Paper AS16

Statistical Programming Methods for Evaluating the Impact of Immunogenicity on Safety and Efficacy Outcomes

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Abstract

Immunogenicity—the immune system's response to biologic therapies—plays a critical role in shaping both the safety and efficacy profiles of these treatments. As biologics become a bigger focus in clinical development, understanding immunogenicity is increasingly important, especially for large molecule drug trials. This paper presents a comprehensive statistical programming framework for integrating and analyzing immunogenicity data within the ADaM (Analysis Data Model) structure, enabling assessment of its impact on safety outcomes (e.g., adverse events), pharmacokinetics (PK), and treatment efficacy. Emphasis is placed on maintaining data traceability and adherence to CDISC standards throughout the process. The paper includes practical examples of table, listing, and figure (TLF) design to effectively summarize immunogenicity-related findings, along with sample SAS code for deriving key ADaM variables and generating TLF outputs. Additionally, it provides guidance on immunogenicity data collection, standardization, and mapping to SDTM and ADaM datasets.

Introduction

Immunogenicity, the immune response to therapeutic proteins, is a key consideration in the development of biologic therapies. This response may result in the formation of anti-drug antibodies (ADA), including binding antibodies and neutralizing antibodies (NAb), which can potentially influence the safety, pharmacokinetics, and efficacy of the treatment. Regulatory guidance recommends systematic assessment of immunogenicity and its potential clinical impact. While the presence of ADA does not inherently indicate adverse clinical consequences, certain antibody characteristics—such as treatment-emergent status, high titers, or neutralizing activity—may need further investigation due to their potential to alter drug exposure or trigger immune-mediated effects. Robust, standardized statistical programming approaches are therefore essential to support transparent, reproducible, and CDISC-compliant analyses. This paper presents a comprehensive framework for integrating immunogenicity data within ADaM, enabling consistent evaluation of its impact across key clinical outcomes.

Data Sources and Structure

Immunogenicity data in clinical trials are typically generated from bioanalytical assays designed to detect immune responses to therapeutic proteins. These assays commonly include a multi-tiered testing strategy consisting of screening assays to identify potential anti-drug antibody (ADA) responses, confirmatory assays to verify specificity, titer and neutralizing antibody (NAb) assays for the ADA positive samples. Immunogenicity samples are collected longitudinally at predefined time points relative to dosing.

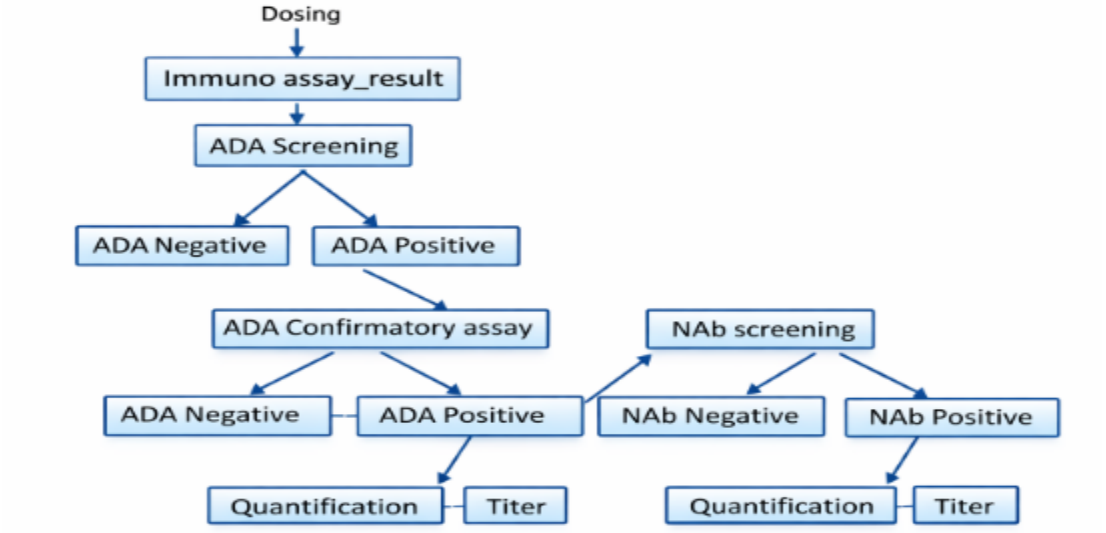

Figure 1: Multi-tiered ADA Testing Strategy

Immunogenicity Data Flow

Immunogenicity data from EDC and central laboratory vendor sources were integrated and mapped to the SDTM IS dataset and transformed into ADaM ADIS dataset to support analysis-ready derivations and generation of immunogenicity TLFs. ADaM ADIS is further integrated to support evaluation of the impact of immunogenicity on safety and efficacy outcomes through integrated TLFs.

