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NORTH CAROLINA • SEP. 28, 2023

Handling Anti-Drug Antibody (ADA) Data for Efficient Analysis

a presentation by
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Meet the Speaker

Sabarinath Sundaram has over 10 years of statistical programming experience working in exploratory research studies to Phase III studies, CDISC standards, handling PK/PD/ADA data, and across multiple therapeutic areas. He has a Ph.D. degree in Life Sciences (Biochemistry) and is the Principal Statistical Programmer at **Seagen, Inc**. as well as PK/PD center of excellence lead.

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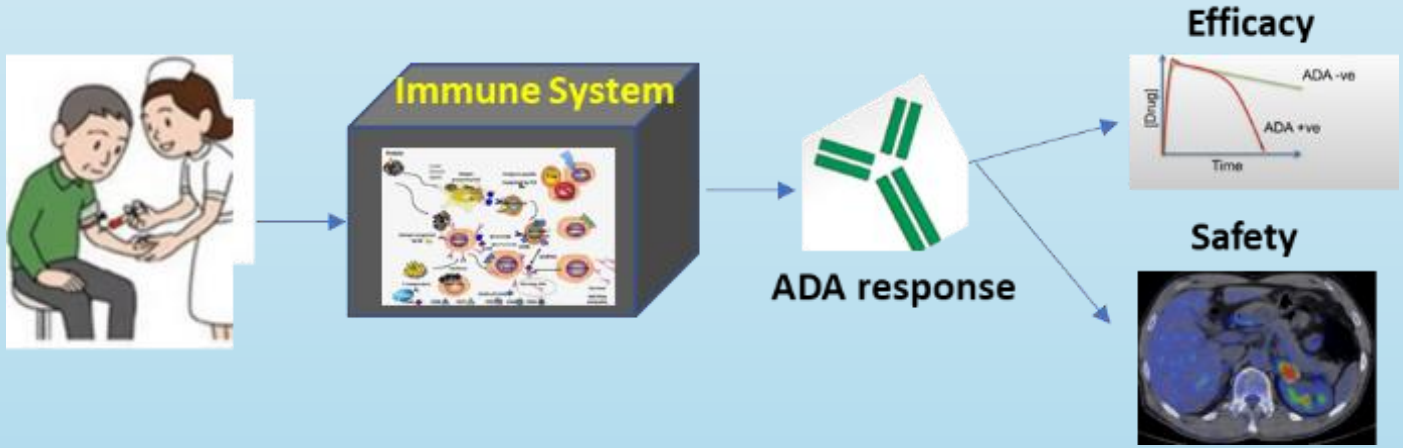
The opinions expressed in this presentation and on the following slides are solely those of the presenters and not necessarily those of Seagen

Agenda

- Introduction
  - ADA Testing Scheme
- Mapping Raw ADA data into SDTM IS Domain
  - Sample ADA DTP Template
  - Sample SDTM IS Domain Dataset
- Analysis Strategy of ADA Results
  - Sample ADaM ADIS Domain Dataset Key parameters & Summary of Anti-Drug Antibody (ADA) Incidence.
- Conclusion

Overview of Immunogenicity

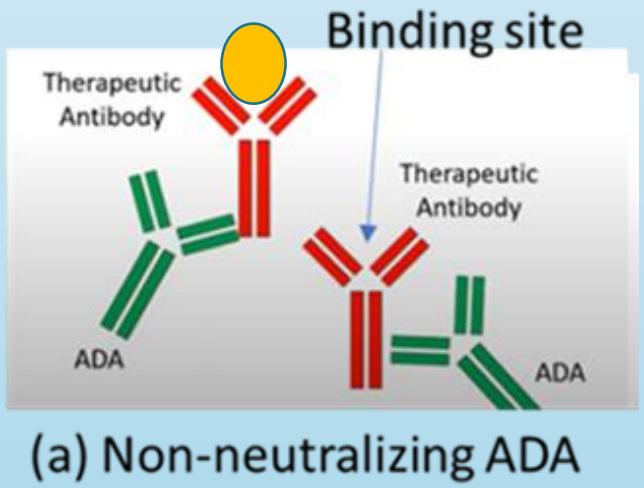
- Large molecules have revolutionized the pharmaceutical industry



- Pharmacokinetics (PK) is how the body responds to a drug.
- Pharmacodynamics (PD) allows us to quantify the relationship between a drug and its pharmacologic or toxicologic effect it has on patients.
- ADA responses can affect the PK, PD, safety, and efficacy of a therapeutic candidate. The clinical effects of ADA formation can be highly variable and may cause adverse events that put the patient at risk.

