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Programming Support for Anti-Drug Antibody Pharmacokinetics in Therapeutic Protein Drug Development

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ABSTRACT

Therapeutic Proteins (TP) are engineered proteins in laboratory for pharmaceutical use. In the last several decades, benefiting from recent advances in biotechnology, TP products have become an important class of medicines treating a wide spectrum of clinical indications. However, due to their high antigenic potential, TP drugs may trigger host immune responses resulting in varying clinical consequences for efficacy and safety, ranging from no apparent effect to life-threatening reactions. The anti-drug antibodies (ADA) generated in unwanted immune response may sustain, clear, or neutralize the TP drug. As the result, ADA can significantly influence pharmacokinetics (PK), pharmacodynamics (PD), bioavailability, and efficacy. Thus, it is critical to understand the essential role of ADA on PK/PD in drug development. Immunogenicity assessments and validations are also regulatory requirements to ensure the safety and efficacy of TP products. In clinical trial practice, high quality programming support is fundamental for a successful ADA-PK analysis. This paper will focus on the programming procedures throughout ADA-PK analysis, including deriving ADA relevant variables, generating analysis dataset, and conducting modeling analysis. The difficulties and strategic considerations in these programming procedures will be discussed in details. To better assist an understanding on the role of ADA in programming community, the basic knowledge on the role of ADA in TP drug development will be introduced briefly and the relevant regulatory guidelines will be highlighted as well.

INTRODUCTION

Protein/peptide-based drug, known as therapeutic protein/peptide (TP), is a fast growing class of biologic drugs treating various diseases and conditions. Boosted by the latest advances in recombinant DNA technology and protein engineering, a large number of TP products are in development and being on the market. Since early 1980s, over 200 TP products have been approved for clinical use by U.S. Food and Drug administration (FDA) (Usmani SS, et al.2017). Moreover, there is increasing rate of approval over the past several years. For example, FDA approved totally 59 TP drugs between 2011 and 2016 (Lagassé HAD, et al. 2017).

Despite the unprecedented achievements for clinical treatment and promising potential to provide advance therapeutics, TPs as a drug class still face major challenges. One significant safety and efficacy concern is the clinical implications of immunogenicity due to the complicated characteristics of TP drugs and many factors in manufacturing processes. In contrast to traditional small molecule drugs that are chemically synthesized, TPs are usually large molecules having complex structures and produced in living organisms through numerous intricate manufacturing processes. Such therapeutics have the high risk of being recognized and eliminated as foreign by a host immune system. Anti-drug antibodies (ADA) can be produced in unwanted immune response provoked by TP drugs, then further alter drug metabolism and distribution. Additionally, TPs often exhibit distinct pharmacokinetics (PK) /pharmacodynamics (PD) properties that are much more complex than those typically associated with small molecule drugs. In terms of drug absorption, distribution, metabolism and elimination (ADME), TP drugs are more likely associated with nonlinear distribution and metabolism (Wan H, 2016). As the growing trend toward using of PK and PD analyses to guide and expedite drug development, it is critical to understand the impact of immunogenicity on PK/PD of TP drugs.

High quality programming support is fundamental for a successful ADA and PK analysis. Clinical trial programmers are encouraged to become familiar with the knowledge on immunogenicity and its assessment in TP drug development. To help clinical trial programmers to explore the field of ADA and PK analysis, this paper will start from a brief introduction on basic immunology concepts followed by the risk-based approach of immunogenicity assessment, then move to the analysis of the influence of ADA on PK. The paper will dissect the programming procedures throughout the analysis and end with the

discussion on the challenges and considerations of programming procedures for ADA and PK analysis in clinical trial programming environment.

IMMUNE RESPONSE, IMMUNOGENICITY, AND ANTI-DRUG ANTIBODY

The immune response is how our body recognizes and eliminates non-self or harmful substances, and protects us against a universe of bacteria, virus, toxin and allergen. The capability of particular substance to activate our immune system and induce an immune response is immunogenicity. Those particular foreign or harmful substances are antigens. Antibody (Ab) is a class of primary products generated by immune system in response to antigens. Ab also known as immunoglobulin (Ig), is a large, Y-shaped glycoprotein developed by immune system to neutralize antigens.

It is the principle function of the immune system to protect our body from harmful invaders by recognizing and cleaning antigens. The TPs are large proteins with a variety of modifications and complex 3-dimensional structure, produced in living organisms, thereby considered as antigens by our body. While using TP product as a treatment, the immune system will do its job to mobilize immune responses against TP products. These immune responses triggered by TP products result in varying clinical consequences, ranging from transient Ab responses with no apparent clinical manifestations to severe life-threatening and catastrophic reactions. For instance, YERVOY® (ipilimumab) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody used for cancer therapy. YERVOY can cause several immune-mediated adverse responses, including enterocolitis, hepatitis, neuropathies, dermatitis, etc. The severity of these immune-mediated adverse events vary from grade 1 (mild) to grade 5 (death) in the patients receiving YERVOY administration (Squibb B-M, 2011).

Anti-drug antibody (ADA) generated in such unwanted immune responses, can bind with TP directly and then influence PK/PD of TP, including ADME process. The development of antidrug antibodies (ADAs) has an important influence on the utility of TP in an individual patient. ADAs are associated with immune mediated reactions and can alternate trough PK levels and the efficacy in patients receiving ongoing TP treatment. Neutralizing Ab (NAb) is a subset of ADAs and inhibits the biological activity of a TP by binding to epitope(s) within or close to the active site(s) of the molecule or by causing conformational changes. ADA analysis includes but not limited to timing and incidence of ADAs and their effect on PK.