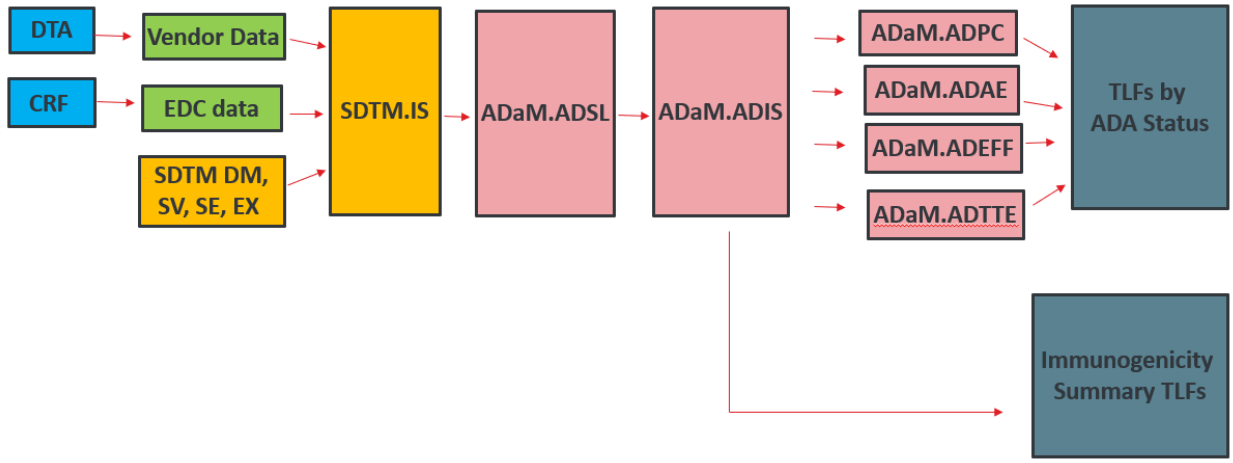

Figure 2: Immunogenicity Data Flow

SDTM Mapping

Immunogenicity data is mapped from multiple sources, including the clinical electronic data capture (EDC) system and a central laboratory vendor responsible for immunogenicity assay analyses. EDC data serves as the primary source for subject identifiers, specimen collection details, visit name and number, collection date/time. Vendor laboratory data provides analytical results from anti-drug antibody (ADA) and neutralizing antibody (NAb) assays, including screening, confirmatory, titer, and quantitative assessments. Vendor-specific test codes, result formats, and assay stages were standardized and mapped to the SDTM IS domain using controlled terminology. Distinct values of ISTESTCD and ISTEST were used to differentiate assay types, while ISORRES and ISSTRES variables capture original and standardized results, respectively. Data integration was performed using sample identifiers and visit information, enabling reliable linkage between EDC specimen records and vendor assay outputs. Sequencing variables (ISSEQ) and collection timing variables (ISDTC) were derived to maintain the chronological order.

ADaM Derivation Framework

This ADaM derivation framework provides a structured programming approach for analysis-ready ADaM datasets in the context of immunogenicity analysis.

ADSL

The Subject-Level Analysis Dataset (ADSL) serves as the foundational dataset for ADaM analyses. For immunogenicity assessments, ADSL is extended to include derived population flags that identify subjects with evaluable anti-drug antibody (ADA) and neutralizing antibody (NAb) data which can be used across downstream ADaM datasets and support subgroup comparisons.