Interaction of Therapeutic with ADA

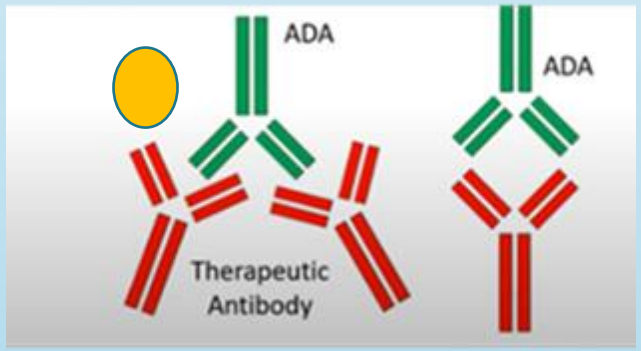
- Two Types, based on Interaction .



(a) Non-neutralizing ADA

Does not affect the binding of the Therapeutic(drug) and its target

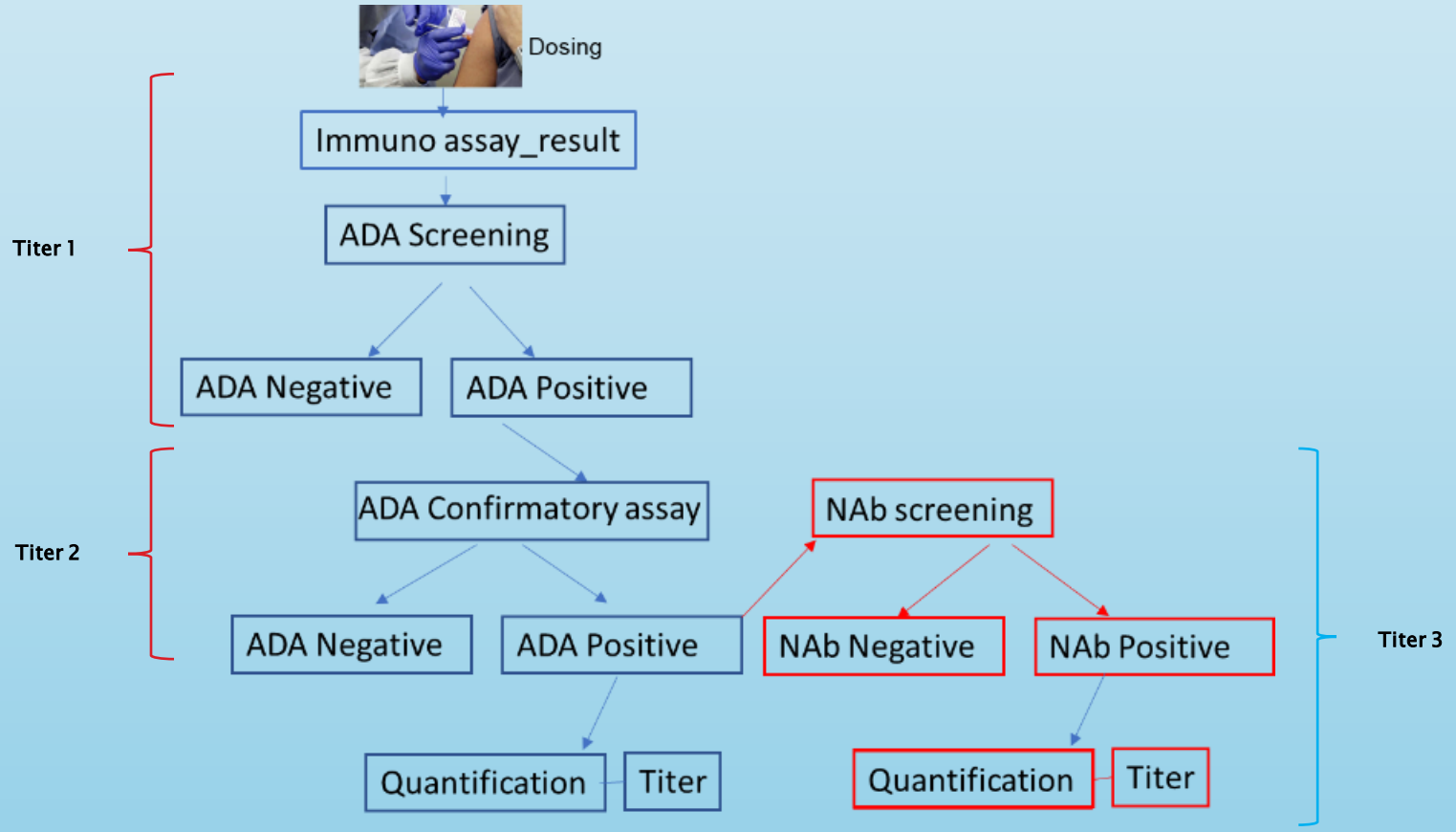
Target



(b) Neutralizing ADA

Prevent interaction between the Therapeutic(drug) and its target

Multi-tiered ADA Testing Scheme



Sample ADA DTP Template & Results

DTP

LBTEST	Description	ISCAT	ISTESTCD	ISTEST	ISORRES	ISORRESU
ADA_Screening	Screening for binding ADA	Binding ADA	ADASCRN	ADA Screening	Positive/Negative	
ADA_Confirm	Confirmation of Binding ADA detection	Binding ADA	ADACONFM	ADA Confirmation	Positive/Negative	
ADA_Quantitative	Quantification of Binding ADA	Binding ADA	ADAQUAN	ADA Quantity	23	RLU
ADA_Titer	Titer ADA	Binding ADA	ADATITER	ADA Titer	<1	dilution
NAB_Screening	Screening for neutralizing ADA	NEUTRALIZING ADA	NABSCRN	NAB ADA Screening	Positive/Negative	
NAB_Confirm	Confirmation of neutralizing ADA detection	NEUTRALIZING ADA	NABCONFM	NAB ADA Confirmation	Positive/Negative	
