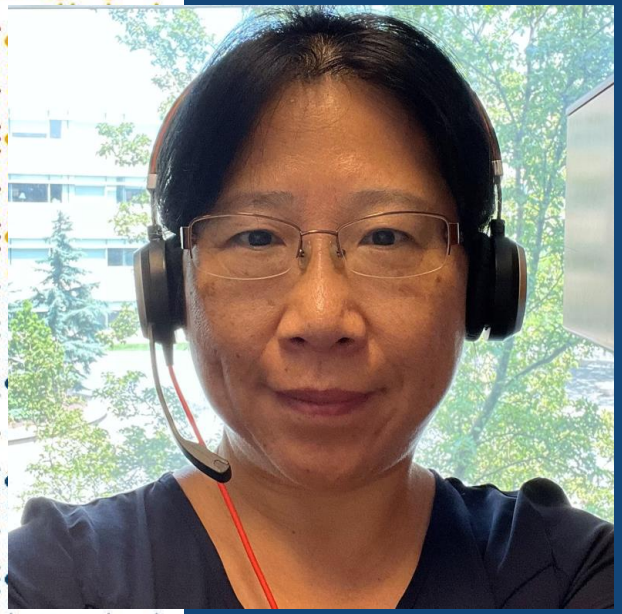
ADaM implementation of Anti-drug Antibody (ADA) Analysis Dataset

CDISC ADaM ADA Sub Team

Presented by Jiannan (Jane) Kang



Meet the Speaker

Jiannan (Jane) Kang

Title: Prin. Scientist

Organization: Merck & Co., Inc., Rahway, NJ USA

Jiannan (Jane) Kang co-leads CDISC ADaM ADA sub team since Aug 2022. Jane earned MS in Computer Science in Towson University and MD in Bio-Medical Engineering from Shanghai Medical College. She gained 19+ years programming experiences in safety, efficacy, and immunogenicity analysis in multiple TA studies at Merck. In recent 8 years, her focus is supporting PK and ADA analysis and reporting.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *We have included examples with recommended terminologies. It may / may-NOT become controlled terminologies. Keep in mind that they called in a certain way shown in the presentation for illustration purpose and for easy discussion.*

ADaM implementation of Anti-drug Antibody (ADA) Analysis Dataset

Agenda

1. Introduction of ADaM ADA Sub Team
2. Introduction to ADA and Immunogenicity Analysis Process
3. Our proposal for standardization
4. Open for comments

Meet the Team

ADaM ADA Sub Team

CDISC ADaM Full Team lead: Brian Harris

Sub Team Leads: David B Radtke (Lilly),
Jiannan (Jane) Kang (Merck)

Facilitator: Alana St. Clair

Members: Diana Montgomery (Merck), Yanchen Zhou (Amgen), Shweta Vadhavkar (Genentech), Xiaohan Zou (BMS), Xiaobin Li (GSK), Luke Reinbolt & Kevin Viel (Navitas Lifesciences), Qing Yu (Amgen), Ranvir Singh (Labcorp)

ADA and Immunogenicity Analysis Process

- Introduction of Immunogenicity
- Overview of ADA Assessment
- Key Data Points for Analysis and Reporting
- Terminology

Introduction of Immunogenicity

- Immune response: recognize/eliminate non-self or harmful substance (Figure 1)
- Immunogenicity: capability to activate immune system and induce an immune response
- Antibody: A class of primary products (Y-shaped glycoprotein) generated by immune system in response to antigens or drugs (Figure 2)
- Anti-drug Antibody formation (Figure 3)
  - Biotherapeutic peptides present as T cell epitopes on MHC (Major histocompatibility complexes) II on an APC (Antigen presenting cells: such as B cell or Dendritic Cell)
  - Recognized by CD4+ helper T cells, result in T cells activation/proliferation and cytokine release
  - Activated T cell interacted with B cells, results in the development of plasma cells secreting high affinity antibodies (Anti Drug Antibodies)

Figure 1

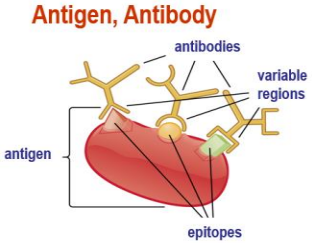


Figure 2

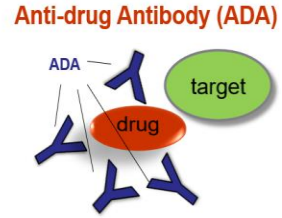
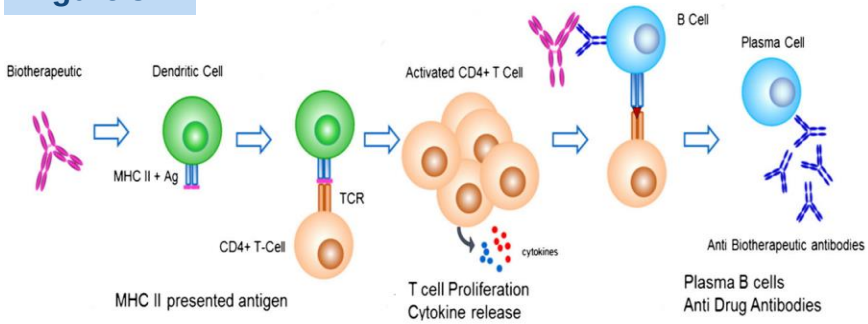


