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Assays / Immunogenicity Strategies

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I would be interested in having a discussion about the production of the positive control to cover ASO program. What technology shoud be prefered, immunisation or phage display? What could be the advantages/disadvantages of using monoclonal or polyclonal ? Many thanks

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1. Pre-existing anti-capsid antibodies (seroprevalence): How predictive are baseline binding and neutralizing antibodies for real-world transduction across different tissues and delivery routes? What thresholds and assays should be used to screen patients consistently across labs?

2. Cross-reactivity among serotypes: To what extent do antibodies to one AAV serotype neutralize others, and can rational capsid design truly evade existing population immunity?"

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Vector based Therapeutic protein Immunogenicity - Filled Capsid vs Empty Capsid.

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Clinical antibody analysis and tight timelines to clinical study reports /Submission.

- We experience increasing demand for faster delivery of ADA data to clinical study reports (CSRs) and to MAA/NDA submissions. In two cases we have asked FDA if it was acceptable to use a stepwise submission of ADA data i.e data from the follow-up visit to be submitted post filing timeline. For one project this approach was accepted and not for the other.
- I would very much like to hear the experience of others and advice of how to handle increasing demands for faster delivery of ADA data both to CSRs and to MAA/NDA submissions?

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1. How to overcome increasing demands for faster delivery of ADA data both to CSRs and to MAA/NDA submissions?

2. Where to present late ADA data for the clinical study reports ?
   - CSRs with data until specific cut date (interim CSR)? + final CSR with all data (or amended CSR)?
   - Part of the D120 safety update ?
   - Other?

3. How to handle submission documents if allowed to submit data later?
   - ISI?, Safety summary (2.7.3)?, Efficacy summary (2.7.4)?, Clin Pharm summary (2.7.2)
   - Label text?

4. Depending on the immunogenicity risk – would you have different approaches
   - Low Risk?
   - High Risk?

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How is the target concentration level determined for biosimilar's ADA assay target tolerance testing? Reported target concentrations in the literature vary by several orders of magnitude depending on the analytical method, and they may still not reflect the amount of target that could be released after acidic dissociation during sample processing. How to establish a reliable and biologically meaningful target concentration for interference evaluation during method development and validation (in the absence of real clinical samples) to minimize the risk of introducing fals positive outcomes in bridging assay setup.

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Calculation and reporting of NAb% incidence. It seems that there is no harmonization, which make it tricky to compare clinical data and declaration is often not clear in the approval documents. What are the cases when you calculate it on all analyzed immunogenicity samples and when only on the number of ADA% positive samples? Is there a general rule or does it depend on the readout you would like to report? Would harmonization be favorable?

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1. What is the best practices in selecting the TCP in Titration assays: 1% (=SCP), 0.1% or 6xSD? Is the involvement of MSR standard practices or still the +/- titer step approach? What would be a suitable MSR to be reached (<3.0, <2.0)?

2. Critical Reagents: what is the best practices to introduce a new durg lot in immunogenicity assays? Bridiging in Confirmatory Assay, bridiging applying PC limits (if available) or as per default a partial validation

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1. For peptide therapeutics with high ADA incidence and no safety or PK/PD impact in early clinical trial, does agency agree with a "sample and hold" strategy for NAb or cross-reactive ADA assessment in ph3 trial?
2. For established low-risk ONTs, such as GalNAc-siRNA, what are the concerns to move towards risk-based "sample and hold" strategy for ADA assessments throughout the clinical development?
3. For patient selection in AAV GT treatment, what are the expectation to lift the threshold? Is there a clear regulatory path about it?
4. AAV GT redosing strategy and requirement to overcome pre-existing Abs and consideration for assay development? (Hansa example)

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Do we have experience to share on the acceptance of S/N data instead of titers in submissions? - Which type of correlation were done and how excessive do we need to evaluate the correlation?

I would like to hear about experiences with authorities in terms of assay signal as ADA magnitude e.g. in type D meetings or other interactions or any pushbacks.

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ADA in combi studies: For a study Pembrolizumab will be used with the combination of Sponsor new drug - both within oncology. Will you set up an ADA assay for Pembro? Will you measure if Pembro interferes with sponsor´s Drug ADA assay?

- A more than a Yes/No answer is requested - like have you seen that regulators ask for this; do not touched an approved drug´s ADA assay - and why not touch it
- Have anyone done it? What if Pembro interferes in Drug´s ADA?
- What if you see more ADA in same patient population than Pembro originally saw in same population?

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"Titer reporting: If CP is low, and the titer you are measuring is just above CP, and the dilution series just fluctuate around the CP - is it then meaningful to add an additional multiplication factor to the CP, and is it allowed?
I can send an example.

Drug tolerance. If the DT is 2 ug/ml, but you then realise during the study that some samples have a PK level of 6 ug/ml, can you then re-do your DT as an amendment to the Validation? During the validation the LPC level with increasing amount of Drug, was just fluctuating around the CP. It looks like it is a co-incidence that the DT of 8 ug/ml did not pass, or that the DT of 2 ug/ml passed.
I can send an example.

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Screening cut-point. The sCP is determined with an addition factor instead of a multiplication factor. The validation was done in 2017, and the study is still ongoing using this cut-point. Is this acceptable to Heath Authorities?
The CP is super low, and several samples are screened pos, confirmed pos, and also have a Titer despite their S/N is <2. Can these data somehow be re-calculated with in example multiplying the CP with an extra factor, and how to determine this Factor? Or would you rather report all data and then make decision on the S/N data? The study is a post-marketing study and will not be repeated.
I can come with an example.
All together is seems as this ADA assay is very sensitive, and therefore gives more pos ADA than actual 'real' ADA. Is the Confirmatory Drug conc too high, as most of these borderline ADA pos samples actually are confirmed pos, even though the S/N is <4."

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I would like to discuss the relevance of statistically calculated cut points.

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