Immunogenicity Analysis Populations

Several immunogenicity-specific population flags are derived in ADSL to ensure consistent subject inclusion across downstream ADaM datasets

- The Immunogenicity population flag: defined as the subjects who received at least one dose of the study drug and have at least one post-baseline Immunogenicity assessment.
- Immunogenicity PK-Evaluable population flag: derived as subjects who received at least one dose of the study drug and have at least one post-baseline Immunogenicity assessment and sufficient PK data to reliably report 1 or more PK parameters.
- Immunogenicity Efficacy population flag: derived as subjects who received at least one dose of the study drug and have at least one post-baseline Immunogenicity assessment and post-baseline efficacy assessment.

ADIS (Analysis Dataset for Immunogenicity)
The Analysis Dataset for Immunogenicity (ADIS) is an ADaM Basic Data Structure (BDS) dataset designed to support longitudinal analysis of immunogenicity endpoints, including anti-drug antibody (ADA) and neutralizing antibody (NAb) responses. ADIS is organized with one record per subject per parameter per analysis time point and uses a PARAM/PARAMCD-driven structure to represent derived immunogenicity parameters such as overall antibody status, treatment-emergent ADA status, and other assay-specific classifications. Source data are primarily derived from SDTM immunogenicity domains and are integrated with subject-level information from ADSL, including treatment assignment, dosing dates, and immunogenicity analysis population flags. Standard ADaM timing and visit variables are used to align immunogenicity assessments relative to treatment exposure and baseline, enabling consistent longitudinal evaluation.

ADIS contains analysis-ready categorical parameters represented in AVALC, supported by analysis flags and value-level metadata to clearly define derivation rules for each immunogenicity endpoint. Parameters such as antibody status and treatment-emergent ADA are derived using standardized baseline definitions and post-baseline assessment. The dataset is designed to support descriptive summaries of immunogenicity incidence and prevalence, time-based evaluations of antibody development, and integration with safety, pharmacokinetic, and efficacy analyses. By consolidating complex immunogenicity derivations into a single BDS-compliant ADaM dataset with full traceability to SDTM, ADIS provides a consistent, transparent, and reproducible foundation for evaluating the clinical impact of immunogenicity.

Below is the table summarizing the parameters that need to be derived in ADIS to evaluate the Immunogenicity.

PARAMCD	PARAM	Derivation Logic
ADASTAT	ADA Status	Subject level ADA Status, Derived as ‘Negative’ for subjects with pre-existing ADA or subjects with Negative results at baseline and post-baseline. Derived as ‘Positive’ for subjects with Treatment Emergent or Treatment Boosted ADA.
NEUTSTAT	Neutralizing Status	Subject level NAb Status, Derived as ‘Negative’ for subjects with Negative results at baseline and post-baseline. Derived as ‘Positive’ for subjects with at least 1 Positive results at post-baseline.
ADAPRE	Pre-Existing ADA	Subjects with ADA positive at baseline and all the post-baseline positive sample titer values are <= x-fold increase from baseline titer values.
ADATRTEM	Treatment emergent ADA	Subjects with ADA negative at baseline and with at least one post-baseline positive ADA
ADATRTBS	Treatment-boosted ADA	Subjects with ADA positive at baseline and any of the post-baseline positive sample titer values are > y-fold increase from baseline titer values.
ADAPRST	Persistent ADA	Treatment emergent ADA subjects with at least 2 consecutive positive post-baseline samples separated by at least a y-week period with no ADA negative results in between
ADAINDT	Indeterminate ADA	Treatment-induced ADA subjects with positive result at last post-baseline visit only
ADATRNS	Transient ADA	Treatment-induced ADA subjects who do not satisfy the conditions for Persistent or Indeterminate ADA
ADATONS	Time to onset of 1st ADA	The time between 1st dose date and first instance of treatment-induced ADA

ADAPDUR	Duration of Positive ADA	The time between 2 positive post-baseline ADA samples with no ADA negative results in between.
ADAMXTIT	Maximum Titer	Maximum Titer value observed for the post-baseline Positive ADA Samples
ADAMXTIC	Maximum Titer Categories	Categories are based on the maximum post baseline titer value 0-<1000 1000-<=10000 >10000