Figure 3



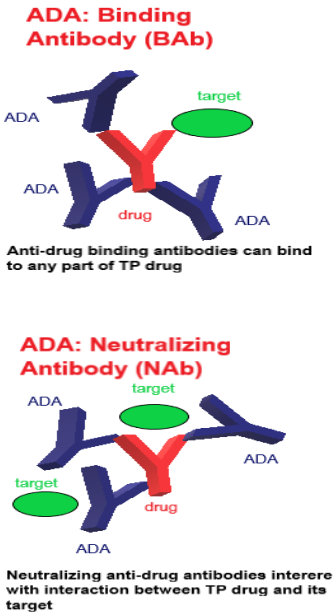
Immunogenicity Analysis in Drug Development

- BAb (Binding Antibody, referred to as ADA) and NAb (Neutralizing Antibody) (Figure 4)

  NAb is a subgroup of BAb: Not only binding the drug, but also may interfere with interaction between drug and its target

- Factors contributing to immunogenicity
  - Drug related factors: Product origin, structure / posttranslational modifications, drug MOA (Mechanics of Action), impurities with adjuvant activity, formulation, etc.
  - Patient related factors: Disease population, prior sensitization/history of allergy, route of administration, dose and frequency of administration, genetic status, immune tolerance status, duration of therapy, etc.
- Immune responses to therapeutic protein products have the potential to affect:
  - Safety (Neutralize activity with unique function causing deficiency syndrome; hypersensitivity reactions)
  - PK (ADA can affect PK exposure level)
  - Efficacy (Affecting efficacy by changing half life or changing biodistribution)
  - None: Despite generation of antibodies, no discernable impact

