Breakout round table discussion - Immunogenicity

Important preliminary note…

CROs, rarely involved by their sponsors in the definition of the immunogenicity strategy

Some of their answers are based on the requests for ADA assays/analysis they get from their sponsors

Oligos - Q1

- “A risk assessment is **performed early in program development**, taking some of the **unique aspects of oligonucleotides** that need to be evaluated (such as chemical composition, mechanism of action, innate immune response activation) in to consideration and **revise as new information becomes available**”

Oligos - Question 1 Responses

- Agree – start early, new(er) modalities can be a learning curve with more unknowns
- Generally considered low risk but molecule specific risk assessment is needed
- Key elements considered in the risk assessment are structure, chemistry, conjugation and outcome on *in vitro* immunotox experiments
- For CROs, this can be sponsor specific
  - CRO experience can be beneficial as they see a large range of molecules
  - Advise sponsors to perform risk assessments
- Overall responses aligned with the statement

Oligos – Q2

- “**Timing** of the immunogenicity assessment is **driven by the observation of PK parameters, activity, and safety, as well as by established class experience, provided other risk factors are unchanged** (patient population, route, etc.), i.e. **a ‘collect and bank’ strategy is applied during the early development and analysis only triggered in case of an atypical PK/PD or safety event** ”

Oligos - Question 2 Responses

- Many agree and using risk assessment to inform strategy
  - Some test clinical in all cases

- Bank and collect - can take time to raise a positive control (PC) so assay may not be ready pre-Ph1
  - Tend to screen multiple chemistries and progress fast into GLP Tox
  - PCs can be hard to generate and an ‘early’ version may be used

- In the preclinical space, cyno is evaluated much more frequently than rodents
  - Some CROs are seeing more requests to follow EBF recommendation on nonclinical immunogenicity assessments https://pubmed.ncbi.nlm.nih.gov/33729007/

Oligos - Question 2 Responses (cont.)

- Observation of anomalous PK triggers ADA samples analysis, performed using dedicated sample sets
  - Usually can see an impact on Ctrough levels over time
  - Biomarker studies are more informative than PK
  - Ph1 can be in healthy individuals so it does not inform disease state
  - Some starting at MAD study

- Sometimes sample collection is not correct, so samples may not be usable for ADA assessment

Oligos – Q3

- "**Current guidance** for immunogenicity method validation **is applied**. PC **anti-Oligonucleotide antibodies are likely to be class specific, not sequence specific**"

Oligos - Question 3 Responses

- Most agree
- PCs can be hard to generate
  - May have to play around with immunization strategies as can be hard to produce a response
  - Some groups don't have in-house groups to generate reagents
  - Phage display libraries used to fish out antibodies that bind
- One company highlights the fact that the PC should be drug specific (i.e. combination of sequence and backbone)

Oligos – Q4

- "**Neutralising antibody assays** for oligonucleotide therapeutics **are not generally considered**, instead **other ways of addressing potential changes to PK/PD are considered appropriate**"

Oligos - Question 4 Responses

- Agreement

- Some have no requests for nAb assays and considered not necessary
- Quite indirect read out
- Cellular uptake mechanism often unclear
- Follow approaches that are used for low risk biotherapeutics
- Use of a PD data is more informative and consider clinical consequence
- No approved oligo have had a severe immune response
  - Consider if new(er) oligos would have a different risk
  - nAb assays are unlikely to be useful for oligos unless it has a ligand, e.g. peptide conjugated

Oligos – Q5

- “**Nonclinical immunogenicity studies** for oligonucleotide therapeutics **are not always required**”

Oligos - Question 5 Responses

- Most agree, some case by case
- Collect and bank widely adopted in non-clinical studies (especially in NHP)
- Preclinical data does not predict human outcomes
  - Ethically questionable to use animals to test ADA when it is not informative and bringing no value
  - PK indicative of immune response
  - In terms of banking and keeping samples, early tox is superseded by later tox studies and samples should be disposed of
  - Companies may do this for their learning but not for regulatory purposes