NAB_Quantitative	Quantification of neutralizing ADA	NEUTRALIZING ADA	NABQUAN	NAB ADA Quantity	23	RLU
NAB_Titer	NAB Titer	NEUTRALIZING ADA	NABTITER	NAB ADA Titer	3	dilution

Raw data

						T1		T2		T3	
USUBJID	VISIT	LBTPT	LBCAT	LBSCAT	SCRQL	SCRQN	SCRQNU	CONFQL	CONFQN	TITER	TiterU
XXXX-1000-100	CIDI	Predose	immunogenicity	ADA	Negative	xxx.x	RLU				
XXXX-1000-100	CIDI	8 hrs post dose	immunogenicity	ADA	Negative	xxx.x	RLU				
XXXX-1000-101	CIDI	Predose	immunogenicity	ADA	Negative	xxx.x	RLU				
XXXX-1000-101	CIDI	8 hrs post dose	immunogenicity	ADA	potential Positive	xxx.x	RLU	Negative			
XXXX-1000-102	CIDI	Predose	immunogenicity	ADA	Positive	xxx.x	RLU				
XXXX-1000-102	CIDI	8 hrs post dose	immunogenicity	ADA	potential Positive	xxx.x	RLU	Postive	xxx.x	1	dilution

Programming Strategies: SDTM

- Historically mapped to PC or LB.
- CDISC guidelines: Mapped to IS (Immunogenicity Specimen Assessments) domain
- Findings domain: assessments that determine whether a therapy induced an immune response
- Data structure: One record per test per time point per visit per subject

