TT 19: Sense or Nonsense of Assessing NAbs

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Background and Aim

- FDA and EMA guidelines on determination of anti-drug-antibodies (ADAs) recommend assessment of the neutralizing potential (NAbs) of positive ADA responses.
- Is there an optimal assay format (cellular versus competitive ligand binding assay) for the detection of NAbs?
- Are alternative approaches feasible? E.g. PK/PD profiles of subjects with ADA responses in comparison with ADA negative subjects?

Team Members

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Ongoing Activities and Current Results

First Survey has been completed

Survey outcome:

- **Pre-clinical studies**
  - It is generally accepted that an immune response to a drug in pre-clinical studies is not predictive for the incidence of potential immunogenicity in human.
  - The goal of ADA testing in pre-clinical studies is to confirm drug exposure and to explain toxicity findings. Therefore neutralization assessment and further characterization might not be required.
- **Clinical Studies**
  - **Expected 'Low risk' compounds**

    Main consequence of ADA response:
    - Impaired efficacy
    - No direct impact on safety

    PD read-out may be considered the most biologically relevant neutralizing assay.

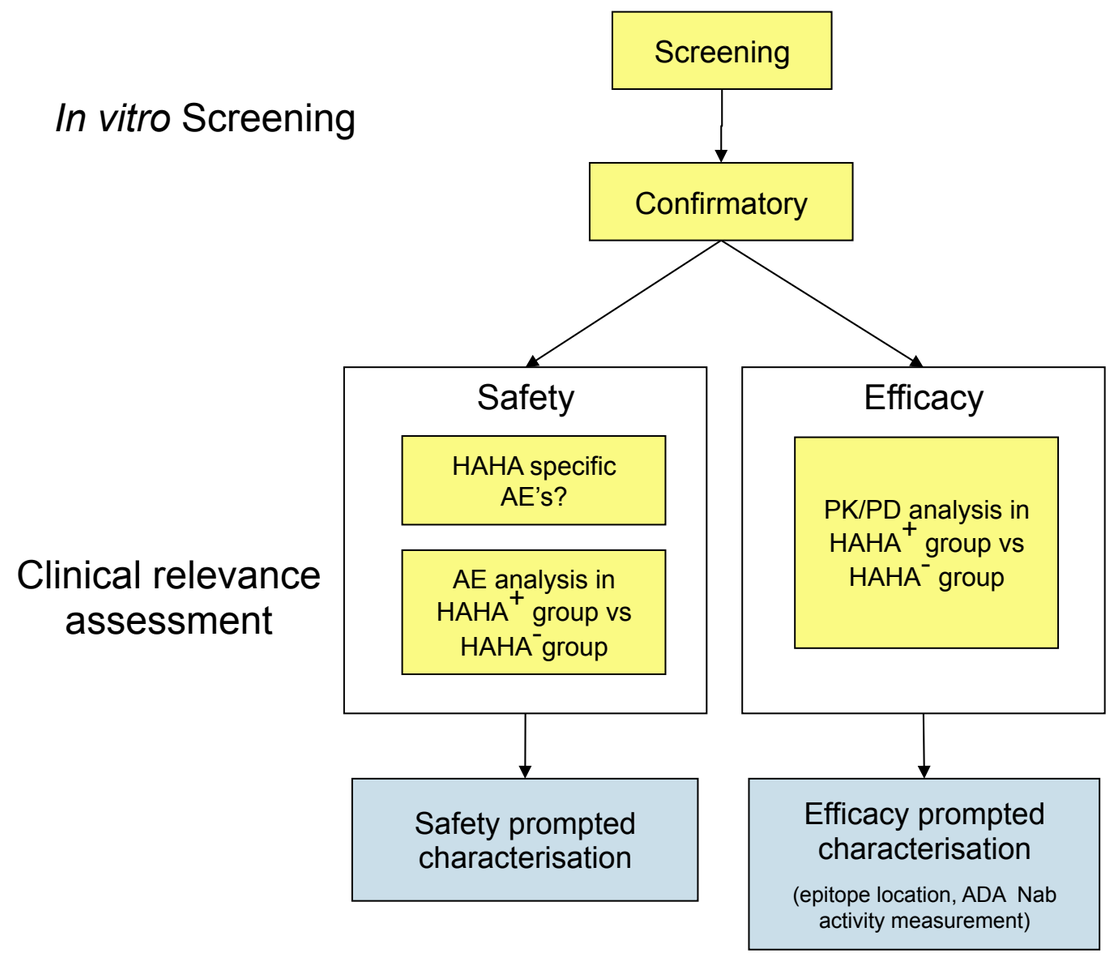
    When this is not possible another assay should be developed (e.g. Competitive Ligand Binding assays or Cell Based NAb assays as required)
  - **Expected 'High risk' compounds**

    Consequence of an ADA response:
    - Impaired efficacy
    - Impact on safety (autoimmune response)

    In addition to PK/PD read-out, NAb assays should be implemented to detect neutralizing antibodies against the drug, the endogenous counterpart and if necessary also against endogenous protein very similar to the drug.

    For high risk projects in case of AE ADA-positive subjects should be called for followed-up assessment until titer has returned to baseline (as requested by the FDA).

- **Possible approach for the analysis of the impact of an ADA response for low risk compounds**
  - Figure 1 outlines a proposal for the analysis of the impact of an ADA response on safety. NAb assays are developed only when safety issues occur.



- **Discussion and Considerations**
  - Should the Neutralizing capacity of an ADA-response be assessed independently from the risk?
  - Are PK/PD markers comparable to NAb assays and sensitive enough?
  - Will we obtain acceptance from health authorities for using PK/PD markers in lieu of NAb assays?

Future Plans

- Follow-up survey to assess prevalence of alternative (non-cell based) determination of NAbs.
- Assessment of differences in approach between clinical and pre-clinical studies.
- Assessment of differences in approach based on risk level of the compound.
- Study examples for possible correlation with cell based approaches.
- Preparation of a position paper including the results of the survey, examples and recommendations.