To Analyse or not to Analyse; that is the question? Changing the Immunogenicity Testing Strategy

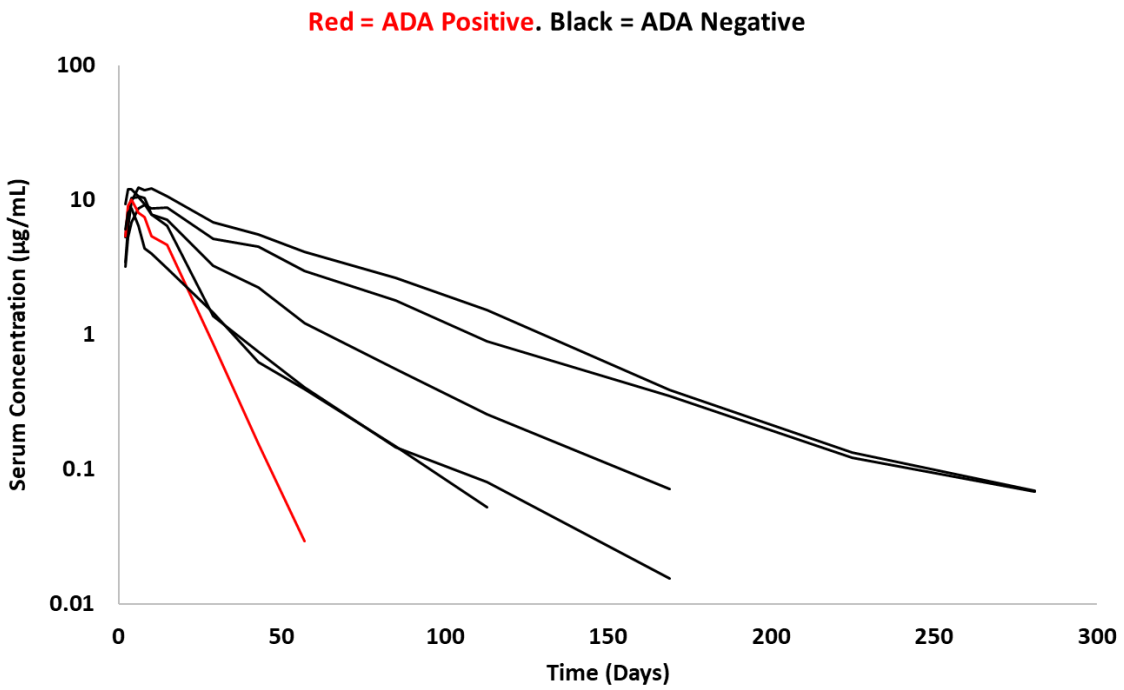
Should it be Mandatory, or would a Science-based Approach be More Appropriate?

Nick White, Integrated Bioanalysis, AstraZeneca

EBF Open Symposium
15-Nov-2023

Immune Responses to Biotherapeutics Protein Products have the Potential to Affect Product Pharmacokinetics

Impact of ADA on Single Dose Pharmacokinetics



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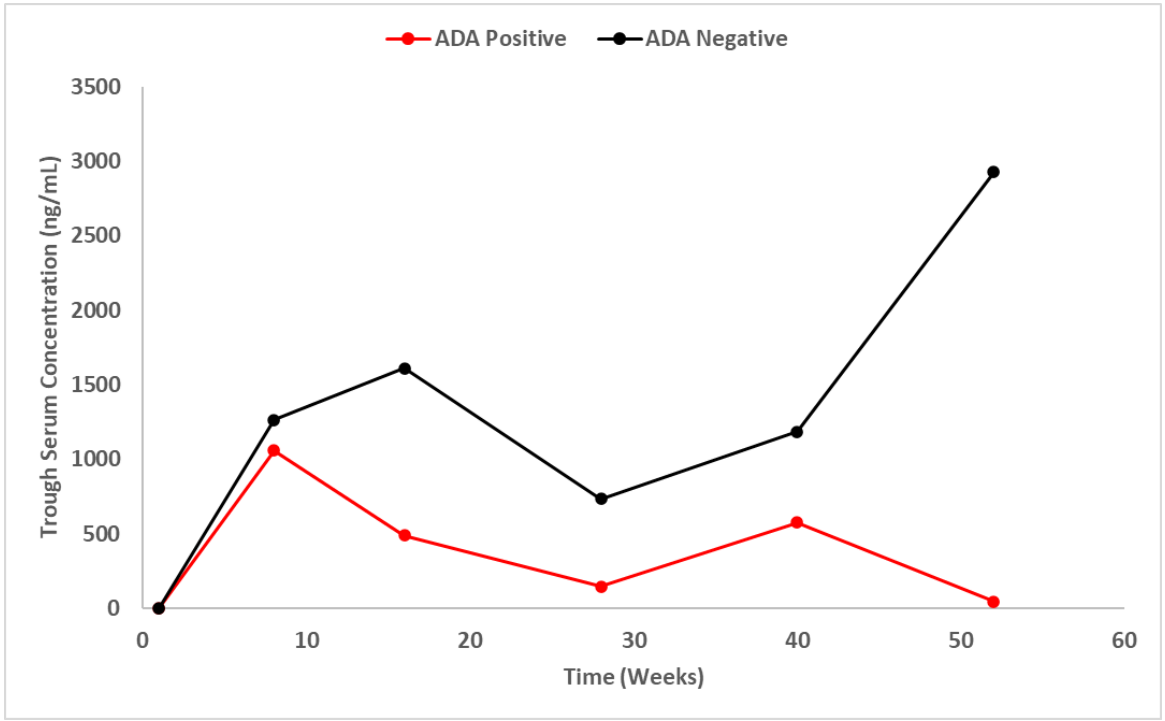

