Paper PP27

Analysis and Reporting of Immunogenicity Anti-drug Antibody Data

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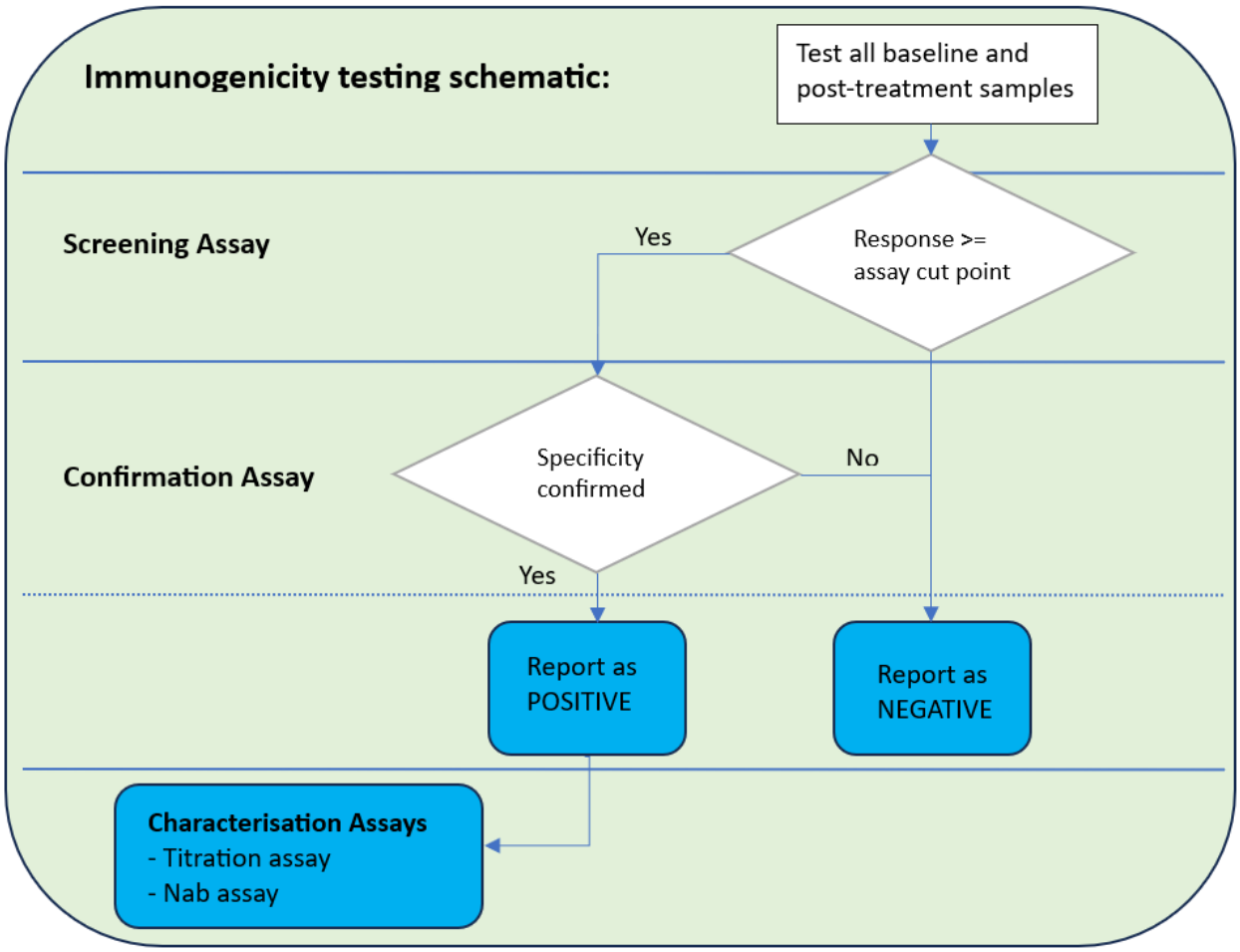
ABSTRACT

Immunogenicity is a measure of the immune response to a therapeutic drug (e.g., a monoclonal antibody) resulting in generation of anti-drug antibodies (ADAs, also known as anti-therapeutic antibodies (ATAs)). It is becoming an increasingly common and important constituent of clinical trial reporting and the FDA is focusing on this topic more and more. This paper aims to provide information on the type of data provided after clinical sample testing through a sequence of assays and a possible approach to converting IS SDTM into CDISC ADaM structure, discussing data handling techniques to support the various analysis and reporting requirements.