IMMUNOGENICITY ASSESSMENT FOR TP PRODUCTS

The immune response to TP products is heterogeneous and the myriad factors can affect immunogenicity of TP products. Given the safe and efficacy issues raised on TP products, immunogenicity assessment is thus critical in the development of TP drugs. FDA and EMA published several guidelines to assist the development and validation of assays for detecting and measuring the immunogenicity of TP products for clinical use. Readers are referred to the recommended reading to understand the immunogenicity assessment of TP products. In these guidelines, a risk-based, multi-tiered approach is recommended to elucidate immunogenicity of TP products.

The key assays of immunogenicity evaluation include screening, confirmatory, neutralizing and titer assays. The quality and quantity of ADA are addressed by using these assays. The strategy for immunogenicity assessment is shown in Figure 1.

First, all samples are subjected to screening assay, which is highly sensitive to detect all serum antibodies that bind to the TP products, including low affinity ADAs. In order to maximize the detection of true positives, false negative results are not acceptable in screening assay, but a low false positive rate (preferably 5%) is desirable.

Second, the positive samples determined in screening assay are further validated by confirmatory assay. It has been shown that antibodies can be induced also against other substances in TP products, such as product- and process-related impurities. The antibodies against these impurities are also detected in the screening assays as “false” positives. In confirmatory assays, any false positive results in the initial screen is eliminated and the confirmed samples are considered as ADA positive samples subjected to further examination for the magnitude the ADA response and specificity for the TP administrated.

In the third tier, the magnitude of the ADA response is determined by titering assays. As a quasi-quantitative expression of the level of ADA in serum, titer is the maximal dilution of the sample that yields

a positive result E.g. the dilution of 1/10 is titer of 10. The highest dilution is determined after serum samples are tested in sequential dilutions. Titers are informative to evaluate the correlation between magnitude of ADA and clinical impact of ADA on safety and efficacy. Furthermore, when patients have pre-existing ADA, treatment-boosted ADA responses may be identified by post-treatment increases in titer.

Neutralizing assays run parallel with titering assays in the third tier. Neutralizing ADAs, block the binding of the drug (TP) with its target. Non-neutralizing ADA's bind to the drug but do not interfere with the binding of the drug with the target. Thus, it is necessary to assess the neutralizing capacity of the ADAs present in positive samples because NAbs often correlate with diminished clinical responses to biological product.

DRUG TOLERANCE LEVEL

The ADA assays can be interfered in certain circumstances. Generally, the ADA assays are designed to detect free ADA, which is not bound with any of TP products or the endogenous counterpart present in serum. ADA-drug complex is formed when ADA binds with TP products. As a result, the bound ADA can't be detected due to the formation of ADA-drug complexes. Therefore, it is critical to know the assay sensitivity in the presence of the expected levels of interfering TP product. The drug tolerance level (DTL) is the maximum amount of free drug in a study sample that allows detection of ADA at an acceptable sensitivity. The ADA assay is not able to detect ADA present in the testing samples with free drug concentration higher than DTL, thus the ADA incidence would be underestimated. The DTL of the same TP product may vary from assay methods and laboratories conducting the ADA assays.

PROGRAMMING SUPPORT TO ADA ASSESSMENT IN PK MODELING

In the case studies, a humanized monoclonal antibody (mAb) is used in cancer immunotherapy.

All subjects in selected studies receive 30 minute IV infusion at Day 1 of each cycle. Treatment cycles are 3 weeks (21-days) based on half-life of 21 days from previous study PK data.

To evaluate TP drug immunogenicity and exposure, PK samples and ADA samples are collected at multiple time points throughout the treatment. Pre-dose trough PK samples are collected within 24 hours before drug infusion. Peak PK samples are drawn within 30 minutes after the end of the infusion. ADA samples are collected with all pre-treatment and pre-dose trough PK samples.

DERIVATION OF VARIABLES USED IN PK MODELING

The raw PK concentration data, unlike other clinical data that is presented in standard format in electronic data capture (EDC) system, but is provided by PK vendors in non-standard format. Before combining PK with ADA data to evaluate the impact of immunogenicity on drug ADME, programmers must handle raw PK data with caution and follow the data specifications provided by pharmacometrician to draft PK analysis dataset. The most common issues in pharmacometric programming are, but not limited to missing values, units, deriving timing variables.

For example, when concentration measurement is below the limit of quantification, the PK concentration is usually presented as "BLQ", but not the actual measurement. Pharmacometrician should define the rules for imputing BLQ values. Depending on the PK error models, BLQ values can be set to missing, 0, or ½ of LLOQ (Lower Limit of Quantification). In the case studies, the post-treatment PK samples with measurement as BLQ, NR (Not Reportable), or including "<" are standardized to missing and excluded from analysis by PK exclusion flag. The concentration of pre-treatment sample is set to "0".

In addition, the unit of PK concentration is converted to align with the unit of DTL for comparison between drug concentration and DTL value. For PK samples collected with corresponding ADA samples, drug concentration is compared with DTL to determine if ADA assay is tested under DTL. DTL is depended on the laboratory conducting ADA assays.