Immune Responses to Biotherapeutics Protein Products have the Potential to Affect Product Pharmacodynamics

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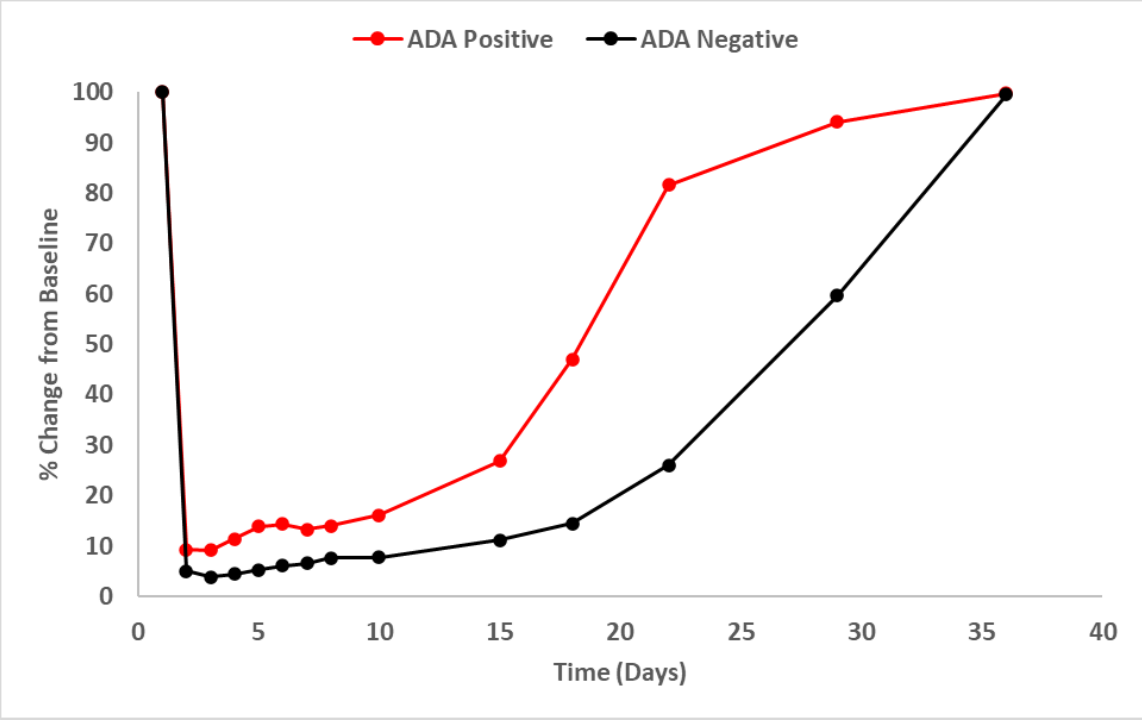