Analysis of Impact

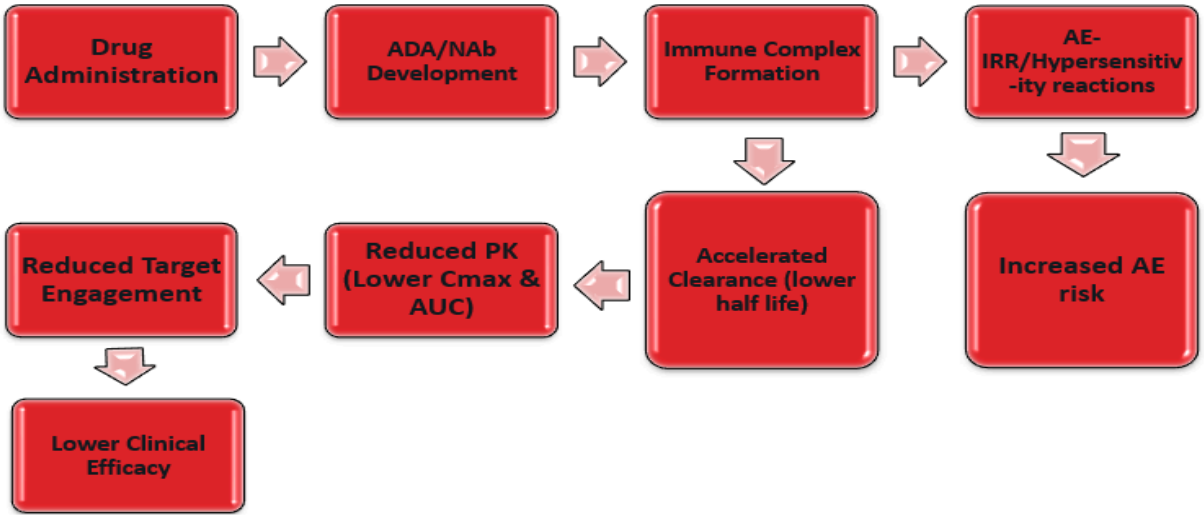

Figure 3: Immunogenicity of Impact on Safety, PK and Efficacy

Safety Impact

Immunogenicity has the potential to influence the safety profile of biologic therapies through immune-mediated mechanisms or indirect effects on drug exposure. While the presence of ADA does not imply increased safety risk, certain antibody characteristics such as treatment-emergent status, high titers, or neutralizing capacity may need further evaluation.

Immunogenicity impact on Adverse Events

Immunogenicity has the potential to impact the safety profile of a drug molecule. Guidance from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) notes that the development of anti-drug antibodies (ADA) may be associated with immune-mediated adverse events, including hypersensitivity reactions, infusion-related reactions, and other immune-related safety signals. To meet these regulatory expectations, there is a need for the integration of the Immunogenicity with AE data. Analyses typically compare the incidence, severity, and seriousness of treatment-emergent adverse events between ADA-positive and ADA-negative subjects and explore whether adverse events occur predominantly before or after confirmed ADA positivity by ensuring traceability from raw data through SDTM and ADaM to final safety outputs. The framework presented in this paper supports these assessments through standardized integration of immunogenicity data into the ADAE dataset and CDISC-compliant evaluation of adverse events in the context of immunogenicity.

Below is the table summarizing the variables that need to be derived in ADAE to evaluate adverse events in the context of immunogenicity. Selected tables and figures are presented as representative examples, while additional TLFs are summarized briefly to describe their structure and intended analyses.

Variable Name	Variable Label	Type	Derivation
IRRFL	Infusion Related Reaction Flag	Char	Derived from SuppAE.QVAL where QNAM=IRRFL
HYPSFL	Hypersensitivity Reaction Flag	Char	Derived from SuppAE.QVAL where QNAM=IRRFL
ADASTAT	ADA Status	Char	Derived from ADIS.AVALC when ADIS.PARAMCD=ADASTAT
ADAMXTIT	ADA Maximum Titer Value	Integer	Derived from ADIS.AVALC when ADIS.PARAMCD=ADAMXTIT
NABSTAT	NAb Status	Char	Derived from ADIS.AVALC when ADIS.PARAMCD=NABSTAT
NABMXTIT	NAb Maximum Titer Value	Integer	Derived from ADIS.AVALC when ADIS.PARAMCD=NABMXTIT
ADATRTEM	Treatment-Emergent ADA Flag	Char	Derived from ADIS.AVALC when ADIS.PARAMCD=ADATRTEM
ADATONS	Time to onset of 1st ADA	Integer	Derived from ADIS.AVALC when ADIS.PARAMCD=ADATONS
AETIMREL	AE Timing Relative to ADA	Char	If the analysis is based on the first confirmed ADA-positive date: if ASTDT >= ADATONS then AETIMREL = POST-ADA'; else If ASTDT < ADATONS then AETIMREL=PRE-ADA. If analysis is based on aligning each AE relative to each ADA Positive sample then use PROC SQL join.