In this study, a population PK model is proposed and nonlinear mixed effect modeling (NONMEM) dataset is required for this model. Then dosing records, timing variables and NONMEM conserved

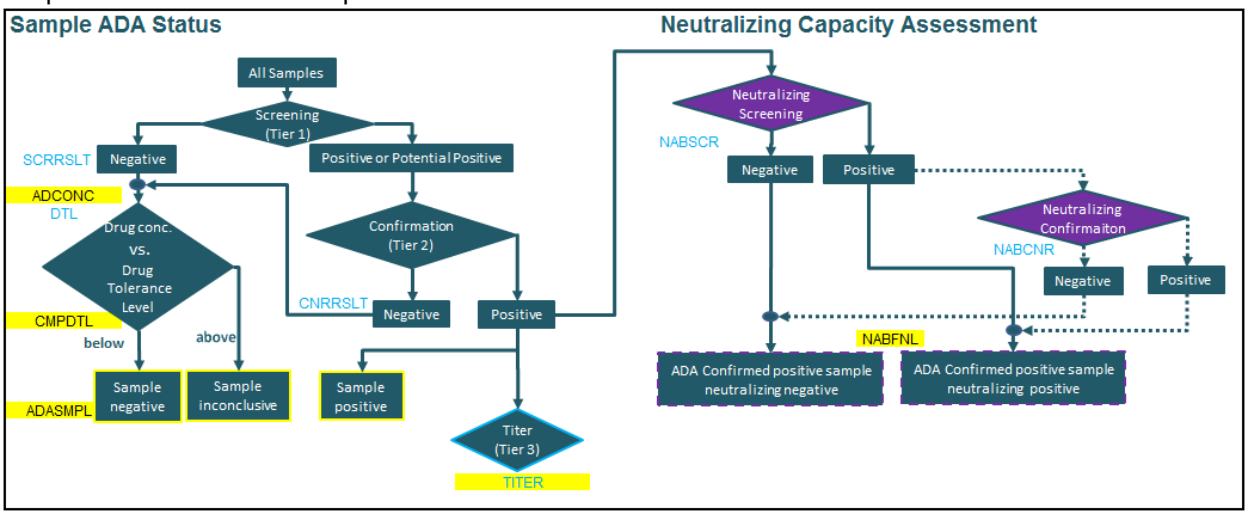
variables are derived as needed. The core variables derived for PK modeling and ADA analysis are listed in Appendix 1 for reference.

ADA ASSAYS AND DERIVATION OF VARIABLES USED IN ADA ANALYSIS

To evaluate the impact of ADA on drug ADME, each ADA sample is tested by a three-tiered approach including multiple assays: screening, confirmatory, neutralizing and titering. The highly sensitive screening assay allowed the detection of low affinity ADAs with large range of DTL. All ADA samples are tested with screening assay. In the positive samples tested by screening assay, the presence of ADA is then validated in the confirmatory assay. The confirmed ADA positive samples are further tested for antibody titer and neutralizing capacity. Similarly, neutralizing assay can be conducted by screening assay first, then followed by confirmatory assay.

A series of observations are collected from the ADA assays. As the result, corresponding sample-level variables are generated to determine the sample ADA status (ADASMPL), titer (TITER), and NAb capability (NABFNL). The positive status of ADA and NAb are determined by the positive result from confirmatory assays. If the PK concentration is greater than DTL, the ADASMPL is inconclusive even if the confirmatory assay gave the negative result, because the sensitivity of the assay is not sufficient when the drug presents high concentration in serum.

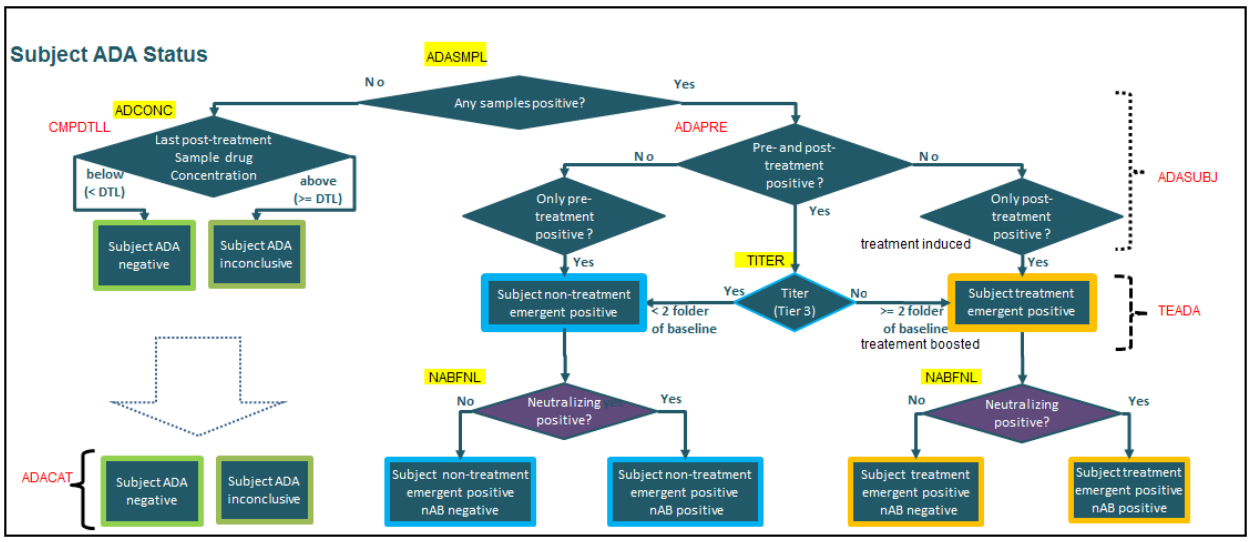
Figure 1: The concept map of three-tier approach for immunogenicity assessment.
The assay is shown in diamond and sample status is shown in rectangle. The arrows directed by solid lines connect the main assays with main assay results. The dot line arrows point to the optional assays and the sample status identified by the optional assays. The derived variables indicating sample status are placed at the side of sample status.