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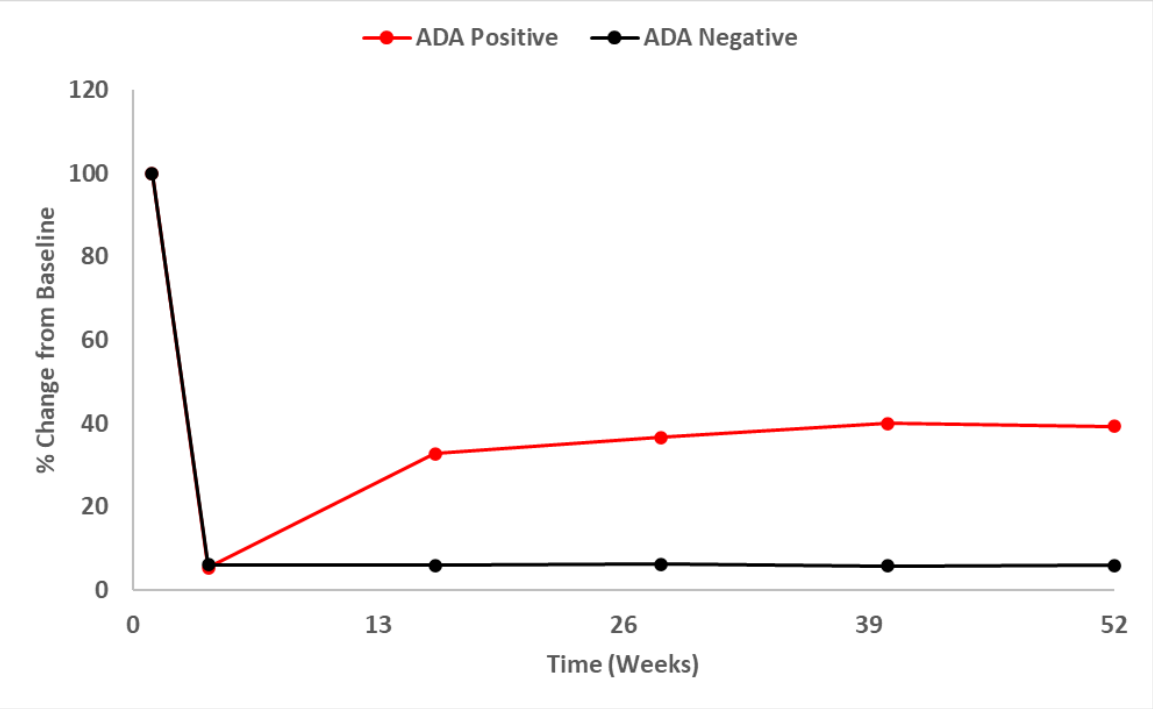


Other Considerations when Drawing Integrated Conclusions on Immunogenicity Impact

- Should ADA incidence rates allow, the relationship between ADA sub-category and impact on the following end-points should also be reflected upon