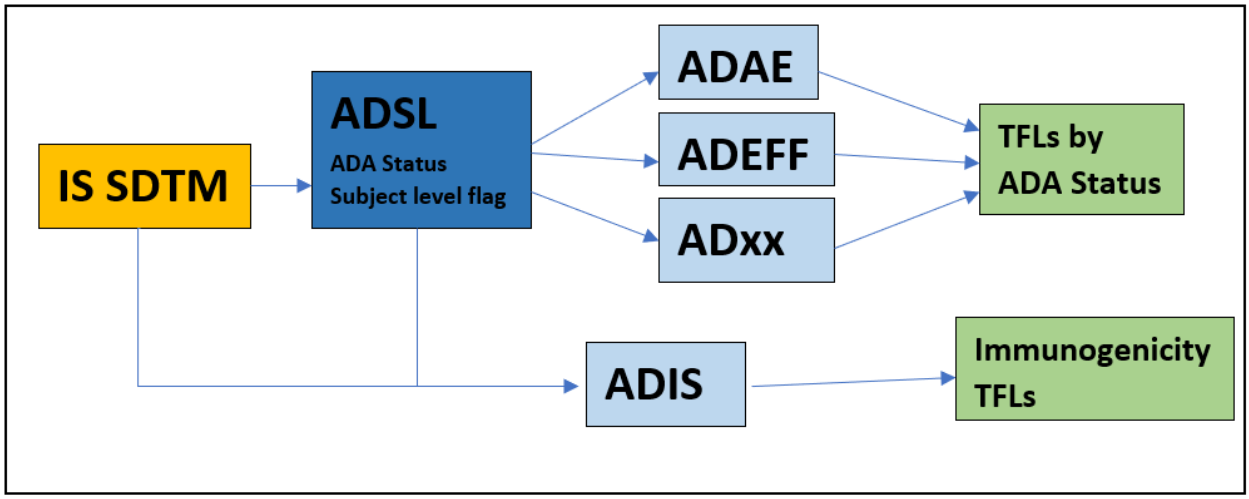
INTRODUCTION

The inclusion of immunogenicity analysis is becoming ever more commonplace in clinical trials. The FDA Study Data Technical Conformance Guide now specifically mentions the requirement to include an ADaM dataset supporting the analysis of immunogenicity data. This paper aims to provide suggestions and guidance on how to include immunogenicity data in ADaM and what additional information above and beyond the IS SDTM is useful to support various analyses.

THE IMMUNOGENICITY TESTING SCHEMATIC



THE FLOW FROM SDTM TO DISPLAY



THE IS SDTM

WHAT'S INCLUDED?

The IS SDTM contains the results of the screening assay for anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NAb) and, if applicable, a confirmation assay and a titration assay.
The screening assay informs you if ADAs are present (POSITIVE) or not (NEGATIVE) and the same for NAbs. If the ADA result is positive, a second assay is carried out to confirm if ADAs are present – the confirmation assay. If the confirmation assay is negative, the overall status is considered negative. The confirmation assay is only performed for ADAs, not NAbs. A titer is usually provided for each positive sample from the confirmation assay. The titer is a quasi-quantitative expression of the level of ADA in a sample. Titer is defined as the reciprocal of the highest dilution of the sample (including minimum required dilution (MRD)) that yields a positive result, with the next lower dilution yielding an ADA-negative result. When a confirmed positive sample does not generate a signal above the titer cut point at MRD, the titer of the confirmed positive sample is reported at the MRD of the assay (ex. <10 or negative titer result=MRD).

THE IMMUNOGENICITY ANALYSIS

WHAT DO WE NEED FOR ANALYSIS?

To determine the type of information to include in ADIS and occasionally, other ADaMs, our immunogenicity Subject Matter Experts (SMEs) were consulted to discuss what analyses need to be supported and what information needs to be presented. The following section describes the information that is included in ADAM to carry out the analyses that are now commonly included in studies based on the SME feedback. This is in addition to what is included in the SDTM.

