Evaluation of clinical impact of immunogenicity and its challenges

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Agenda

- Regulatory Considerations
- Fit for purpose evaluation of ADA assay based on clinical data
- Immunogenicity subject classification and evaluation of clinical impact – theoretical examples
- Conclusions

Regulatory considerations

What we learn of available guidelines

- The anti-drug antibody (ADA) assay should be sensitive to low levels of **low and high affinity ADA** and detect **all isotypes**
- FDA recommends that ADA assays achieve a **sensitivity of a least 100 ng/ml** and that assays are capable of sensitive ADA detection **despite the presence of trough level of drug**
- ADA assays are being developed using **positive control antibodies** which may **not be reflective of clinical ADA responses**
- ADA assay results are directly influenced by assay design, assay reagents, sample characteristics (timing of sample collection, etc)

→ **Not possible to compare ADA results between therapeutics and between studies that are using different ADA assay formats**

Regulatory considerations

What we learn of available guidelines

- FDA recommends a **risk based approach** driving the immunogenicity testing strategy and the extent of ADA characterization, monitoring and mitigation strategy during clinical development and post-marketing period
- Immunogenicity data should be analysed **in context of their relevance to the PK, PD, efficacy** of the therapeutic and **safety** consequences which is the primary concern
- ADA assay are being developed via a **fit for purpose approach = method is suitable for its intended use and meaningful for patient safety and product efficacy**
- Recommendation that ADA is being detected before clinical impact (effect on PK, PD, efficacy and safety) is observed

→ **How do we evaluate the clinical impact throughout clinical development?**

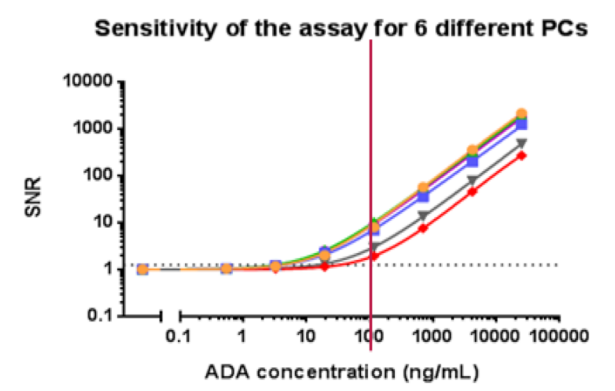
→ **How do we determine whether the ADA assay is suitable for detecting clinical samples?**

ADA data characteristics - complexity

Sensitivity and drug tolerance dependent on positive control Ab

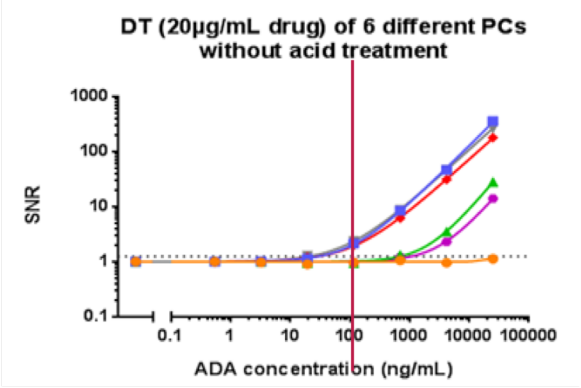
Comparison of 6 anti-idiotypic mAb (Kd = 10 to 400 pM)