Subjects can have multiple confirmed ADA-positive assessments over time as well as multiple adverse events, requiring adverse events to be evaluated relative to each ADA occurrence. In such cases, the traditional DATA step merge may not be appropriate due to many-to-many relationships; integration must be implemented as a controlled Cartesian join using PROC SQL, with explicit join conditions based on subject identifiers and timing variables to ensure correct record pairing and traceability.

Selected tables and figures are presented as representative examples, while additional TLFs are summarized briefly to describe their structure and intended analyses.

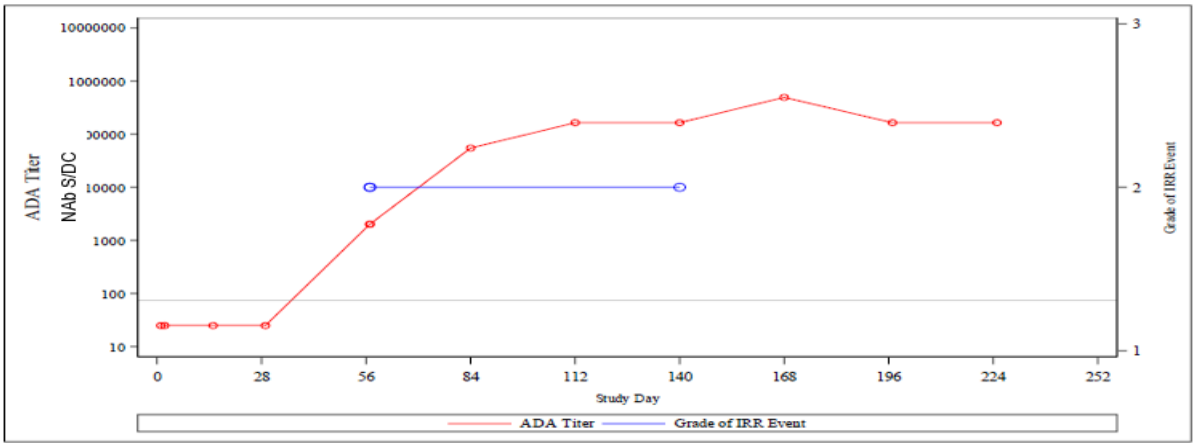

Figure 4: Figure to evaluate individual IRR event grades vs Titer for each patient

(ADA/NAb Status)/ Adverse Events Grade	Treatment 1 (N=XX)	Treatment 2 (N=XX)	Total (N=XX)
All Safety patients	xx	xx	xx
IRR Events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			
Immunogenicity-Evaluable Patients	xx	xx	xx
IRR Events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			
ADA Negative (Immunogenicity-Evaluable Patients)	xx	xx	xx
IRR Events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			
ADA Positive (Immunogenicity-Evaluable Patients)	xx	xx	xx
IRR Events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			
NAb Negative (Immunogenicity-Evaluable Patients)	xx	xx	xx
IRR Events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…			
NAb Positive (Immunogenicity-Evaluable Patients)	xx	xx	xx
IRR Events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Grade 3	xx (xx.x)	xx (xx.x)	xx (xx.x)

Figure5: Summary table of IRR events summarized by ADA/NAb Status

Output Type	Title	Description
Table	Incidence of Treatment-Emergent Adverse Events by ADA Status	Summarizes subject-level incidence of treatment-emergent adverse events stratified by ADA status.
Table	Timing of Treatment-Emergent Adverse Events Relative to ADA Detection	Summarizes treatment-emergent adverse events classified as occurring before or after first confirmed ADA positivity
Table	Severity and Seriousness by ADA Status	Displays incidence of Grade ≥3 adverse events, serious adverse events, and adverse events leading to discontinuation, stratified by ADA status.
Table	Kaplan–Meier Plot of Cumulative Incidence —Time to First TEAE by ADA Status	Illustrates cumulative incidence of first treatment-emergent adverse event stratified by ADA status, enabling exploratory evaluation of event timing.
Listing	Listing of Subjects with Treatment-Emergent ADA and Related AEs	Provides subject-level details for treatment-emergent ADA-positive subjects, including ADA timing, AE onset, severity, seriousness, and relationship to treatment.
Figure	Bar Chart of AE Incidence by ADA Group	Displays percentage of subjects with at least one TEAE by ADA subgroup, providing a high-level visual comparison of safety incidence.