The ADA status of pre-treatment sample (ADAPRE) is defined as the baseline ADA. A subject is TEADA positive if the ADAPRE is negative, but one or more post-treatment sample is confirmed as ADA positive. If the titer of post-treatment ADA is elevated at least two folds of the titer in pre-treatment sample, this subject is also TEADA positive.

Besides deriving sample-level ADA status, subject-level ADA result (ADASUBJ) is necessary to determine overall immunogenicity property based on results from screening assay, confirmatory assay and comparison of drug concentration with DTL at most recent ADA sampling time. At last, subject-level ADA status category (ADACAT) is determined with titer change from baseline and Nab capacity results in all positive ADA samples on the basis of ADASUBJ. The programming flow to determine the subject-level ADA status is shown in Figure 2.

Figure 2: The concept map of the workflow to determine types of subject ADA status.
The judgement condition is shown in diamond and subject status is shown by color-coded rectangle.



ANALYSIS AND REPORTING THE CHARACTERISTICS OF ADA IMMUNE RESPONSE

In this section, PK-time plots and C-peak box plots by ADA response variables are created to illustrate programming strategy in supporting immunogenicity assessments and analysis. The x-axis of PK profile plot shows time variable “sampling time after first dose” in weeks. The x-axis of C-peak box plots shows time variable “sampling time after last dose” in hours. The y-axis shows PK concentration in ug/mL (ADCONC). Each circle in the plots stands for one PK sample. The label on the top-left of the circle indicates PK sampling time (cycle) and time point ADA response at ADA sampling time. The time point ADA response is shown in a format of “ADASMPL + (TITER)+ NABFNL”, in which P stands for positive, N stands for negative, and I stands for inconclusive. Results of titering assay and neutralizing assay are only applied for positive sample based on SCRNRLT, CNRRSLT.

1. ADAPRE (Pre-treatment ADA status)

   Definition: Positive if ADASMPL = Positive ; Negative if ADASMPL in (Negative, Inconclusive) ; Missing if ADASMPL = Missing

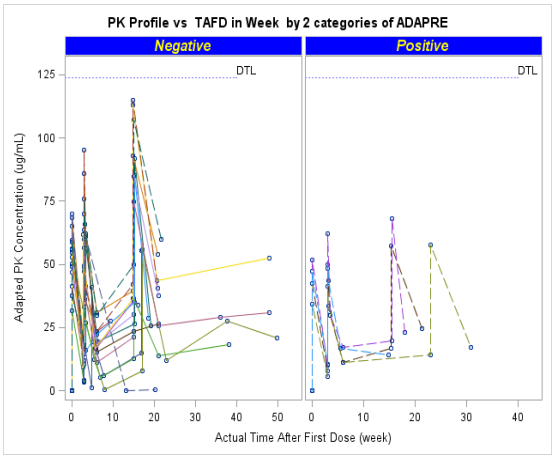
   Shown in figure, 19 subjects are selected from a study with PK and ADA sampling time points in study design as below

   PK sampling in C1, C2, 24 and 96 hours after C2 dosing, C3, C6, C8, C13, C17, and every 8 cycles thereafter

   Peak PK sampling in C1, C2, and C6.

   ADA sampling at trough PK sampling in C1, C2, C3, C6, C8, C13, C17 and every 8 cycles thereafter

Figure 3: Comparison of PK profiles by pre-treatment ADA status (below-left)