Figure 4



Multi-tier ADA Assessments

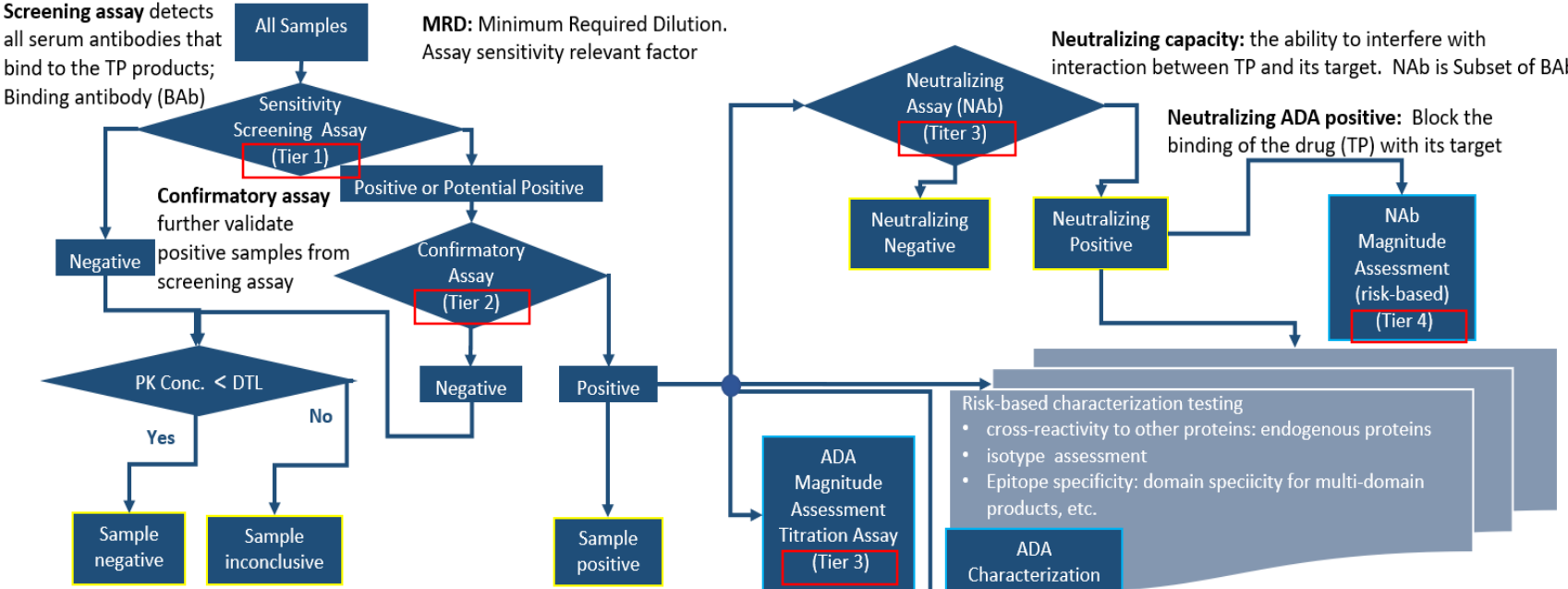


Figure 5

Key Data Points for Immunogenicity Analysis and Reporting

- ADA summary table
  - ADA Subject level status
    - ADA only, NAb only, combined, Persistent/transient ADA (ADA duration), Boosted/Induced/Emergent
    - Overall or summarized at planned visit/time point, or at baseline, on treatment
  - For subject with positive ADA
    - NAB subject level status
    - Maximum Post-treatment Titer / SN (usually in figure)
  - ADA sample
    - Sample level status (ADA /SN level)
    - ADA sampling condition: summary of PK concentration vs DTL
  - Time to ADA onset
  - Population: Exclusion, Evaluable, Treated

  Note: By study, by indication, by dosage level

- ADA listing table
  - Raw assay result, sample status, dose, drug concentration
  - Treatment, Subject identifier, visit, study day, nominal / actual time relative to reference dose or to the first dose
  - Subject level status (ADA only, NAB only, or combined), Maximum titer/SN for ADA positive ADA

Key Data Points for Immunogenicity Analysis and Reporting – cont.

- ADA impact on PK
  - Individual PK profile by ADA
  - Mean of post-BL trough PK by ADA
  - Trough PK by ADA + maximum SN level
  - Statistical summary of trough PK at ADA sampling timepoint
  - Others driven by PK analysis: AUC, CL, Cmax, post hoc estimate by ADA; As covariates in PopPK analysis
- ADA impact on efficacy
  - Efficacy endpoint (e.g. change from baseline overtime) by ADA subject level status
  - Additional definition of ADA status (e. g. combining ADA status and category of Titer/SN)
    - Binning subjects in some categories, Quartile of titers, group subjects
    - Exploratory work to describe type of subjects
- ADA impact on safety
  - AE of interest by ADA subject status

Terminology

- Anti-drug antibody (ADA)
- Neutralizing ADA (NAb)
- Non-neutralizing ADA
- Binding ADA
- Pre-existing ADA
- Treatment-induced ADA
- Treatment-boosted ADA
- ADA prevalence
- ADA incidence
- ADA Titer (Titer)
- ADA positive (sample)
- ADA negative (sample)
- ADA inconclusive (sample)
- Drug tolerance level
- ADA positive (subject)
- ADA negative (subject)
- ADA inconclusive (subject)
- Persistent ADA
- Transient ADA

<See appendix for detailed definition>

Our proposal for standardization

- New sub-class ADADA along with basic conformance rules

Structure of analysis dataset in industry

Two different varieties observed

Depending on company standards/approach,

- SDTM(IS) and Analysis dataset vary structure-wise to be in vertical or horizontal format.
- May include individual sample results [including screening , confirmatory, tittering, neutralizing, characterizing assay results] or only subject level ADA results.
- May include other types of data necessary for analysis/modeling e.g. PK concentration data or safety/efficacy endpoints.
- Different analysis related variables are either included as Variables or Parameters or Flag Variables.

Figure 6

Vertical Format – BDS

USUBJID	PARCAT	PARAMCD	PARAM	AVALC
705-1085	Anti-RO1234567 Antibody	R1234567	Anti-RO1234567 Antibody	2.14
705-1085	Anti-RO1234567 Antibody	R1234567	Anti-RO1234567 Antibody	NEGATIVE SCREEN
705-1085	Anti-RO1234567 Antibody	R1234567	Anti-RO1234567 Antibody	NEGATIVE SCREEN
705-1085	Anti-RO1234567 Antibody	R1234567	Anti-RO1234567 Antibody	NEGATIVE SCREEN
705-1085	Anti-RO1234567 Antibody	RESULT	AD interpreted per sample result	Positive
705-1085	Anti-RO1234567 Antibody	RESULT	AD interpreted per sample result	Negative
705-1085	Anti-RO1234567 Antibody	RESULT	AD interpreted per sample result	Negative
705-1085	Anti-RO1234567 Antibody	RESULT	AD interpreted per sample result	Negative
705-1085	Anti-RO1234567 Antibody	BFLAG	Baseline (Positive/Negative/Missing)	Negative
705-1085	Anti-RO1234567 Antibody	INDUCADA	Treatment induced ADA(Y/N)	
705-1085	Anti-RO1234567 Antibody	ENHANADA	Treatment enhanced ADA(Y/N)	
705-1085	Anti-RO1234567 Antibody	EMERGPOS	Treatment Emergent - Positive(Y/N)	
705-1085	Anti-RO1234567 Antibody	ADASTAT	ADA Status of a patient(Positive/Negative/Missing)	Negative
705-1085	Anti-RO1234567 Antibody	TRTUNAFF	Treatment unaffected(Y/N)	
705-1085	Anti-RO1234567 Antibody	EMERGNEG	Treatment Emergent - Negative (Y/N)	
705-1085	Anti-RO1234567 Antibody	NOTRTREL	No treatment related ADA(Y/N)	
705-1085	Anti-RO1234567 Antibody	TIMADA	Time to onset of ADA(Weeks)	
705-1085	Anti-RO1234567 Antibody	PERSADA	Persistent ADA	
705-1085	Anti-RO1234567 Antibody	TRANSADA	Transient ADA	
705-1085	Anti-RO1234567 Neutralizing Antibody	R1234568	Anti-RO1234567 Neutralizing Antibody	NEGATIVE
705-1085	Anti-RO1234567 Neutralizing Antibody	NABSTAT	NAB Status of a patient(Positive/Negative/Missing)	Negative