Immunogenicity impact on Pharmacokinetic Concentrations

Immunogenicity may influence pharmacokinetic (PK) behavior of biologic therapies by altering drug disposition, clearance, or bioavailability. The development of anti-drug antibodies (ADA), particularly neutralizing antibodies (NAb), has the potential to reduce circulating drug concentrations through immune complex formation, enhanced clearance, or direct neutralization of pharmacologic activity. Regulatory guidance from both the U.S. Food and Drug

Administration (FDA) and the European Medicines Agency (EMA) recommend evaluating PK exposure in relation to immunogenicity to understand whether antibody development is associated with clinically meaningful changes in drug concentrations. Analyses typically evaluate PK concentrations and derived PK parameters (e.g., Cmax, AUC, trough concentrations) stratified by ADA or NAb status. In addition, PK samples are often categorized as occurring before or after confirmed ADA positivity. The framework presented in this paper enables traceable, CDISC-compliant integration of immunogenicity and PK data within ADaM, supporting transparent evaluation of potential immunogenicity-related effects on drug exposure.

Below is the table summarizing the additional variables that can be derived in ADPC/ADPP to evaluate PK concentrations and PK Parameters in the context of immunogenicity.

Variable Name	Variable Label	Type	Derivation
ADASTAT	ADA Status	Char	Derived from ADIS.AVALC when ADIS.PARAMCD=ADASTAT
ADAMXTIT	ADA Maximum Titer Value	Integer	Derived from ADIS.AVALC when ADIS.PARAMCD=ADAMXTIT
NABSTAT	NAb Status	Char	Derived from ADIS.AVALC when ADIS.PARAMCD=NABSTAT
NABMXTIT	NAb Maximum Titer Value	Integer	Derived from ADIS.AVALC when ADIS.PARAMCD=NABMXTIT
ADATRTEM	Treatment-Emergent ADA Flag	Char	Derived from ADIS.AVALC when ADIS.PARAMCD=ADATRTEM
ADATONS	Time to onset of 1st ADA	Integer	Derived from ADIS.AVALC when ADIS.PARAMCD=ADATONS
PCTIMREL	PC Timing Relative to ADA	Char	If analysis is based on the first confirmed ADA-positive date: if ADT >= ADATONS then PCTIMREL = POST-ADA'; else If ADT < ADATONS then PCTIMREL=PRE-ADA. If analysis is based on aligning each Concentration record relative to each ADA Positive sample then use PROC SQL join.

Subjects can have multiple confirmed ADA-positive assessments over time as well as multiple PK samples collected over time. In such cases, the traditional DATA step merge may not be appropriate due to many-to-many relationships; integration must be implemented as a controlled Cartesian join using PROC SQL, with explicit join conditions based on subject identifiers and timing variables to ensure correct record pairing and traceability.