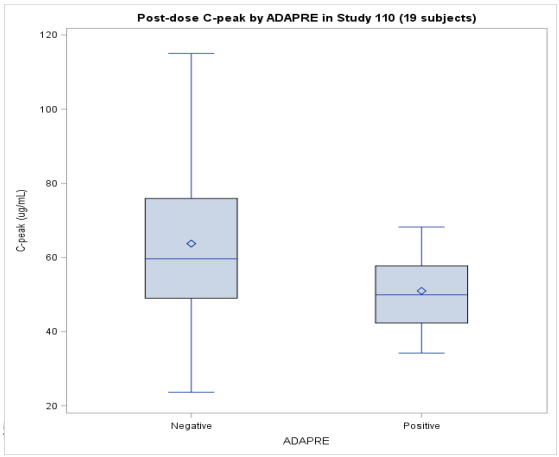
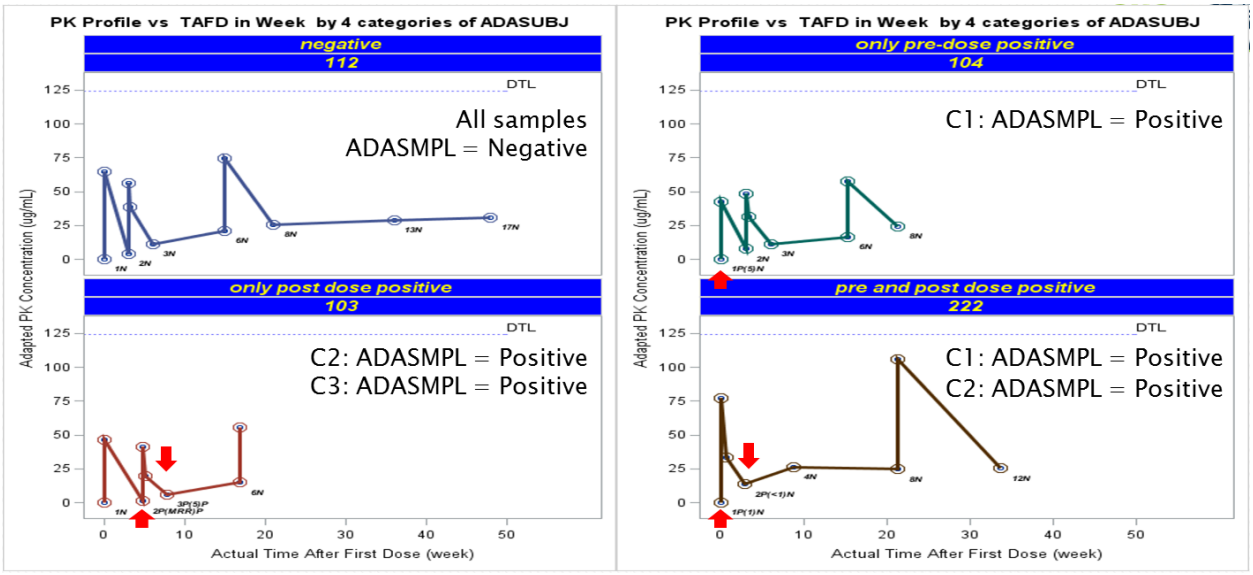


Figure 4: Comparison of C-peak by pre-treatment ADA status (above-right)

In Figure 3 and Figure 4, subjects with pre-treatment ADA (ADAPRE) positive are more likely have lower C-peak concentration. It explains that pre-existing immunogenicity status of study individual could cross interact with responder against TP, and farther prevent rising of PK concentration.

2. ADASUBJ (Subject-level ADA result)

Figure 5: Comparison of PK Profiles by subject ADA status based on only screening assay and confirmatory assay



Definition of ADASUBJ is based on Tier 1 and Tier 2 assessments. ADASUBJ is derived from ADAPRE, ADASMPL, and CMPDTLL. All individual ADA samples (ADASMPL) are evaluated according to assessment results from both Tier 1 (screening assay) and Tier2 (confirmatory assay), and comparison of PK concentration at ADA sampling time and DTL. ADASUBJ is the summary of ADASMPL of all available ADA samples and comparison of PK concentration at most recent ADA sampling time and DTL.

In order to show category of “pre-dose and post-dose positive”, additional subject (patid=222) is added in discussion from another study. Below are the PK and ADA sampling time points in study design.

> **PK sampling** in C1, 72 -168 hours after C1, C2, C4, C8 and every 4 cycles thereafter, 30 days and 3 months after EOT OR DIS;
>
> **Peak PK sampling** in C1 and C8.
>
> **ADA sampling** at trough PK sampling in C1, C2, C4, C8 and every 4 cycles thereafter, 30 days and 3 months after EOT OR DIS.

Subject (patid=222) This subject is to illustrate scenario when subject have ADA positive pre-treatment sample (Cycle 1, Positive, and 1 in titer assessment) and post-treatment sample (Cycle 2, Positive, and <1 in titer assessment). Titer of <1 means the sample is “Negative” in the titer assay at Minimum Required Dilution (MRD) of the assay (which is 10 fold)

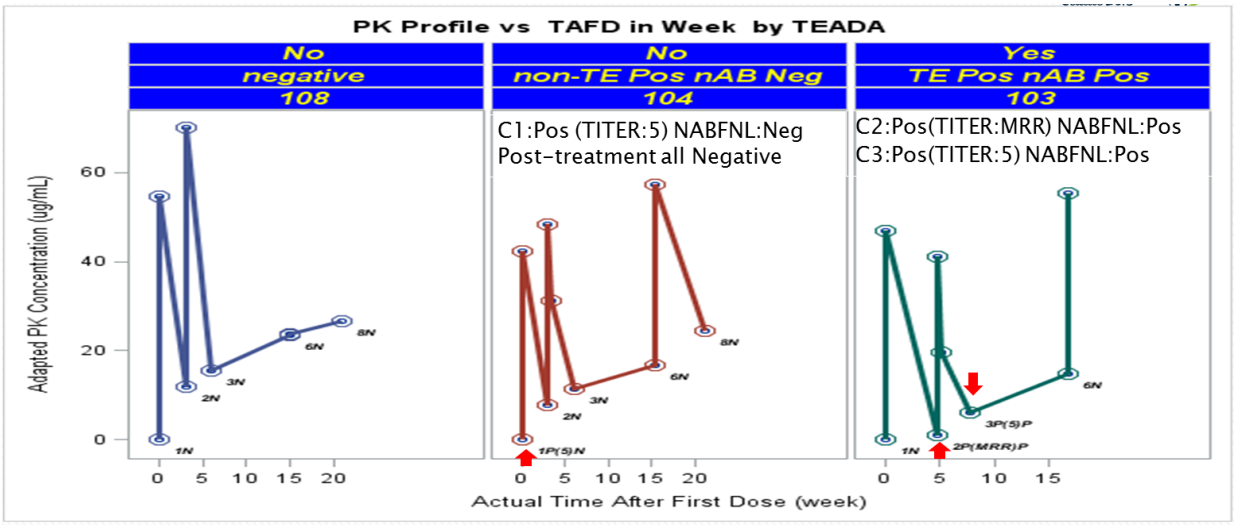
3. TEADA (Treatment Emergent ADA)