1. **OVERALL SAMPLE STATUS**
   For ADAs, this will be the result of the confirmation assay, if available, otherwise the screening assay.
2. **NEGATIVE INCONCLUSIVE/CONCLUSIVE**
   The determination of whether post-baseline ADA negative samples are inconclusive or conclusive uses the pharmacokinetic (PK) drug concentration and a validated screening assay drug tolerance value. The drug concentration at the post-baseline visit is compared with the tolerance value. If it is less than or equal to the tolerance value, the sample is considered negative conclusive, if it is greater than the tolerance value, the sample is considered negative inconclusive.
3. **TEATMENT-INDUCED ADA PARTICIPANT**
   A participant with at least one post-baseline ADA-positive sample and an ADA negative or missing baseline sample.

4. **TREATMENT-BOOSTED ADA PARTICIPANT**
   A participant with an ADA-positive sample at baseline, in which at least one post-baseline sample titer value is four-fold greater than the baseline titer value (titer > 4x baseline titer) or if titer result is missing at baseline or missing at all post-baseline assessments but confirmation assay at baseline is ADA-positive and there is at least one ADA-positive sample post-baseline.

5. **TREATMENT-UNAFFECTED ADA PARTICIPANT**
   - A participant with an ADA-positive sample at baseline, in which all post-baseline sample titer results are less than or equal to a four-fold increase in titer value relative to the baseline titer value (titer ≤ 4x baseline titer)

   OR
   - If baseline titer value is missing or all post-baseline titer values are missing, A participant with an ADA-positive sample at baseline, and all timepoints post-baseline were ADA-negative.

6. **DURATION OF ADA POSITIVE STATUS**
   For treatment-induced ADA participants, this is the time, usually in days, between the first and last ADA- positive samples.
   Scenario 1: If only one post-baseline timepoint is positive, duration is not determined but is flagged as '1 Timepoint only'.
   Scenario 2: If a participant has a positive sample at visit 'a', negative at visit 'b', positive at visit 'c' and negative at visit 'd', then duration is calculated from visit 'a' to visit 'c', ignoring the negative result at visit 'b'.
   Scenario 3: if a participant has a positive sample at visit 'b' and at the last visit in the study, then duration is calculated from visit 'b' to end of study and flagged as 'x days – Last timepoint'.

7. **ADA-POSITIVE PARTICIPANT**
   A treatment-induced or treatment-boosted participant. This flag is of particular use for including in ADSL so it can be copied to other ADaMs that require subgroup analysis by ADA status.

WHAT ELSE COULD WE USE FOR ANALYSIS?

The following section describes some additional information that is sometimes included in ADaM for use in the immunogenicity analysis.

1. **TRANSIENT ADA RESPONSE**
   - Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up period (if applicable), excluding the last sampling time point (which ought to be considered persistent unless shown to be undetectable at a later time point).

   OR
   - Treatment-induced ADA detected at two or more sampling time points during the treatment or follow-up period (if applicable), where the first and last ADA-positive samples, irrespective of any negative samples in between, are separated by a period less than 16 weeks, and the participant's last sampling time point is an ADA-negative sample. Note: 16 weeks is a standard interval but may vary depending on the length of the treatment/follow-up period.

2. **PERSISTENT ADA RESPONSE**
   - Treatment-induced ADA detected at two or more sampling time points during the treatment or follow-up period (if applicable), where the first and last ADA-positive samples, irrespective of any negative samples in between, are separated by a period of 16 weeks or longer. Note: 16 weeks is a standard interval but may vary depending on the length of the treatment/follow-up period.

   OR
   - Treatment-induced ADA only at the last sampling time point of the treatment or follow-up period (if applicable).

3. **ADA PREVALENCE**
   - The proportion of all participants with an ADA-positive sample at any point in time (including baseline positive sample).

4. **ADA INCIDENCE (%TREATMENT-EMERGENT ADA):**
   - The sum of participants with treatment-induced ADA or treatment-boosted ADA during the study period relative to evaluable participants. An evaluable participant is a participant with at least one sample taken after drug administration during the treatment or follow-up period that is appropriate for ADA testing with a reportable result.

5. **ONSET OF ADA**
   - The time between the initial administration of the drug and the first instance of treatment-induced ADA. Participants with pre-existing ADA should be excluded.