Horizontal Format – non-BDS

USUBJID	AVISIT	ISREFID	ATPT	ATPTN	ISDTC	LDSDTM	NOMTAFL	FARELTM	LARELTM	CONC	DTL	EXDTLFL	ADAEVLFL	LSTADAFL
ABC-1001	cycle 1 day 1	ABCD 01	PREDOSE	1	2016-10-05T15:20	2016-10-05T15:50	0	0	0	0	10000	N	Y	
ABC-1001	cycle 2 day 1	ABCD 18	PREDOSE	1	2016-10-25T11:20	2016-10-25T11:50	21	21.05	21.08	7400	10000	N	Y	
ABC-1001	off-treatment	ABCD 20			2016-12-29T09:25	2016-10-25T11:50	126	126.21	104.26	5400	10000	N	Y	Y

SCRRSLT	CNRRSLT	TITER	TITERN	ADASAMPL	TITERBL	TITERMXN	NABSUBJ	PREPOSFL	PSTPOSFL	ADASUBJ	ADASBTE	ADACAT
NEGATIVE				NEGATIVE		0.5	NEGATIVE	N	Y	ONLY POST DOSE POSITIVE	TREATMENT EMERGENT POSITIVE	TE NAB NEG
POSITIVE	POSITIVE	<1	0.5	POSITIVE		0.5	NEGATIVE	N	Y	ONLY POST DOSE POSITIVE	TREATMENT EMERGENT POSITIVE	TE NAB NEG
NEGATIVE				NEGATIVE		0.5	NEGATIVE	N	Y	ONLY POST DOSE POSITIVE	TREATMENT EMERGENT POSITIVE	TE NAB NEG

New BDS sub-class ADADA

- A BDS-like structure is needed to support proper analysis of ADA
- ADADA will require additional variables / analysis parameters
  - Multiple specific nominal and actual timing variables
    - Relative to first dose, Relative to most recent Dose
  - Assay attributes
  - Maximum change in ADA magnitude for ADA positive subjects
  - PK concentration at ADA sampling time
- The ADADA document will acknowledge BDS and focus on what new pieces need to be added
- A similar approach was used for ADNCA and ADPPK

New BDS sub-class ADADA

PARQUAL

PARCATx | PARAM | PARAMCD

Figure 7

Comb-Therapy	Category of ADA Data	Sub-category of ADA Data (Evaluation and Interpretation)
Drug X	Primary Assay results	ADA screening, confirmatory, titer, SN, NAB screening, NAB, confirmatory, domain A ADA, domain B ADA,
Drug Y	Sample Interpretation	ADA status, NAB status
	Subject Summary	ADA status, NAB status, Combined BAb and NAb status, Baseline ADA, Post BL/Post Treatment ADA, Treatment emergent, Maximum Titer/SN, Change of Titer/SN, Persistent, Transient, Duration, Time to ADA onset
	ADA Assay Attribute	*Drug Tolerance Level, Minimum Required Dilution, Lab Identification*

Additional variables:

1. *Actual/nominal time to first dose, actual/nominal time to reference dose,*
2. *Is subject evaluable? Is the sample the last valid? PK concentration at ADA sampling.*
3. *Subject level flags*
4. *Other SDTM variables*

Key data points -

- SDTM variables:
  - ISDTC, ISREFID, ISMETHOD, ISSPEC, PCREFID, ISNAM, ISSTRESC, etc.
- **ADA – Assay Attributes (Constant values)**
  - PARAM or Variables: DTL, MRD, ISNAM
- **ADA – Primary/Collected Results**
  - PARAM
  - Variables (PK concentration – can be either variables or in PARAM)
- **ADA – Sample level Interpretation and Flag**
  - PARAM
  - Variables (flags: Last valid ADA, Whether has corresponding PK)
- **ADA – Subject level Summary and Flag**
  - PARAM
  - Variables (flags: Evaluable subject? Other population flags from ADSL, ADA status flag as need)