TEADA is defined as “**Yes**” if (ADASUBJ = "only post-dose positive") or (ADASUBJ = Positive & at least one post-treatment sample Titer change from baseline great than 2).

Figure 6 shows PK profiles for subjects who have either only pre-treatment positive, only post-treatment positive, or all negative ADA samples. Even though the PK-time file from subject with “**Yes**”

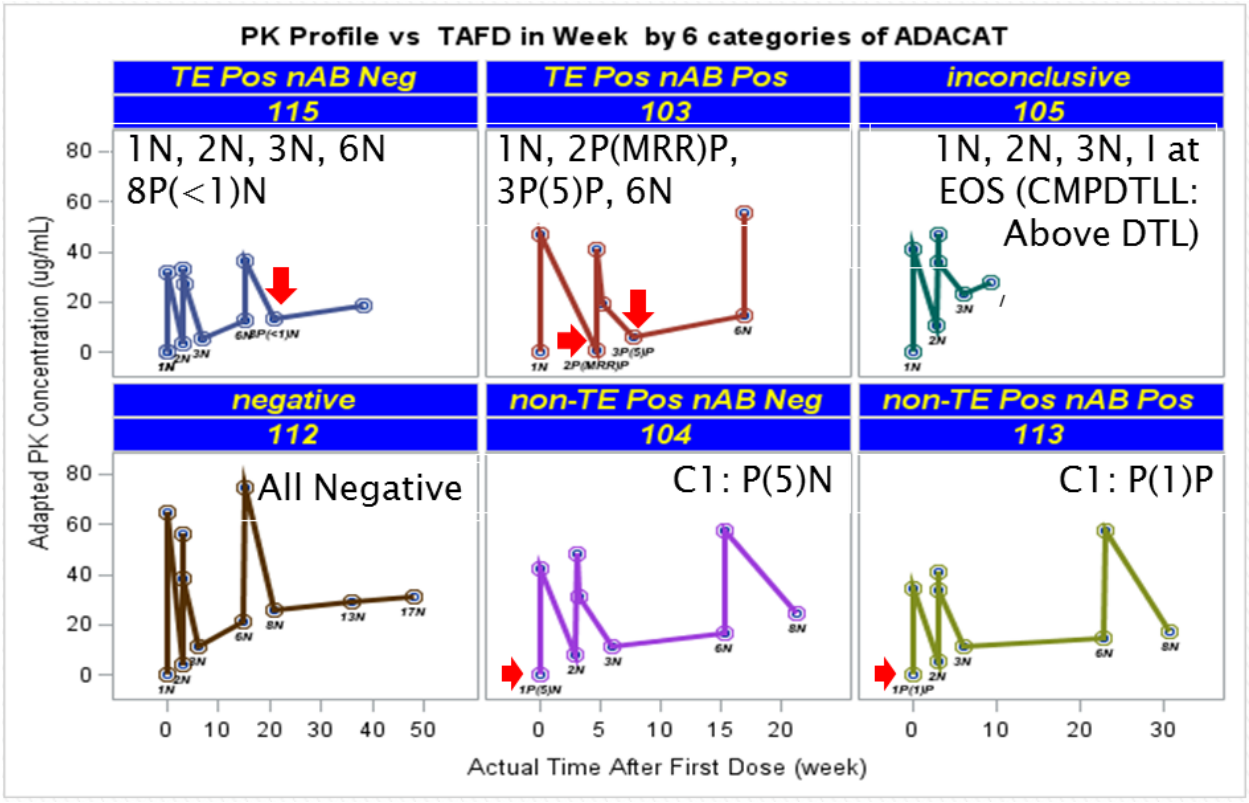
in TEADA similar to the ones from subjects with "**No**" in TEADA, it is important to look into safety data and efficacy data of those subjects with treatment emergent ADA responses.

Figure 6: Comparison of PK Profiles by TEADA



4. ADACAT (Subject-level ADA Category)

Figure 7: Comparison of PK-time Profiles by subject ADA category



ADACAT is to summarize all assay assessments results including screening assay, confirmatory assay, titering assay and neutralization assay. Six categories are defined as "**negative**", "**inconclusive**", "**non-TE positive nAB negative**", "**non-TE positive nAB positive**", "**TE positive nAB negative**" and "**TE positive nAB positive**".

In Figure 7, six PK profiles shown in six panels illustrate PK change by time in these six different subject ADA categories. These PK profiles look alike, which suggests the incidence of ADA positive response in earlier treatment cycles only has limited impact to PK concentration than persistence of ADA positive response does. In TP product development, it is crucial to assess the impact in Safety and Efficacy data for subjects with ADACAT as "**TE positive nAB negative**" and "**TE positive nAB positive**".