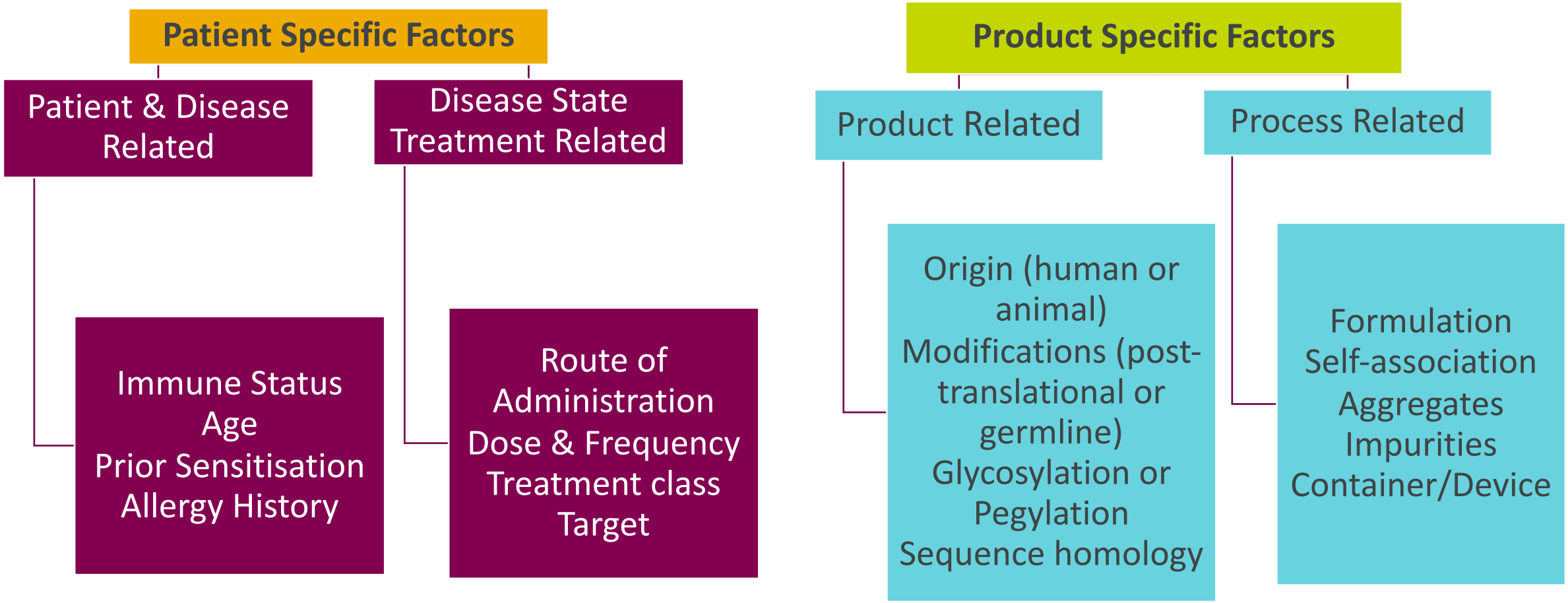
Safety

- Adverse Event (AE) category
- Hypersensitivity

Efficacy

- Clinical outcomes
- Patient reported outcomes
- Disease severity

Can we take Health Authority Guidance Verbatim & Conduct a Risk-Based Approach on Immunogenicity Testing by Employing a Robust Risk Immunogenicity Risk Assessment



Currently Clinical Immunogenicity Testing Strategies are Driven by Risk

Immunogenicity risk is centred around predicted incidence rate and the clinical consequence, specifically the impact on safety and efficacy

- Phase 1 clinical trial in HV helps to understand ADA onset
  - Predose, Day 8-14, Week 3-6
- Later Stage clinical trial in relevant patient populations allows interpretation of prevalence/incidence, ADA kinetics, magnitude of ADA response, ADA impact on PK, PD, efficacy and safety

Low-to-Medium Risk Molecule Testing Paradigm

- All health agencies accept tiered approach to testing (ie. screening, confirmatory and titration assays)
- Potentially neutralising assays for Ph 3
- Medium risk assets may require additional assessments at HA requests

For Molecules considered Low-to-Medium Risk, can the community move away from this expectation to ‘Test’ in Phase 1 HV Trials?

Case Study 1: Monoclonal Antibody; Phase 1 FTIH SAD Low Risk Molecule

Background & Risk Assessment

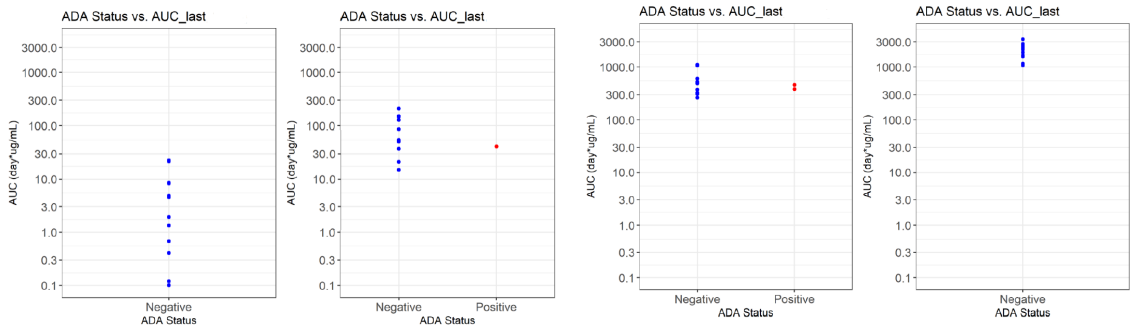
- Humanised IgG4 with stabilising linker
- Single SC dose in Heathy volunteers

	Risk Factor	Lower risk		Higher risk
Product-Specific Factors	Primary origin (foreign/human)	Fully human	Partially human	Foreign
	Homology with endogenous equivalent	No homology	Partial homology	Significant homology
	Glycosylation, PEGylation	Fully human	Partially human	Foreign
Patient-Specific Factors	Frequency of dosing	Short term	Long term	Intermittent
	Route of administration	IV	SC	Inhaled
	Patient immune status	Normal	Compromised	Primed
System Biology	Redundancy of target	Redundant	Partially redundant	Non-redundant