Oligos – Q6

- “Immunogenicity samples are **always collected in clinical trials**. The timing and frequency of sample acquisition may be influenced by the nature of the study (eg, number of doses, early or pivotal trial), while **sample testing during the early clinical development is determined by clinical findings and risk assessment**. If the class of oligo is considered **low risk ADA samples will only be collected and banked**”

Oligos - Question 6 Responses

- Generally agree
- As long as a subject is enrolled, ADA samples are always collected
  - Early studies are not statistically powered so what decisions are made on limited datasets
  - Some ethical considerations on collecting samples that are not analysed
- Timing and frequency depending on study type
  - Consider patient centricity and ethical considerations
- Analysis triggered by clinical findings

Oligos – Q7

- "If the Oligonucleotide **results in increases in protein expression or alteration of a protein, an assessment of the immunogenicity of the resulting protein may be needed**"

Oligos - Question 7 Responses

- Agreement
- Only in case of upregulation of the downstream protein
- Use of risk assessment

Peptides – Q1

- “We utilize **current regulatory guidelines** for peptide therapeutics for immunogenicity assessment and immunogenicity method validation **for peptide therapeutics as we would for biologics**”

Peptides - Question 1 Responses

- Most agree
- In case of very small linear or cyclic peptides, typically less then 15 AA, these are treated as SM
  - Only risk assessment is performed
  - A change in PK (not explained by time dependent metabolism) can trigger ADA measurement
- CRO reps never experienced requests for ADA analysis for small peptides
- Use guidance as a starting point but case by case
  - 100 ng/mL sensitivity was set on one example and a different modality
  - Use science and not tick boxes!
- Non-natural amino acids, conjugation, endogenous counterpart can change risk
- Responses can be transient, high incidence but low clinical consequence
- Drug is in molar excess
- Questions around viability of nAbs as drug tolerance and sensitivity can be challenging

Peptides – Q2

- “**Nonclinical immunogenicity studies** for peptide therapeutics **are not always required**”

Peptides - Question 2 Responses

- Mostly agreement
- As per Oligo responses, ethical consideration of 3Rs
- If performed, then not all the tiers
  - Business purposes
  - CRO challenges on scheduling slots so assay may be developed but only triggered on findings
  - Not needed for filings
  - PK is usually indicative or use of PD endpoints

Peptides – Q3

- "A **'collect and bank' strategy can be applied during early development** (nonclinical and early stage clinical studies) and **analysis only triggered in case of atypical PK/PD or safety event**"

Peptides - Question 3

- Generally agree in collect and bank strategy
  - Agreement for nonclinical but a few less convinced for clinical
  - Early clinical studies are often not informative
    - Statistical power
    - Population
    - Can take time to break tolerance
    - Check that the assay is working before getting to pivotal studies
    - Regulatory expectation is validated assays for pivotal studies

Peptides – Q4

- “**Regulatory expectations** for peptide therapeutics **can be high even in the absence of clinical consequence**”

Peptides - Question 4 Responses

- Most agree that expectations are high
  - One company: endogenous counterpart or potential cross-reactivity to analogous molecules, full evaluation should be performed, so the regulatory expectations are considered to be appropriate
- Need to push back and scientifically discuss with regulators
- Build justification and state strategy rather than asking should we do this or not
  - Response will be yes!
- Follow up ADA is challenging
  - Database is locked, often no correlating safety/PK/PD data, no treatment change for the patient
- Assay requirements for nAb – sensitivity and drug tolerance requirements can be too high

Science, no tick boxes, patient centricity, value to the patient

Bonus item

- **Several comments related to “Collecting and Banking” approach**
  - Whilst this strategy reduces unneeded analysis, there are some downstream challenges
  - GLP
    - SD control, 3Rs
  - GCP
    - Consent, retention times and ensuring disposal
    - Ethical considerations
    - Paediatric/Adolescent studies and re-consent mechanisms
      - May be considered original use rather than future use
    - Health Authorities – may reserve the right to request re-testing if they deem assays not to be appropriate
    - However, even if you receive this request, you may be able to justify your rationale
  - Cost and sustainability

Contact Information

Questions: info@e-b-f.eu

European Bioanalysis Forum

www.e-b-f.eu