sensitivity in absence of drug



All mAb sensitivity < 100 ng/ml

drug for tolerance at 20 µg/mL



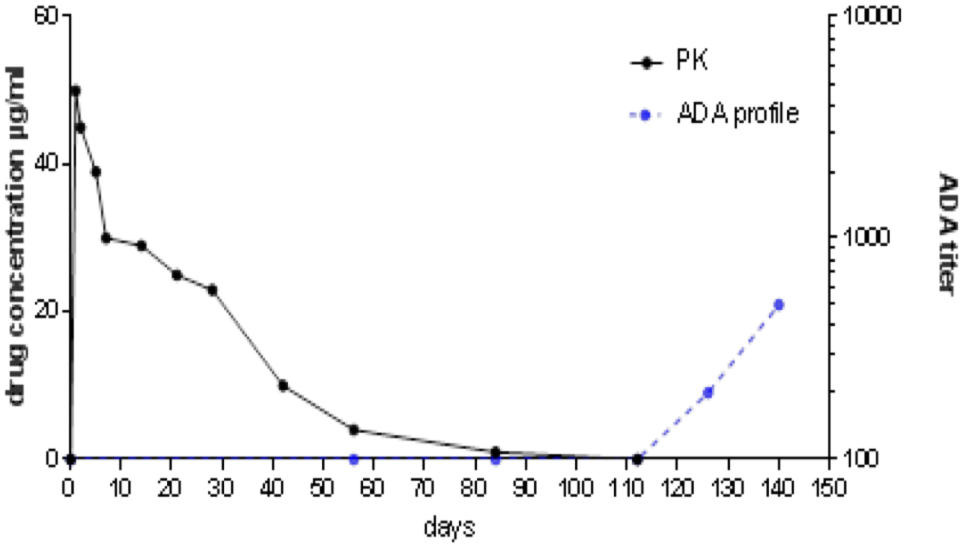
High difference in drug tolerance

Fit for purpose evaluation of ADA assay based on clinical data

Are the assay characteristics relevant for clinical samples? Theoretical example 1

Assay characteristics

- Anti-idiotypic mAb as positive control
- Sensitivity = 24 – 50 ng/mL
- Drug tolerance = up to 50 µg/mL for 100 ng/ml positive control



Outcome

- ADA detected if drug levels are BQL
- Drug tolerance might be overestimated with positive control antibody used
- Consider assay redevelopment to enchance drug tolerance in support of phase II

Fit for purpose evaluation of ADA assay based on clinical data

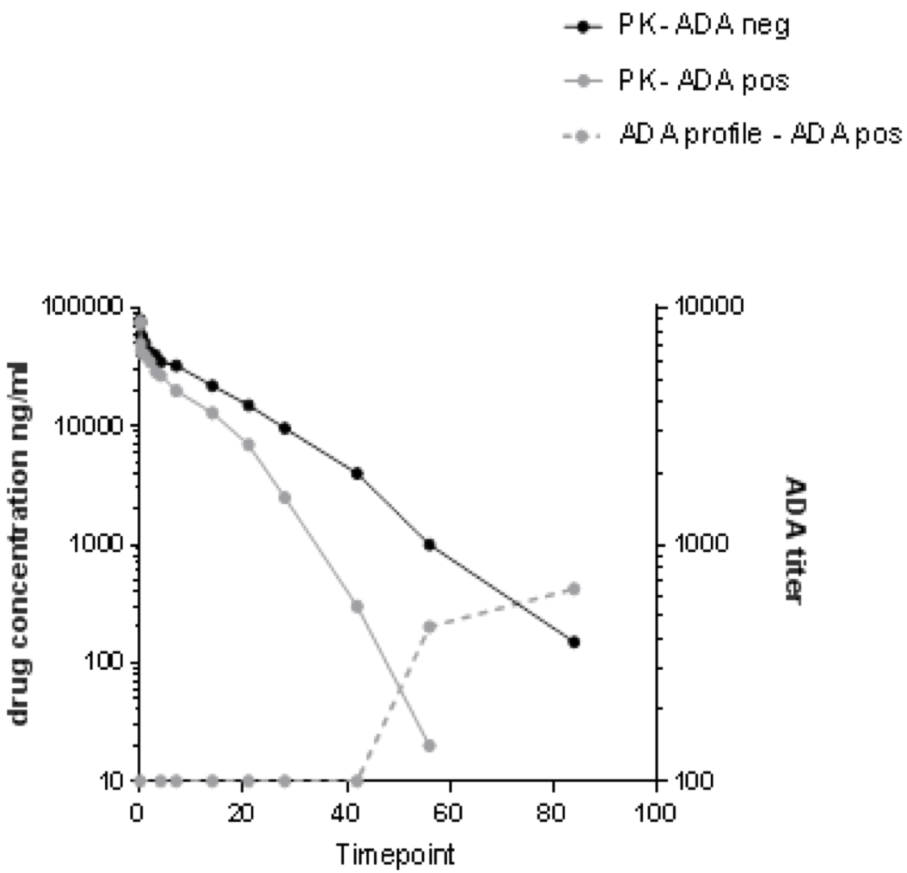
Are the assay characteristics relevant for clinical samples? Theoretical example 2