Subject (patid=105) ADACAT = **inconclusive**

This subject has 4 ADA samples collected in C1, C2, C3 and at EOS or DIS visit. All four samples are ADA negative in screening assessment; however the last sample are marked as "inconclusive" because PK concentration (ADCONC= 27.485ug/ML) is higher than the DTL (25ug/ML).

Subject (patid=112) ADACAT = **negative**

This subject has all samples negative from C1 to C17.

Subject (patid=104) ADACAT = **non-TE positive nAB negative**

C1 ADA sample has "Potential Positive" from screening, and "Postive" in confirmatory assessment, titering result of 5, and negative in NABSCR, and NABFNL from neutralizing assessment. All later post-treatment samples are all negative which conclude this subject wih only ADA positive before treatment is given. No TP induced ADA response observed.

Subject (patid=113) ADACAT = **non-TE positive nAB positive**

This subject only has all post-treatment samples negative except for C1 positive sample with neutralization positive.

Subject (patid=115) ADACAT = **TE positive nAB negative**

This subject has only positive sample in C8 with neutralizing capacity as negative;

Subject (patid=103) ADACAT = **TE positive nAB positive**

This subject has only positive samples in both C2 and C3 with positive result in neutralization assessment. MMR means Multiple Results reported in titering assay.

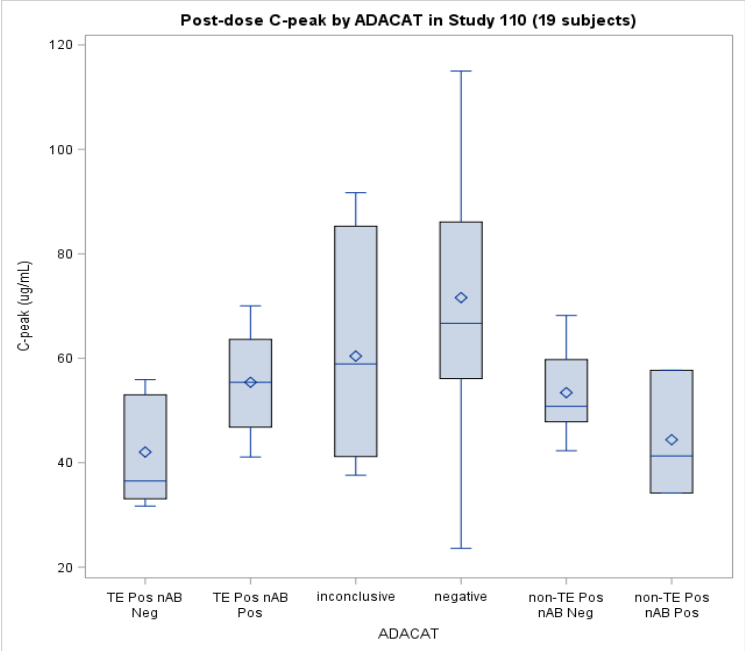


Figure 8: Comparison of C-peak by subject ADA category

Box plot shown in Figure 8 plot 19 subjects' Peak concentration by subjects' ADA categories defined in ADACAT. Subjects in categories 'negative' or inconclusive' have higher C-peak in general. There is no significant difference among the other four categories, we had discussed already in section about ADAPRE, ADASUBJ and TEADA.

CONCLUSIONS

To observe and analyze immunogenicity response on TP product, all three-tiered assessments along with neutralization assessment are equally important. Positive sample from screening assessment need further test for its specificity with confirmatory assay. The impact of ADA on safety and efficacy may correlate with ADA titer, persistence and NAb activity rather than ADA incidence. Therefore, titering assays are used to test magnitude of ADA response and neutralization assays are used to access the ability of ADA to interfere with the TP product-target interactions. This is the guidance recommended for assessment of immunogenicity of TP products during the clinical trial.

In programming support of immunogenicity analysis of TP production development, derivation of corresponding variables accordingly is essential. Because of various results from immune assays for assessments, and various standards of different laboratory, it is complicated to derive ADA response variables at each sampling time point at sample-level and overall ADA response variables at subject-level. Both time point ADA response and overall ADA response categorization are equally important in drawing a full picture of ADA responses during TP product development among all study population

1. ADAPRE subject pre-treatment ADA status suggests the pre-exiting immunogenicity condition. It helps to predict possible immunogenicity outcomes. It is important to evaluate ADAPRE before apply TP product into study subject because immune responses to TP products have potential to affect product safety and efficacy
2. Incidence of positive ADA response may not be as important in clinical effects of subject immune responses as its persistence. It is important to monitor the incidence of ADA induction and implications of ADA responses for TA production safety and efficacy. All evaluable ADA samples should be included to determine overall subject ADA response to TP product. PK concentration level at last ADA sampling is important to determine overall ADA subject status.
3. Per guidance, it is important to observe immune response on TP product at real time, a quick summary of ADA response based on available assessment result is recommended. Because of lack of neutralization assay result due to sequential of assessment process, ADASUBJ is recommended to summarize ADA response from tier 1 and tie 2 assessment at early stage when only a few ADA samples are available, titering comparison with baseline are not possible and NAb assessments results are not available.
4. TEADA flag subjects who have ADA response emerged with treatment of TP product. It is useful for us to focus on these treatment-emergent positive samples, evaluate impact to safety and efficacy.
5. Variables SCRRSLT, CNRRSLT, NABFNL, TITER, CMPDTL, ADASMPL, ADAPRE, ADASUBJ, CMPDTLL, TEADA, and ADACAT reflect different aspects of ADA activities in study subjects. ADA response varies in each individual and changes constantly in study course because of its sensitivity, variability, and complexity due to complicated characteristics of ADA. ADA response on TP products need to be closely monitored and assessed in order to prevent unwanted impact on safety and efficacy of TP production development.