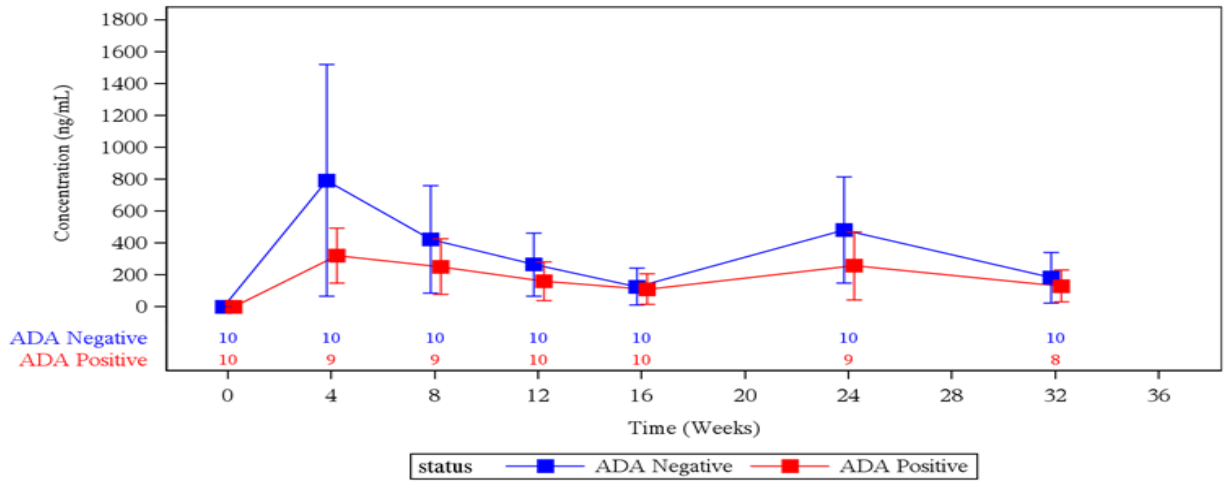

Figure6: Example figure to evaluate mean PK Concentrations by ADA Status

Visit	ADA/NAb Status	Summary statistics	Scheduled Timepoint						% Change in EOI vs C1D1 EOI
			D1 Predose	D1 End of Infusion	D1 2-4 Hours	D2 Visit	D8 Visit	D15 Visit	
Cx	ADA-	n	xx	xx	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Maximum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Geometric mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Geometric CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
	ADA+/NAb-	n	xx	xx	xx	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Maximum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Geometric mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Geometric CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
	ADA+/NAb+	n	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx
		Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Minimum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Maximum	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
		Geometric mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	

Figure7: Summary table of PK Concentrations summarized by ADA/NAb Status

Selected tables and figures are presented as representative examples, while additional TLFs are summarized briefly to describe their structure and intended analyses.

Output Type	Title	Description
Table	Summary of PK Exposure Parameters by ADA Status	Summarizes geometric mean of PK exposure parameters (e.g., Cmax, AUC, trough, CL) stratified by ADA and NAb status using the immunogenicity PK-evaluable population
Table	PK Exposure by ADA and NAb Titer Quartiles	Presents PK exposure parameters across increasing ADA and NAb titer categories
Table	PK Concentrations Before and After ADA Development	Summarizes PK concentrations classified as pre-ADA or post-ADA based on time alignment to the first confirmed ADA-positive assessment
Figure	Individual PK Concentrations Relative to ADA Timing	Scatter plot Showing the distribution of individual PK concentrations before and after ADA development among ADA-positive subjects
Figure	Scatter or Box Plots of PK Exposure vs ADA/NAb Titer	Illustrates the relationship between PK exposure parameters and ADA or NAb titers, providing a visual assessment of potential exposure–titer associations.

Immunogenicity impact on Efficacy

Immunogenicity may influence the clinical efficacy of biologic therapies through both direct and indirect mechanisms. The development of anti-drug antibodies (ADA), particularly neutralizing antibodies (NAb), has the potential to reduce therapeutic effectiveness by neutralizing the drug's pharmacologic activity or by altering drug exposure through increased clearance. Regulatory guidance from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend evaluating efficacy outcomes in the context of immunogenicity to assess whether treatment response differs between ADA-positive and ADA-negative subjects. Assessment of the relationship between immunogenicity and efficacy requires integration of immunogenicity data with efficacy endpoints at both the subject and visit level. Analyses typically compare response rates, change-from-baseline measures, or

time-to-event endpoints across immunogenicity subgroups and explore the timing of efficacy assessments relative to ADA development. The analytical framework described in this paper enables standardized integration of immunogenicity flags into efficacy analysis datasets (e.g., ADTL, ADRS, ADEFF or ADTTE) using CDISC-compliant ADaM derivations.