Assay Attributes

- DTL: Assay Drug Tolerance Level
  - Drug concentrations > DTL present in samples may interfere with ADA assay
  - The assay DTL is determined during assay validation testing in different combinations of drug and ADA positive control
  - In ADaM data set, one way to describe this is to consider a sample result inconclusive if the sample has a [drug] > DTL
  - It is important that the units of the DTL are the same as that of the drug concentration
- MRD: Minimum Required Dilution
  - Assay performance property; Assay sensitivity relevant factor; For example: samples must be diluted at least 1:4
- Assay Lab Identification
  - Name of lab providing data; In some case, the DTL can be different at different labs
  - Identification is needed if have data from more than one lab

Assay Attributes:
Option 1 (Figure 8) in PARAM
Option 2 (Figure 9) as variables

Figure 8

PARQUAL	PARCAT1	PARAMCD	PARAM	AVAL	AVALC
Drug X	Assay Attributes	DTL	Drug Tolerance Level	2000	2000
Drug X	Assay Attributes	ISNAM	Assay Lab Name		LABabc
Drug X	Assay Attributes	MRD	Minimum Required Dilution	4	4

Figure 9

PARQUAL	PARCAT1	PARAMCD	PARAM	DTL	MRD	ISNAM	AVAL	AVALC
Drug X	Collection			2000	4	LABabc		
Drug X	Sample Interpretation							
Drug X	Subject Summary							

Primary/collected Results

- ADA – Sample Primary/collected Results
  - Screening
  - Confirmatory
  - Titer
  - SN
  - NAB
  - Domain level ADA, NAB
- Others
  - PK concentration at ADA sampling

Primary/Collected Assay Results in PARAM (Figure 10)

Utilize BDS variables to derive BASE, CHG in ADA Titer/SN;

Maximum change in Titer/SN is included in "Subject Summary" with an option to transpose to variables

PK concentration:
Option 1 (Figure 10) in PARAM
Option 2 (Figure 11) as a variable

Figure 10

PARQUAL	PARCAT1	PARCAT2	PARAMCD	PARAM	AVAL	AVALC	BASE	CHG
Drug X	Collection	Sample	SCRRSLT	Screening Result	1	POSITIVE		
Drug X	Collection	Sample	CNRRSLT	Confirmatory Result	1	POSITIVE		
Drug X	Collection	Sample	ADARSLT	Binding Antibody	1	POSITIVE		
Drug X	Collection	Sample	TITER	Titer	2			
Drug X	Collection	Sample	SN	Signal to Noise	4.56789			
Drug X	Collection	Sample	NABRSLT	Neutralizing Antibody	-1	NEGATIVE		
Drug X	Collection	Sample	NABSCR	Neutralizing Screening Result	1	POSITIVE		
Drug X	Collection	Sample	NABCNR	Neutralizing Confirmatory Result	-1	NEGATIVE		
Drug X Domain A	Collection	Domain	ADADRSLT	Domain ADA	1	POSITIVE		
Drug X Domain A	Collection	Domain	NABDRSLT	Domain NAB	-1	NEGATIVE		
Drug X	Collection	PK	PKCONC	PK Concentration	890			

Figure 11

PARQUAL	PARCAT1	PARCAT2	PARAMCD	PARAM	AVAL	AVALC	PKCONC	DTL
Drug X	Collection	Sample	SCRRSLT	Screening Result	1	POSITIVE	890	2000
Drug X	Collection	Sample	CNRRSLT	Confirmatory Result	1	POSITIVE	890	2000

Sample Interpretation

- ADA – Sample level Interpretation

- **Sample Interpretation:** Display in PARAM for ADA only, or NAB only, or combined at sampling time
- **PARCAT2** allows further risk-based characterization of interest: e.g. domain level, ADA or NAB, Titer, etc.