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RECOMMENDED READING

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APPENDIX

APPENDIX 1. DERIVATION RULES OF CORE VARIABLES USED IN PK AND ADA ANALYSIS

Variable Name	Variable Label	Type	Derivation/Comments
CYCLE	Cycle Number of Planned Dose	Num	
TAFDWEEK	Actual Time After First Dose (week)	Num	PK/ADA Sampling Date/Time - First Dose Date/Time
TALDHOUR	Actual Time After Last Dose (hour)	Num	PK/ADA Sampling Date/Time - Previous Dose Date/Time
ADCONC	Adapted PK Concentration (ug/mL)	Num	Convert unit of original PK measurements to ug/mL Imputation rules are applied (which includes but not limits to the list below) = 0 for pre-treatment PK sample of dose cycle 1 = . for post-treatment PK samples if measurement is BLQ, NR, or including “<”
CFLAG	Flag for issues	Num	Exclude PK records per analysis need based on CFLAGCMT
CFLAGCMT	Comment for data issues	Char	Comments from bioanalyst and pharmacometrician on concentration record
SCRRSLT	Result of ADA Screening Assay	Char	Original screening assay result, can be one of Positive, Negative, Possible Positive, and ""
CNRRSLT	Result of ADA Confirmatory Assay	Char	Original confirmatory assay result, can be one of Positive, Negative, NA and ""
COMADA	Comments for ADA assays	Char	Comments from Bioanalyst on ADA assays
DTL	Drug Tolerance Level (µg/mL)	Num	From BA laboratory
CMPDTL	Drug concentration compare with DTL of ADA sample	Char	Below DTL if .< ADCONC < DTL Above DTL if ADCONC >= DTL

ADASMPL	Sample-level ADA result compared with DTL	Char	Positive if (CNRRSLT = Positive) Negative if (CNRRSLT ^= Positive) and CMPDTL = Below DTL Inconclusive if (CNRRSLT ^= Positive) and CMPDTL = Above DTL Missing if (SCRRSLT = "" & CNRRSLT = "")
CMPDTLL*	Drug concentration compare with DTL of most recent ADA sample	Char	Below DTLif .< ADCONC < DTL at most recent ADA sample with SCRRSLT not in ("", "NR", "QNS") Above DTL if ADCONC >= DTL at most recent ADA sample with SCRRSLT not in ("", "NR", "QNS")
ADAPRE*	Pre-treatment ADA status	Char	For pre-treatment sample of Dose Cycle 1 Positive if ADASMPL = Positive Negative if ADASMPL in (Negative, Inconclusive) Missing if ADASMPL = Missing
ADASUBJ*	Subject-level ADA result	Char	negative if ADAPRE ^= Positive and all post-treatment ADASMPL ^= Positive inconclusive if ADAPRE ^= Positive and subject with no positive ADA samples and CMPDTLL= Above DTL only pre-dose positive if ADAPRE=Positive and no positive post treatment ADA samples pre and post dose positive if ADAPRE=Positive and one or more positive post treatment ADA samples only post dose positive if ADAPRE=Negative and one or more positive post treatment ADA samples post dose positive and pre dose missing if ADAPRE=Missing and one or more positive post treatment ADA samples
TITER	Titer ADA	Num	The original titer is presented as ratio of dilution, e.g. 1:25, 1:50, etc. 25 if dilution is 1:25 50 if dilution is 1:50 <1: “Negative” in the titer assay at Minimum Required Dilution (MRD) of the assay (which is 10 fold). 1: the first dilution @ MRD is positive. NTR: No Valid Titer Result obtained upon repeat. This usually happens when the result is fluctuating btw negative and positive. MRR: Multiple Results reported.
NABSCR	Result Neutralizing Screening Assay	Char	Positive, Negative, or NA
NABCON	Result Neutralizing Confirmatory Assay	Char	Positive, Negative, NA or ""
NABFNL	Final result Neutralizing Assay	Char	=NABCON if NABCON in (Positive, Negative); =NABSCR if NABCON is not available
TEADA*	Treatment Emergent ADA	Char	Yes if ((ADAPRE = Negative & at least one post-treatment sample Positive) or (ADAPRE = Positive & at least one post-treatment sample Positive & at least one positive sample with titer change from baseline great than 2)) No if otherwise
ADACAT*	Subject-level ADA Category	Char	= ADASUBJ if ADASUBJ in (negative, inconclusive) non-TE Pos nAB Neg if TEADA = No & no sample with NABFNL = Positive non-TE nAB Pos if TEADA = No & at least one sample NABFNL = Positive TE nAB Neg if TEADA = Yes & no sample with NABFNL =Positive TE nAB Pos if TEADA = Yes & at least one sample with NABFNL = Positive non-TE Pos nAB Missing or TE Pos nAB Missing if TEADA =Yes and NABFNL = " "
* indicates Subject-level variables			

CONTACT INFORMATION

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