Low Risk Molecule

Clinical Immunology Data

- ADA incidence 6.3% (3 of 48 volunteers dosed)
- PK profiles of the ADA-positive subjects are within the overall PK exposure range of all subjects



- No apparent impact of ADA on PD
- **No clinical impact of ADA**

Case Study 2: Monoclonal Antibody; Phase 1 FTIH SAD in Oncology Indication; Low Risk Molecule

Background & Risk Assessment

- Humanised IgG1κ TM

	Risk Factor	Lower risk		Higher risk
Product-Specific Factors	Primary origin (foreign/human)	Fully human	Partially human	Foreign
	Homology with endogenous equivalent	No homology	Partial homology	Significant homology
	Glycosylation, PEGylation	Fully human	Partially human	Foreign
Patient-Specific Factors	Frequency of dosing	Short term	Long term	Intermittent
	Route of administration	IV	SC	Inhaled
	Patient immune status	Normal	Compromised	Primed
System Biology	Redundancy of target	Redundant	Partially redundant	Non-redundant

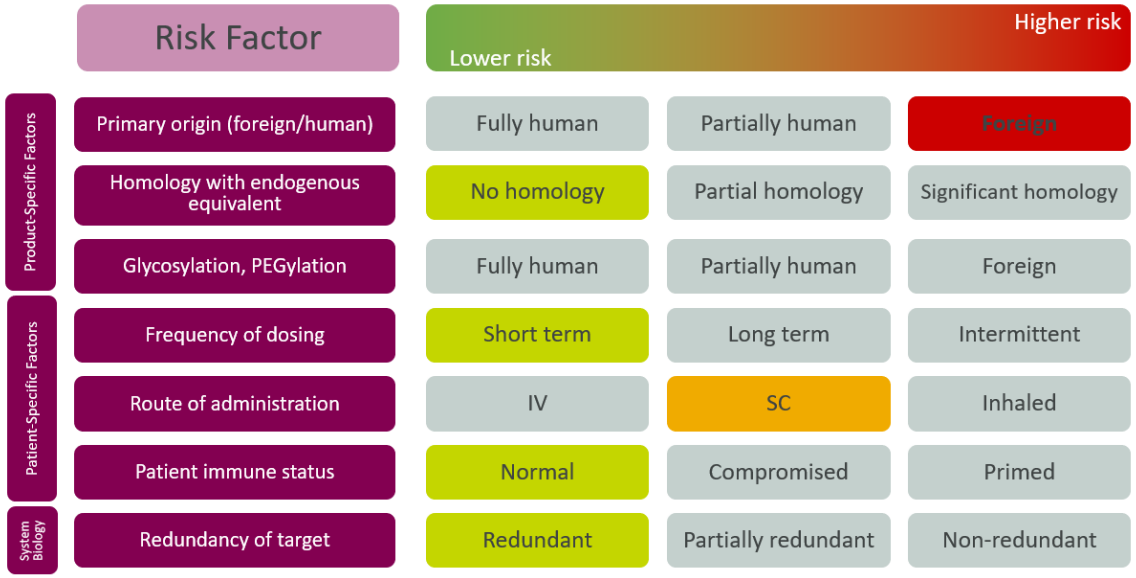
Low Risk Molecule

Clinical Immunology Data

- ADA incidence 7.4% (2 of 27 volunteers dosed)
- PK profiles of the ADA-positive subjects are within the overall PK exposure range of all subjects
- No impact of ADA on PD Endpoints
- **No apparent clinical impact of ADA**

Case Study 3; Assessment of Immunogenicity in Oligonucleotide Therapies; Low Risk Molecules