Figure 12

PARQUAL	PARCAT1	PARCAT2	PARAMCD	PARAM	AVISIT	AVAL	AVALC
Drug X	Sample Interpretation	Sample	ADASAMP	Sample ADA Status	CYCLE 1	1	POSITIVE
Drug X	Sample Interpretation	Sample	NABSAMP	Sample NAB Status	CYCLE 1	1	POSITIVE
Drug X	Sample Interpretation	Sample	ADANABS	Sample ADA and NAB Status	CYCLE 1	3	ADA POSITIVE NAB POSITIVE
Drug X	Sample Interpretation	Domain	ADADOMN	Domain ADA Status	CYCLE 1	1	POSITIVE
Drug X	Sample Interpretation	Domain	NABDOMN	Domain NAB Status	CYCLE 1	-1	NEGATIVE
Drug X Domain A	Sample Interpretation	Domain	ADANABD	Domain ADA and NAB Status	CYCLE 1	2	ADA POSITIVE NAB NEGATIVE

- ADA – Sample level flags and timing variables

- Flag variables as needed for further clarification
- Timing variables: Naming of relative time variables follows what're available in published IG

Figure 13

PARQUAL	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC	EXDTLFL	PKADAFL	LSTADAFL	AFRLT	NFRLT
							Does PK Concentration Exceed DTL?	Has corresponding PK?	Is it last valid ADA sample?	Actual Time to First Dose	Nominal Time to First dose
Drug X	Sample Interpretation	ADASAMP	Sample ADA Status	CYCLE 1	-1	NEGATIVE	N	Y	N	0	1
Drug X	Sample Interpretation	ADASAMP	Sample ADA Status	CYCLE 6	1	POSITIVE	N	Y	Y	106	106

Subject Summary

- Subject level summary based on all samples for a subject
  - Treatment-induced ADA
  - Treatment-boosted ADA
  - Treatment-emergent ADA
  - Transient ADA Response
  - Persistent ADA Response
  - Time to onset ADA
  - Duration of positive ADA
  - Baseline ADA Status, Post Treatment ADA status
  - ADA Subject Status
  - Nab Subject Status
  - Overall Subject Status

Option 1 (Figure 14) Display ADA subject level summary using PARAMCD/PARAM. PARAMCD values are designed with 6 characters, offering the flexibility to append 'FL' when transposed as a variable in Option 2

PARAMCD/PARAM with multi-level-value: e.g. ADAOVAL: Negative, Inconclusive, TI Positive NAB Negative, TI Positive NAB Positive, TB Positive NAB Negative, TB Positive NAB Negative

Option 2 (Figure 15) Display ADA subject level summary in variables

Figure 14

PARQUAL	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC
Drug X	Subject Summary	ADATRI	Treatment-induced ADA Positive		0	N
Drug X	Subject Summary	ADATRB	Treatment-boosted ADA Positive		1	Y
Drug X	Subject Summary	ADATRE	Treatment-emergent ADA Positive		1	Y
Drug X	Subject Summary	ADATSP	Transient ADA Response Positive		0	N
Drug X	Subject Summary	ADAPSP	Persistent ADA Response Positive		1	Y
Drug X	Subject Summary	ADABL	Baseline ADA Sample Status		1	POSITIVE
Drug X	Subject Summary	ADAPSBL	Post Baseline ADA Sample Status		1	POSITIVE
Drug X	Subject Summary	ADASUBJ	ADA Subject Status		1	POSITIVE
Drug X	Subject Summary	MTTCHG	Maximum Change in Titer		40	40
Drug X	Subject Summary	NABSUBJ	NAb Subject Status		1	POSITIVE
Drug X	Subject Summary	ADAOVAL	Overall Subject Status Summary		1	POSITIVE
Drug X	Subject Summary	TIMOSADA	Time to onset ADA (day)		15	
Drug X	Subject Summary	ADADUR	Duration of Positive ADA (day)		20	

Figure 15

Variable label →

Variable name →

		Treatment-induced ADA Positive	Treatment-boosted ADA Positive	Treatment-emergent ADA Positive	Transient ADA Response Positive	Persistent ADA Response Positive
USUBJID	PARQUAL	ADATRIFL	ADATRBFL	ADATREFL	ADATSPFL	ADAPSPFL
xxxxx-xxxx	Drug X	N	Y	Y	N	Y

Subject Summary (cont.)

- Display multi-level-value subject summaries as variables
  - This allows flexibility to use as by-category comparison.
  - This also allows to combine “Maximum Change in Titer” with other subject summary as by-category comparison as well

Figure 16

		ADA Subject Status	NAb Subject Status	Overall Subject Status Summary	Maximum Change in Titer
USUBJID	**PARQUAL**	**ADASUBJ**	**NABSUBJ**	**ADAOVAL**	**MTTCHG**
xxxxx-xxxx	Drug X	TI Positive	Negative	TI Positive NAB	40

- Subject level cumulative summary at analysis timepoints of interest
  - This allows to report cumulative summary at AVISIT=CYCLE5, CYCLE10, and End of study

Figure 17

PARQUAL	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC
Drug X	Subject Summary	ADASUBJ	ADA Subject Status	CYCLE 5	-1	NEGATIVE
Drug X	Subject Summary	ADASUBJ	ADA Subject Status	CYCLE 10	1	POSITIVE
Drug X	Subject Summary	ADASUBJ	ADA Subject Status	End of study	1	POSITIVE