SDTM Domain IS

DOMAIN	USUBJID	ISSEQ	ISTEST	ISTESTCD	ISTSTOPO	ISORRES	VISIT	ISTPT	ISDTC
IS	1000-100	1	Binding Antidrug Antibody	ADA_BAB	Screen	Negative	Cycle 1 Day 1	Predose	2019-07-08T00:53
IS	1000-100	2	Binding Antidrug Antibody	ADA_BAB	Screen	Negative	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-101	1	Binding Antidrug Antibody	ADA_BAB	Screen	Negative	Cycle 1 Day 1	Predose	2019-04-30T04:39
IS	1000-101	2	Binding Antidrug Antibody	ADA_BAB	Screen	Positive	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
IS	1000-101	3	Binding Antidrug Antibody	ADA_BAB	Confirm	Negative	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
IS	1000-102	1	Binding Antidrug Antibody	ADA_BAB	Screen	Positive	Cycle 1 Day 1	Predose	2019-07-08T00:54
IS	1000-102	2	Binding Antidrug Antibody	ADA_BAB	Screen	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-102	3	Binding Antidrug Antibody	ADA_BAB	Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-102	4	Binding Antidrug Antibody	ADA_BAB	Quantity	234	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-102	5	Binding Antidrug Antibody	ADA_BAB	Titer	4	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-102	6	Neutralizing Binding Antidr	ADA_NAB	Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-102	7	Neutralizing Binding Antidr	ADA_NAB	Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-102	8	Neutralizing Binding Antidr	ADA_NAB	Quantity	100	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
IS	1000-102	9	Neutralizing Binding Antidr	ADA_NAB	Titer	2	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54

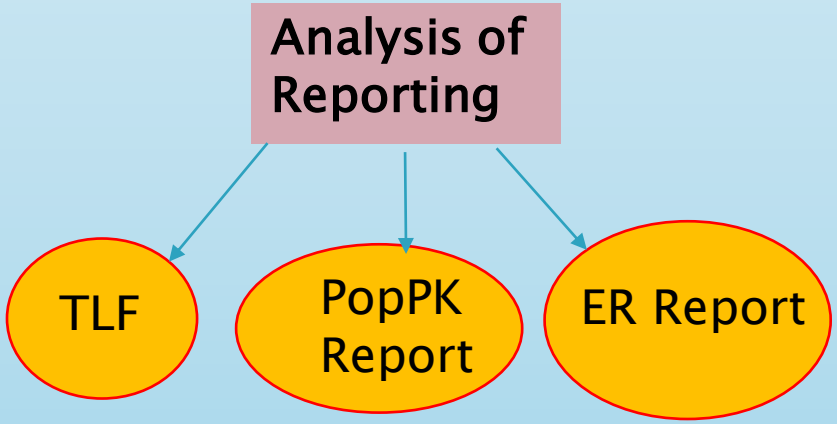
Programming Strategies: ADaM

- ADIS
- Class: Basic Data Structure (BDS)
- One record per analysis parameter per timepoint per visit per subject
- Additional records - new derived parameters based on ADA results to support the analysis
- ADSL flag variables for summarization of ADA data:
  - ADA-evaluable flag (ADAFL)
  - NAb evaluable flag (NABFL)

ADaM Domain ADIS

USUBJID	ASEQ	PARCAT	PARAMCD	PARAM	AVALC	AVISIT	ATPT	ADT
XXXX-1000-100	1	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	predose	2019-07-08T00:54
XXXX-1000-100	2	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-101	1	Binding ADA	ADASCRN	ADA Screening	Negative	Cycle 1 Day 1	predose	2019-04-30T04:40
XXXX-1000-101	2	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
XXXX-1000-101	3	Binding ADA	ADACONFM	ADA Confirm	Negative	Cycle 1 Day 1	8 hrs post dose	2019-04-30T12:40
XXXX-1000-102	1	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	Predose	2019-07-08T00:54
XXXX-1000-102	2	Binding ADA	ADASCRN	ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	3	Binding ADA	ADACONFM	ADA Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	4	Binding ADA	ADAQUAN	ADA Quantity (RLU)	234	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	5	Binding ADA	ADATITER	ADA Titer	4	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	6	Neutraizing ADA	ADASCRN	NAb ADA Screening	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	7	Neutraizing ADA	ADACONFM	NAb Confirm	Positive	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	8	Neutraizing ADA	NABQUAN	NAb Quantity (RLU)	100	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	9	Neutraizing ADA	NABTITER	NAb Titer	2	Cycle 1 Day 1	8 hrs post dose	2019-07-08T08:54
XXXX-1000-102	10	Binding ADA	INDUCADA	Treatment induced A	N			
XXXX-1000-102	11	Binding ADA	NOTRTREL	No Treatment relate	N			
XXXX-1000-102	12	Binding ADA	TIMEADA	Time to onset of Firs	42			
XXXX-1000-102	13	Binding ADA	POSTADA	Post baseline ADA	Y			
XXXX-1000-102	14	Binding ADA	LVADA	Last visit ADA	Cycle 3			

