



Planning Ahead: A Novel Approach to Creating Synthetic Immunogenicity Data AS04

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Agenda

- Introduction to Immunogenicity Analysis
- Challenges for Blinded Study
- Our Approach
- Summary

Introduction to Immunogenicity (IS)

What

The ability of a foreign substance to provoke an immune response

Why

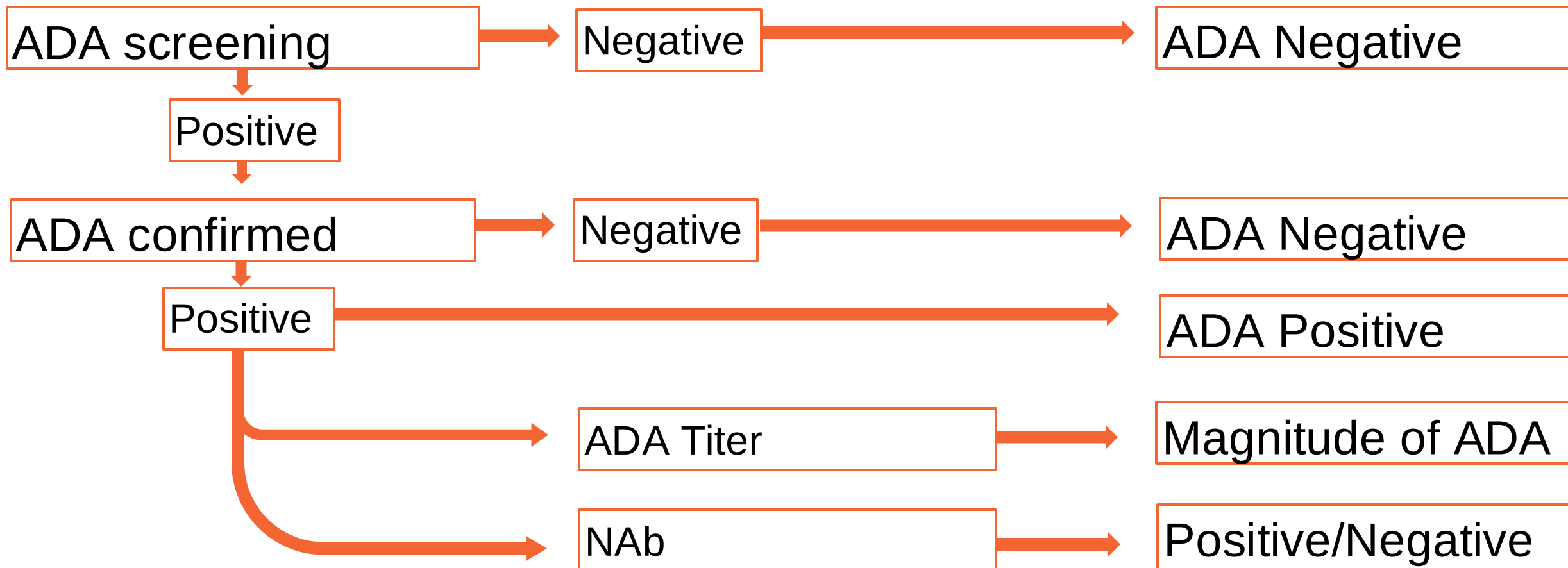
Impact a drug's safety and efficacy
Required for NDA Submission

How

IS assays measure formation and persistence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

Testing is Tiered

Up to 4 tests per timepoint



► Analysis Parameters in ADIS

- Treatment-unaaffected ADA
- Treatment-boosted ADA
- Treatment-induced ADA
- Treatment-emergent ADA Positive
- Treatment-emergent ADA Negative
- Persistent ADA
- Transient ADA
- ADA Titer
- NAb positive

Derivations-1

Parameter	Definition
Treatment-unaffected	• Subject with positive at baseline • and either • post-baseline titer $\leq 4x$ baseline • or post-baseline negative
Treatment-boosted	• Subject positive at baseline • and at least one post-baseline positive titer $> 4x$ baseline • or titer missing at baseline or missing at all post-baseline
Treatment-induced	• Subject with negative/missing at baseline • and ≥ 1 post-baseline ADA positive

Derivations-2

Parameter	Definition
Treatment-emergent Positive	Subject with treatment-induced/boosted
Treatment-emergent Negative	• Subject with treatment-unaffected or • Subject with • Treatment-boosted = no and • Treatment-induced = no

Derivations-3

Parameter	Definition
Persistent ADA	• Subject with treatment-induced ADA at the final timepoint, or • Subject with treatment-induced ADA at ≥ 2 timepoints and first and last positive are separated by • ≥ 6 weeks on chemotherapy period, or • ≥ 12 weeks on the maintenance period

Note: Study adjusted parameter. Chemotherapy (15 weeks) then maintenance (≤ 3 years)

Derivations-4

Parameter	Definition
Transient ADA	• Subject with ADA negative at the final timepoint and • treatment-induced ADA at one timepoint, or • treatment-induced positive at ≥ 2 timepoints and first and last positive are separated by • < 6 weeks in chemotherapy period or • < 12 weeks in maintenance period

Note: Study adjusted parameter. Chemotherapy (15 weeks) then maintenance (≤ 3 years)

Challenges in our Study

- Study Design
 - Randomized, double-blinded and phase 3 clinical trial
 - chemotherapy treatment period (15 weeks)
 - followed by maintenance period (up to 3 years)

Challenges

- Tests only performed on the active arm
- Could not access data until unblinding
- Test data by vendor not sufficient for parameter derivation
- Due to the tight timeline, no time for programming the parameters after unblinding
- Need to derive all the IS parameters in advance

Approach

- Generated simulated immunogenicity SDTM including all the cases to make sure all parameters were derived
- In parallel SDTM.IS using vendor test data
- ADIS used simulated IS for dry runs then switched to IS after unblinding

► Advantage

- Successfully delivered within the timeline
- Approach adapted by another study

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

Questions?

Refer to the paper AS04 for details

Feel free to contact at Ruilan.x.wei@gsk.com for any questions and comments