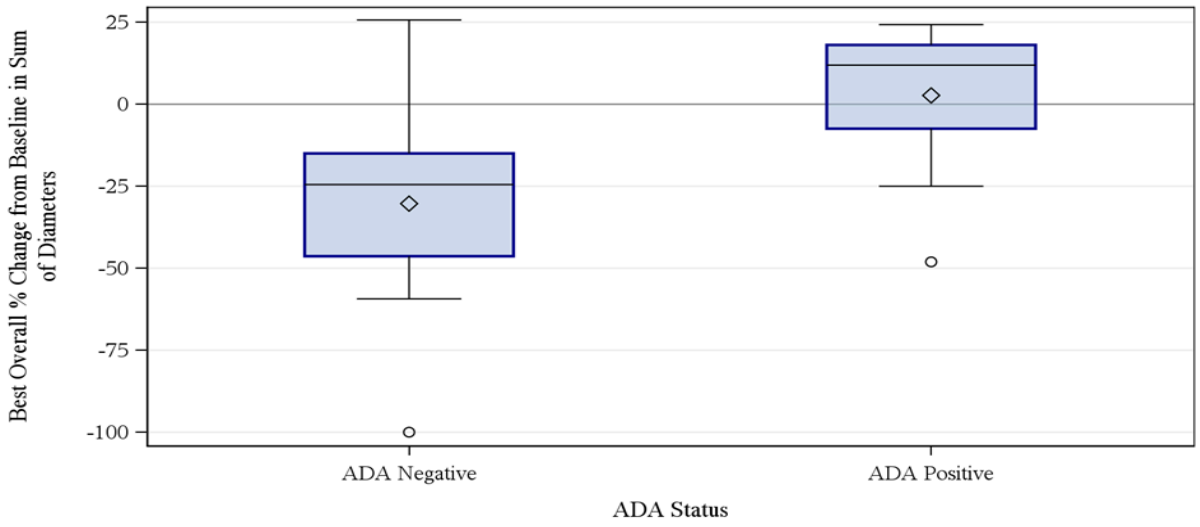

Figure8: Best Overall %Change from Baseline in Sum of Diameters by ADA Status (Sum of diameters represents the total of the longest diameters of selected target lesions measured at each assessment.)

(ADA/NAb Status)/ Efficacy Assessment	Treatment 1 (N=XX)	Treatment 2 (N=XX)	Total (N=XX)
All patients	xx	xx	xx
ORR, n(%) [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)
PFS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x*)	xx.x, (xx.x*, xx.x)
OS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
TTR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOT, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
Immunogenicity-Evaluable Patients	xx	xx	xx
ORR, n(%) [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)
PFS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
OS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
TTR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOT, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
ADA Negative (Immunogenicity-Evaluable Patients)	xx	xx	xx
ORR, n(%) [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)
PFS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
OS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
TTR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOT, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
ADA Positive (Immunogenicity-Evaluable Patients)	xx	xx	xx
ORR, n(%) [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)
PFS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
OS, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
TTR, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)
DOT, median (min, max)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)	xx.x, (xx.x, xx.x)

Figure9: Summary of Efficacy Assessments by ADA/NAb Status
ORR= Objective Response Rate; PFS=Progression Free Survival; OS=Overall Survival; DOR= Duration of Response; TTR= Time to Response; DOT= Duration of Treatment

Selected tables and figures are presented as representative examples, while additional TLFs are summarized briefly to describe their structure and intended analyses.

Output Type	Title	Description
Table	Change from Baseline in Efficacy Endpoints by ADA Status	Summarizes change-from-baseline efficacy measures stratified by ADA and NAb status using the immunogenicity efficacy population
Table	Efficacy Outcomes Before and After ADA Positive	Presents efficacy assessments classified as occurring before or after confirmed ADA positivity, supporting time-aligned evaluation of treatment response
Table	Tumor Response Categories by ADA Status	Displays distribution of response categories (e.g., CR, PR, SD, PD) stratified by ADA status for descriptive comparison
Figure	Spider Plot of Efficacy Changes Across Time Points by ADA Status	Provides a visual summary of change-from-baseline efficacy measures comparing ADA-positive and ADA-negative subjects
Figure	Kaplan–Meier Plots for Time-to-Event Efficacy Endpoints by ADA Status	Displays percentage of subjects with at least one TEAE by ADA subgroup, providing a high-level visual comparison of safety incidence.

Conclusion

Immunogenicity remains a critical consideration in the clinical development of biologic therapies due to its potential impact on safety, pharmacokinetics, and efficacy**.** This paper presents a standardized, ADaM-based statistical programming framework that enables traceable and reproducible evaluation of immunogenicity across these domains.

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