Analysis Strategy of ADA Results



Key analysis parameters

1) **Treatment-induced ADA**: Incidence of ADA induction is determined if both baseline and post-baseline samples have positive titers, and the subject is only considered positive for the induction of ADA when the post-baseline titer is at least 4-fold greater than the titer prior to initial dosing.
2) **No Treatment-related ADA**: Subjects with negative post-baseline ADA results
3) **Post-baseline Positive ADA**: Incidence of ADA is determined by counting at least 1 positive result at any timepoint after initial dosing.
4) **NAb Negative**: NAb negative at baseline includes patients who are ADA-negative.
5) **NAb Incidence**: defined as having at least one positive NAb result at any time, including baseline and/or post baseline.
6) **Time to Onset of First ADA**: Select the analysis day of the first record with ADA-positive result after dosing.
7) **Last Visit ADA**: The latest visit on which a subject had a positive ADA result after dosing.
8) **Persistently Positive ADA**: Defined as ATA positive at 2 or more post-baseline assessments (with ≥ 16 weeks between first and last positive) or ATA positive at the last post-baseline assessment.
9) **Transiently Positive ADA:** Defined as having at least one post-baseline ATA positive assessment and not fulfilling the conditions of ATA persistently positive.

Sample Summary of Anti-Drug Antibody (ADA) Incidence

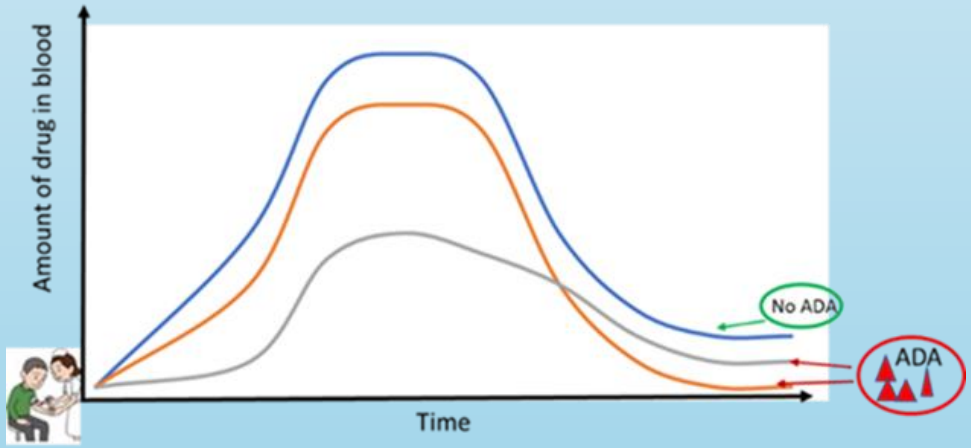
	Total (N=xx) n (%)
Subjects with a baseline and at least one post-baseline sample	n
Baseline Negative	n
Negative post-baseline[2]	m (%)
Positive post-baseline[3]	m (%)
Baseline Positive	n
Negative post-baseline[2]	m (%)
Treatment induced ADA[1]	m (%)
NAb negative[8] at baseline	n
NAb incidence[9]	m (%)
Total positive post-baseline	m (%)

The percentage denominators are the first row counts of evaluable subjects, not the analysis set population.
Superscript numbers refer to the derived parameters explained in the above section.

Conclusion

- Use of ADA Results
- Explain PK results
- Clinical Observations (Loss of Efficacy and AE/SAE)
- Few Important Clinical Development-Stage Questions

Early-stage Development	Late-stage Development
▪ Do any pre-existing x-reactive antibodies increase after dosing ▪ Is ADA observed increase or decrease after repeated dosing ▪ Can any mitigation strategies likely decrease or increase risk profile	▪ Will a dosing regimen, change in manufacturing or Patient population change in immunogenicity profile



Drug concentration by time. Model showing the effect of ADA on PK plot.

Acknowledgement

I would like to thank Johnny Maruthavanan, Shang-Ying Liang, Christine O Day, Daping Zhang, Bala Pitchuka, Shefalica Chand and Michiel Hagendoorn for their feedback, constant support, and guidance.

Thank you for your attention !

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