Example ADA data in one subject

Figure 18

Proposed

USUBJID	PARQUAL	PARCAT1	PARAMCD	PARAM	AVISIT	AVAL	AVALC	ISSTRESC	BASE	CHG	DTL	MRD	ISNAM	PKCONC	EXDTLFL	PKADAFL	LSTADAFL	NFRLT	AFRLT
xxxx-xxx1	Drug X	Collection	SCRRSLT	Screening Result	CYCLE 1	1	POSITIVE	Positive			2000	4	LABabc	890	N	Y	N	1	1
xxxx-xxx1	Drug X	Collection	CNRRSLT	Confirmatory Result	CYCLE 1	1	POSITIVE	Positive			2000	4	LABabc	890	N	Y	N	1	1
xxxx-xxx1	Drug X	Collection	TITER	Titer	CYCLE 1	2		<4	2		2000	4	LABabc	890	N	Y	N	1	1
xxxx-xxx1	Drug X	Collection	SN	Signal to Noise	CYCLE 1	4.56789		4.56789	4.56789		2000	4	LABabc	890	N	Y	N	1	1
xxxx-xxx1	Drug X	Collection	NABRSLT	Neutralizing Antibody	CYCLE 1	-1	NEGATIVE	Negative			2000	4	LABabc	890	N	Y	N	1	1
xxxx-xxx1	Drug X	Sample Interpretation	ADASAMP	Sample ADA Status	CYCLE 1	1	POSITIVE				2000	4	LABabc	890	N	Y	N	1	1
xxxx-xxx1	Drug X	Sample Interpretation	NABSAMP	Sample NAB Status	CYCLE 1	-1	NEGATIVE				2000	4	LABabc	890	N	Y	N	1	1
xxxx-xxx1	Drug X	Collection	SCRRSLT	Screening Result	CYCLE 9	1	POSITIVE	Positive			2000	4	LABabc	1890	N	Y	Y	25	26
xxxx-xxx1	Drug X	Collection	CNRRSLT	Confirmatory Result	CYCLE 9	1	POSITIVE	Positive			2000	4	LABabc	1890	N	Y	Y	25	26
xxxx-xxx1	Drug X	Collection	TITER	Titer	CYCLE 9	40		40	2	38	2000	4	LABabc	1890	N	Y	Y	25	26
xxxx-xxx1	Drug X	Collection	SN	Signal to Noise	CYCLE 9	24.56789		24.56789	4.56789	20	2000	4	LABabc	1890	N	Y	Y	25	26
xxxx-xxx1	Drug X	Collection	NABRSLT	Neutralizing Antibody	CYCLE 9	-1	NEGATIVE	Negative			2000	4	LABabc	1890	N	Y	Y	25	26
xxxx-xxx1	Drug X	Sample Interpretation	ADASAMP	Sample ADA Status	CYCLE 9	1	POSITIVE				2000	4	LABabc	1890	N	Y	Y	25	26
xxxx-xxx1	Drug X	Sample Interpretation	NABSAMP	Sample NAB Status	CYCLE 9	1	POSITIVE				2000	4	LABabc	1890	N	Y	Y	25	26
xxxx-xxx1	Drug X	Subject Summary	ADATRI	Treatment-induced ADA Positive		0	N												
xxxx-xxx1	Drug X	Subject Summary	ADATRB	Treatment-boosted ADA Positive		1	Y												
xxxx-xxx1	Drug X	Subject Summary	ADATRE	Treatment-emergent ADA Positive		1	Y												
xxxx-xxx1	Drug X	Subject Summary	ADATSP	Transient ADA Response Positive		0	N												
xxxx-xxx1	Drug X	Subject Summary	ADAPSP	Persistent ADA Response Positive		1	Y												
xxxx-xxx1	Drug X	Subject Summary	ADABL	Baseline ADA Sample Status		1	POSITIVE												
xxxx-xxx1	Drug X	Subject Summary	ADAPSBL	Post Baseline ADA Sample Status		1	POSITIVE												
xxxx-xxx1	Drug X	Subject Summary	ADASUBJ	ADA Subject Status		5	TB Positive												
xxxx-xxx1	Drug X	Subject Summary	MTTCHG	Maximum Change in Titer		20	20												
xxxx-xxx1	Drug X	Subject Summary	NABSUBJ	NAb Subject Status		-1	NEGATIVE												
xxxx-xxx1	Drug X	Subject Summary	ADAOVAL	Overall Subject Status Summary		8	TB Positive NAB Negative												
xxxx-xxx1	Drug X	Subject Summary	TIMOSADA	Time to Onset ADA (day)		1													
xxxx-xxx1	Drug X	Subject Summary	ADADUR	Duration of Positive ADA (day)		26													

