Paper AS04

# Planning Ahead: A Novel Approach to Creating Synthetic Immunogenicity Data

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## ABSTRACT

For the NDA submission, immunogenicity analyses, including ADA and NAb, are required. The testing follows a tiered approach: an initial ADA screening test is conducted, and if positive, it is followed by a confirmatory test. If the confirmatory test is also positive, titer and NAb tests are performed. The immunogenicity endpoints encompass ADA positivity, treatment-unaffected, treatment-emergent, treatment-induced, treatment-boosted, persistent ADA, transient ADA, titer, and NAb.

In a blinded clinical trial, the sensitivity of ADA and NAb results prevents access until unblinding, creating delays in pre-programming activities. Often, the test files provided by vendors fall short in accurately capturing the tiered approach necessary to derive the required parameters. This presentation will introduce a novel approach to generate simulated immunogenicity data, which will facilitate pre-programming and accelerate the production of immunogenicity-related outputs during database lock (DBL) and the final analysis package creation cycle. We will explore the critical role of immunogenicity in drug development, the process of assaying immunogenicity data, and the algorithm designed to create synthetic data that covers all endpoints, visits, and timepoints based on the study design.

## INTRODUCTION

Immunogenicity is the ability of a foreign substance to provoke an immune response in the body. The response leads to the development of anti-drug antibodies (ADAs). The response may not only decrease the therapeutic activity but can potentially threaten patient safety. In addition, the neutralizing fraction of ADA (NAb) inhibits the interaction between the drug and its target and could thus neutralize the therapeutic effect. Biotherapeutics, such as proteins, antibodies, conjugated peptides, or oligonucleotides can induce such immune response. Assessment of immunogenicity, i.e. formation and

persistence of ADAs and NAb is a fundamental and crucial part of drug development. In those cases, immunogenicity data are generally required for an NDA submission.

## IMMUNOGENICITY ASSAYS-TIERED TESTING

Immunogenicity assays feature a tiered testing procedure. The first step is a screening assay to detect antibodies (ADAs) that bind to the drug. If result is negative, then ADA test is negative. If the result is positive, then a confirmation assay will be performed. If the confirmatory result is negative, ADA test is negative. If the result is positive, then ADA test is positive.

For the samples with ADA confirmed positive, a titer assay will be performed to measure the magnitude of anti-drug antibodies. In addition, NAb assay will be conducted for the characterization of the neutralizing capacity of the anti-drug antibodies.

Figure One shows the diagram of the tiered testing approach for ADAs:

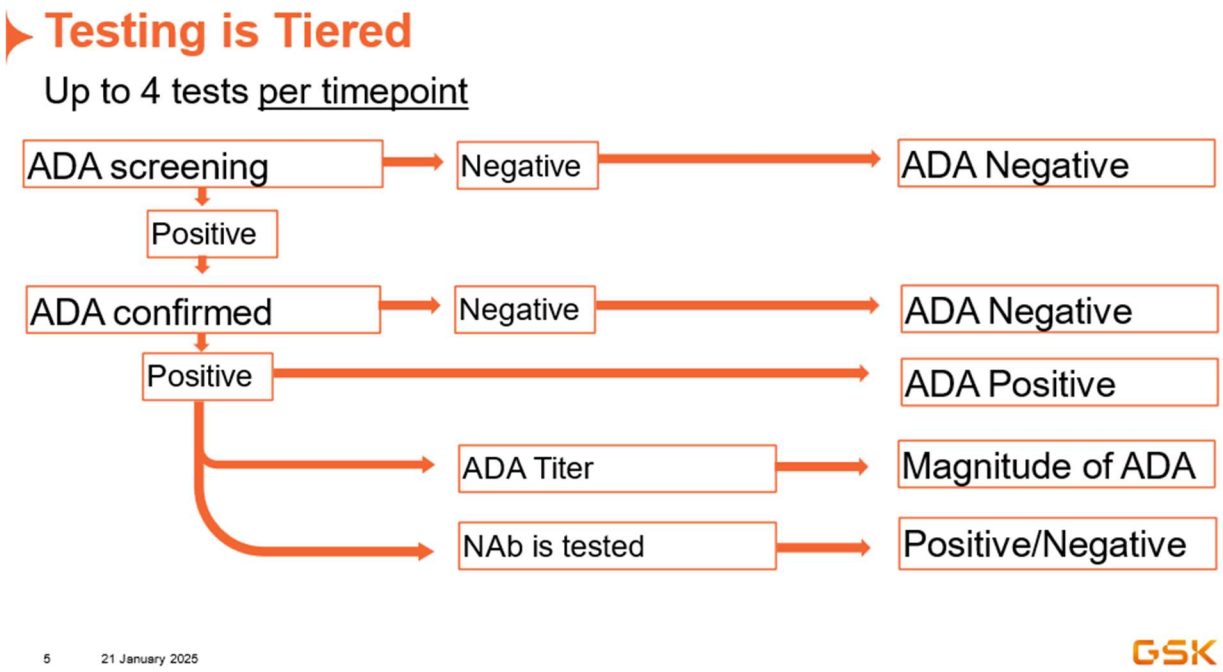


**Figure 1**: Tiered Testing Approach for ADA

## IMMUNOGENICITY ANALYSIS IN OUR STUDY

Our study is a randomized, double-blinded, phase 3 clinical trial with chemotherapy treatment period (15 weeks) followed by maintenance period (up to 3 years). Immunogenicity assays were performed at baseline and post-baseline visits.

Here is the list of analysis parameters specified in SAP:

Treatment-unaffected ADA: subject with positive at baseline and either

1) post-baseline titer ≤ 4x baseline value, or
2) post-baseline negative.

Treatment-boosted ADA: subject with ADA positive at baseline and at least one post-baseline positive sample

1) with titer value four-fold greater than the baseline titer value, or
2) titer missing at baseline or missing at all post-baseline samples.

Treatment-induced ADA: subject with ADA negative or missing at baseline and at least one post-baseline ADA positive sample.

Treatment-emergent ADA Positive: subject with treatment-induced ADA or treatment-boosted ADA.

Treatment-emergent ADA Negative:

1) Subject with treatment-unaffected or
2) Subject with neither treatment-boosted and nor treatment-induced ADA.

Persistent ADA:

1) subject with treatment-induced ADA at the final timepoint, or
2) subject with treatment-induced ADA at >=2 timepoints and the first and last ADA-positive are separated by
    a. >= 6 weeks in chemotherapy period, or
    b. >= 12 weeks on the maintenance period.

Transient ADA: subject with the ADA result is negative at the final timepoint, and

1) treatment-induced ADA at one timepoint, or
2) if there are >= 2 treatment-induced ADA timepoints and the first and last ADA-positive are separated by
    a. < 6 weeks in the chemotherapy period, or
    b. < 12 weeks in the maintenance period

ADA Titer

NAb Positive

## CHALLENGES

Our study is a randomized, double-blinded and phase 3 clinical trial with chemotherapy treatment period for 15 weeks followed by maintenance period (up to 3 years). ADAs and NAb were tested only on the active treatment arm at baseline and post-baseline visits. Since it is a blinded study and the data contain subjects in active arm, accessing the data will reveal treatment randomization information. Therefore, we could not access the data until unblinding.

The test files provided by vendors fell short in accurately capturing the tiered approach covering all the cases to derive the required parameters described above. The test file had the cases with ADA screening positive, but no confirmation assay done. The subjects and visits were so limited and random that we could not derive persistent and transient ADA at all. Due to the tight timeline, we were left no time for those parameter derivations after unblinding.

## APPROACHES

We generated simulated immunogenicity SDTM covering all the cases described above to make sure all parameters were derived. In parallel we produced IS using vendor test data. ADIS used simulated IS data for dry runs then switched to IS after unblinding. Using this approach, we successfully delivered within the timeline, and the approach has been adapted by another study in GSK.

## SOME SOURCE CODES

Here we are including some of the source codes to generate synthetic (with modifications, subjid was not real).

```
data one;
set two;
  where 11 le subjid le 20;
     if subjid =11 and visitnum in (11) or
        subjid =12 and visitnum in (5) or
        subjid =13 and visitnum in (4, 6, 17) or
        subjid =14 and visitnum =8 or
        subjid =15 and visitnum in (4, 5) or
        subjid =16 and visitnum in (17, 19) or
        subjid =17 and visitnum in (8, 17) or
        subjid =18 and visitnum in (7, 8) or
        subjid =19 and visitnum in (5) or
        subjid =20 and visitnum in (8090)
```

```
      then do;
       istest ="Anti-Drug Binding AB Detection";
       isscat ='SCREENING';
       ISSTRESC ='POSITIVE';
       output;
       isscat ='CONFIRMING';
       ISSTRESC ='POSITIVE';
       output;

       isscat ='TITER';
       ISSTRESC ='100';
       isstresn=100;
       output;
      end;

     else do;
     istest ="Anti-Dostarlimab Binding AB Detection";
     isscat ='SCREENING';
     ISSTRESC ='NEGATIVE';
     output;
   end;
run;
```

## SUMMARY

For a blinded study if immunogenicity data is not available until unblinding, and analysis requires complicated parameters, we recommend to simulating SDTM data covering all the cases to make sure all the parameters are derivable in advance.


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