Immunogenicity Risk Assessment



Ligand conjugation may impact Risk Assessment

Clinical Immunogenicity Strategy

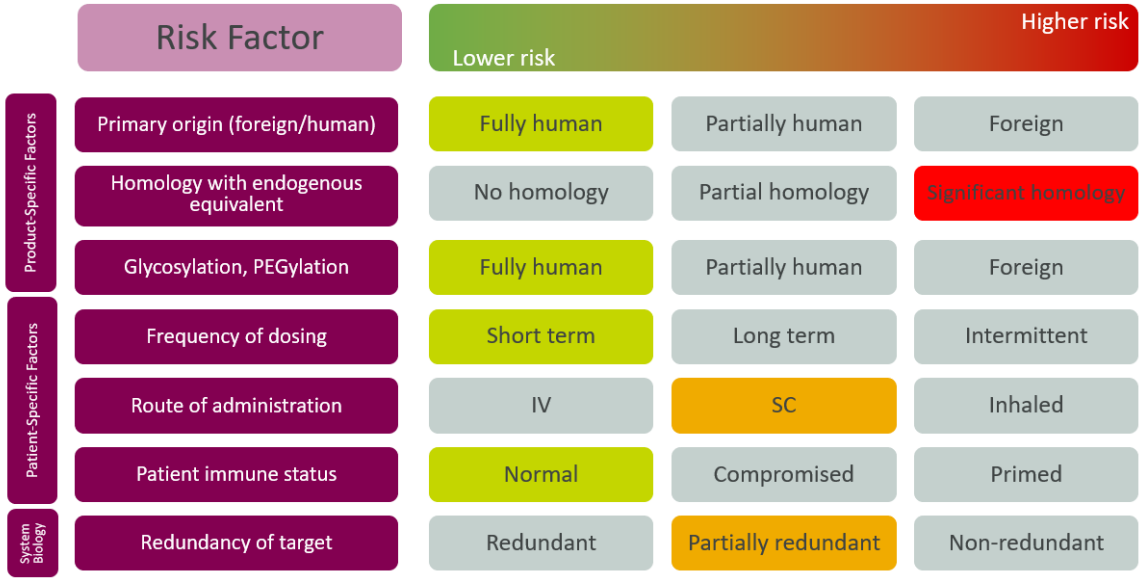
- Follow the principles outlined in Henry, Scott P et al., 2022

1. Conduct a robust Risk Assessment
2. Collect & bank appropriate ADA samples
3. Analysis driven by the observation of PK, PD, and safety, as well as by established class experience.

Scott P et al. “Assessment of the Immunogenicity Potential for Oligonucleotide-Based Drugs.” Nucleic acid therapeutics vol. 32,5 (2022): 369-377. doi:10.1089/nat.2021.0112

Case Study 4; Peptide Therapy, Phase 1 FTIH HV SAD

Immunogenicity Risk Assessment



Medium Risk Molecule

Clinical Immunology Summary

- No volunteers were ADA positive either pre- or post-dose
- No observed changes in PK indicating ADA
- No observed changes in PD markers indicating ADA
- **No apparent clinical impact of ADA**

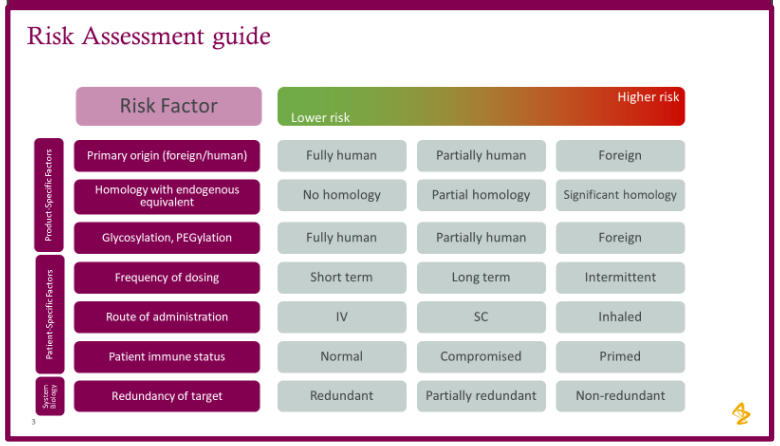
RISK RE-CATEGORISED FOR FUTURE TRIALS

What Conclusion can we Draw from these Case Studies? How does is it inform the Clinical Immunology Package and Safety Profile

- For low-to-medium risk molecules, analysis of immunogenicity samples from HV SAD studies has limited utility in understanding the immunogenic potential and clinical immunological impact on PK, PD, Safety and Efficacy of a compound.
- Immunogenicity Testing in SAD trials does not elicit clinically meaningful information on
  - Prevalence/incidence
  - ADA kinetics
  - magnitude of ADA response
  - ADA impact on PK, PD, efficacy and safety

Proposed Paradigm Shift for Low-to-Medium Risk Molecules will Allow for More Patient Centric & Streamlined Bioanalytical Support of Clinical Trials

1). Robust Risk Assessment



2). Collect and Bank

- Immunogenicity samples will always be collected for clinical trials.
- The timing and frequency of sample acquisition may be influenced by the nature of the study & HA guidance

3). Analyse 'For Cause'

- Immunogenicity analysis will be driven by observed clinical immunology impact on PK, PD, Safety and Efficacy of a compound

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