Next step: Creating an implementation Guide

- Design a data structure and general rules for standardization
  - Standardize format of ADA analysis dataset
  - Define the content for ADA analysis dataset
  - Guide the consistencies across industry
  - Ensure readiness for analysis/reporting, submission to health authorities
- Provide guidance along with adequate flexibilities to be adapted easily
  - Illustrate in corresponding examples for alternative approaches
  - Recommend terminologies and derivation definitions for PARAM/PARAMCD, which are not restricted/controlled, but for user to decide per study-driven requirement and/or analysis need

Open for Comments

- Currently in progress to define a new sub-class ADADA
- Basic conformance rules are to be defined
- Follow CDISC review and release process
- Your comments are more than welcome

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To provide feedback during ADaM Team or Internal Review, you'll need to fill out volunteer form. https://www.cdisc.org/volunteer/form

To provide feedback during public review, let us know and create a Wiki account.

References

- FDA/EMA relevant
  - Immunogenicity Assessment for Therapeutic Protein Products (2014) - FDA
  - Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection (Guidance for Industry) (2019) - FDA
  - Guideline on Immunogenicity assessment of therapeutic Proteins (2017) - EMA
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  - "Pilot OCE/OOD Safety Team Standard Data Requests" https://www.fda.gov/media/133252/download
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- Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, et al. Assessment and reporting of the clinicalimmunogenicity of therapeutic proteins and peptidesharmonized terminology and tactical recommendations. AAPS J. 2014;16(4):658–73
- Jochem Gokemeijer, Vibha Jawa, and Shibani Mitra-Kaushik, How Close Are We to Profiling Immunogenicity Risk Using In Silico Algorithms and In Vitro Methods?: an Industry Perspective. The AAPS J, 2017; 19(6):1587-92.

Thank You!

Appendix

Terminology

Term	Definition
Anti-drug antibody (ADA)	A biologic drug-reactive antibody, that includes pre-existing host antibodies that are cross-reactive with the administered biologic drug. Is synonymous with Anti-therapeutic antibody (ATA), Anti-product antibody (APA), Anti-biologic antibody (ABA), and binding ADA
Neutralizing ADA (NAb)	A biologic drug-reactive antibody that binds to the drug product in such a way as to diminish or prevent its pharmacologic activity (e.g., blocking the active binding site)
Non-neutralizing ADA	A biologic drug-reactive antibody that binds to the drug product but does not reduce or interfere with the drug activity
Binding ADA	Any biologic drug-reactive antibody that binds to the drug product regardless of clinical outcome
Pre-existing ADA	A drug-reactive antibody that is present prior to treatment. Also referred to as baseline ADA.

Terminology

Term	Definition
Treatment-Induced ADA	A biologic drug-reactive antibody that is produced (sero-conversion) any time following initial drug administration in a subject with no detectable pre-existing ADA.
Treatment-boosted ADA	A biologic drug-reactive antibody, present in the patient prior to drug administration, that was increased to a higher measurable level after initial drug administration. (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a scientifically reasonable/defined margin such as a four or ninefold increase)
Treatment-emergent ADA	Biologic drug-reactive antibody grouping that includes both the categories of treatment-induced and treatment-boosted ADA
ADA prevalence	The proportion of all individuals having drug-reactive antibodies (including pre-existing) at any point in time. (distinct from ADA incidence)
ADA incidence	The proportion of the study population found to have seroconverted or boosted preexisting ADA during a study period (see Treatment-emergent ADA)

Terminology

Term	Definition
ADA Titer (Titer)	An expression referencing the numeric quantification of ADA present in a sample. Typically expressed as the reciprocal of the highest dilution of the sample e.g., 1:1000 being a titer of 1000, or alternatively derived through interpolation of the cut point value from the assay dilution curve.
ADA positive (sample)	Any biological sample, tested for ADA, that shows a measurable amount of antibody
ADA negative (sample)	Any biological sample, tested for ADA, that shows no measurable amount of antibody and also shows no measurable amount of drug (target) or an amount of drug deemed not to interfere with the detection
ADA inconclusive (sample)	Any biological sample, tested for ADA, that shows no measurable amount of antibody but also contains a measurable amount of drug at levels determined to interfere with the detection assay
Drug tolerance level	The drug concentration within an assay sample above which has demonstrated the ability to mask or alter the measured ADA assay result

Terminology

Term	Definition
ADA positive (subject)	A subject with at least one treatment induced or treatment boosted ADA positive sample during the treatment or follow-up period related to drug administration
ADA negative (subject)	A subject without a treatment induced or treatment boosted ADA positive sample during the treatment or follow-up period related to drug administration and the last ADA sample was deemed ADA negative (drug levels were low enough not to interfere with ADA detection.
ADA inconclusive (subject)	Despite all ADA-negative samples during a subject's treatment (including follow-up observation period) with a lower risk drug, the last evaluable sample was found to be inconclusive, lending to a conservative ADA-inconclusive subject status