THE ADIS ADAM

The ADIS ADaM follows CDISC Basic Dataset Structure (BDS). The following is a suggestion of how to include the information as in the 'What do we need for Analysis' section above. The SDTM data is carried forward as this provides the results from the testing of the clinical samples. It is possible that the results from the screening and confirmation assay are stored in the same SDTM parameter and distinguished using variable ISSCAT. It is recommended this becomes two separate parameters in ADIS.

PARAMETERS

PARAMCD	PARAM	Comment
ADBABDS	Anti-XXX Binding AB Detection Screening	Sourced from IS SDTM, visit level data
ADBABDC	Anti-XXX Binding AB Detection Confirmation	Sourced from IS SDTM, visit level data. Only provided if the ADA screening assay is positive.
ADBNABDC	Anti-XXX Binding Neutralizing AB Detection	Sourced from IS SDTM, visit level data.
ADBABTT	Anti-XXX Binding AB Detection Titer	Sourced from IS SDTM, visit level data. Only available at visits with confirmed positive results.
ADBABDSS	Anti-XXX Binding AB Detection Sample Status	Used to show the overall status for a sample. This will be the result from the confirmation assay, if available, otherwise the screening assay. Negative results can be further categorized into conclusive and inconclusive.
DURADA	Duration of ADA	Derived for treatment-induced participants using sample dates.
DRGCONC	Drug Concentration (unit)	Sourced from PC SDTM. Assigned at the like for like visits between IS and PC SDTMs.

PARTICIPANT LEVEL VARIABLES

VARIABLE	VARIABLE LABEL	Comment
TRTINDFL	Treatment-induced Subject Level Flag	If the assay results show a participant has treatment-induced ADAs, all records for that participant are flagged with Y, else N.

		If an ADA-positive participant level flag is required in ADSL, this variable could also be derived in ADSL to avoid re-derivation in ADIS.
TRTBSTFL	Treatment-boosted Subject Level Flag	If the assay results show a participant has treatment-boosted ADAs, all records for that participant are flagged with Y, else N. If an ADA-positive participant level flag is required in ADSL, this variable could also be derived in ADSL to avoid re-derivation in ADIS.
TRTUNFFL	Treatment-unaffected Subject Level Flag	If the assay results show a participant has treatment-unaffected ADAs, all records for that participant are flagged with Y, else N.
ADPOSFL	ADA-positive Subject Level Flag	If the assay results show a participant has treatment-induced ADAs or treatment-boosted ADAs, all records for that participant are set to Y, else N. This flag is ideally derived and stored in ADSL as it may be required for subgroup analyses, for example, in ADAE.

ANALYSIS FLAGS

VARIABLE	VARIABLE LABEL	Comment
ANL01FL	Analysis Flag 01	For each participant, assign to Y for the record having maximum titer value where PARAM="Anti-XXX Binding AB Titer"
ANL02FL	Analysis Flag 02	For treatment-induced participants assign to Y for the earliest post-baseline positive result.

OTHER ADA SUBGROUP ANALYSES

High affinity ADA can influence both safety and efficacy data. If an impact on results is observed after ADA testing, additional analyses by ADA status (positive or negative) may be appropriate as. These conditional analyses will involve adding the ADA-positive participant level flag to the relevant ADaM datasets. For example:

ADAE: Adverse event overview by participant ADA status. A summary of the number and percentage of participants with adverse events and various subcategories of adverse events, by participant ADA status.

ADEFF (or equivalent ADaM with efficacy data):

- Efficacy measures by participant ADA status. A summary of the number and percentage of subjects with different compound specific efficacy measures, by participant ADA status.
- Influence of ADAs on compound specific efficacy measures. A plot of the percentage of subjects achieving a compound specific efficacy measure over time, by participant ADA status.

ADPC: Mean PK concentration-time plots, by participant ADA status.

CONCLUSION

The recommendations provided in this paper for the inclusion of immunogenicity data in ADIS and other ADaMs should help meet the requirements for analysis and presentation of immunogenicity data, as recommended by immunogenicity SMEs.

REFERENCES

FDA Study Data Technical Conformance Guide (June 2023)

CONTACT INFORMATION

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