Assay characteristics

- Anti-idotypic mAb as positive control
- Sensitivity = 25 ng/mL
- Drug tolerance = up to 500 µg/mL for 100 ng/mL positive control

Outcome

- ADA is detected only once PK profile affected and drug level is reduced
- Drug tolerance might be overestimated
- Consider assay redevelopment to enchance drug tolerance in support of phase II



Fit for purpose evaluation of ADA assay based on clinical data

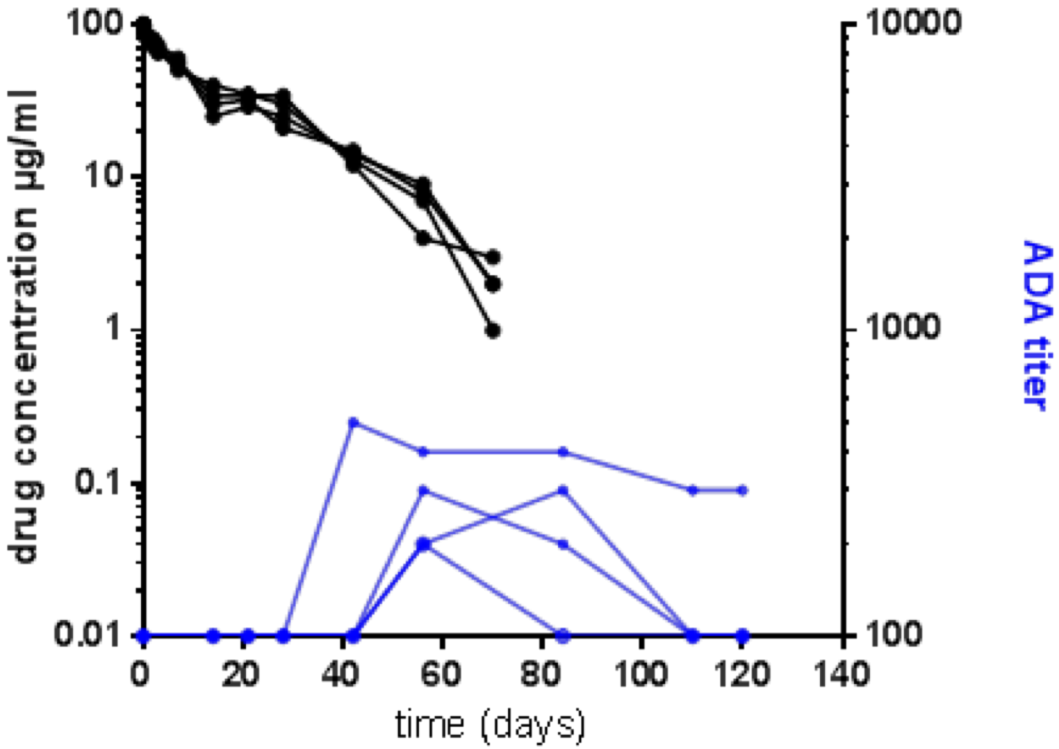
Are the assay characteristics relevant for clinical samples? Theoretical example 3

Assay characteristics

- Anti-idotypic mAb positive control
- Sensitivity = 150 ng/mL
- Drug tolerance = up to 1,6 µg/mL for 450 ng/mL positive control

Outcome

- ADA is detected under drug treatment
- No impact on PK observed
- Adequate drug tolerance
- Assay fit for purpose for next study (might be too sensitive to be evaluated during further development)



ADA testing and development during clinical development

Refinements or revision if need required

ADA assay life cycle – fit for purpose and fully validated in support of phase III
Immunogenicity risk assessment with refinements/revision during product development process

Phase I

- Assay development based on available positive control Ab
- data interpretation in function of assay limitations
- Info on target levels might be absent or limiting
- Drug tolerance is less critical as drug wash-out sampling time points often available

Phase II

- Assays should allow detection of ADA in presence of anticipated Ctrough values
- Target tolerant to allow correct data interpretation
- Assay dev based on theoretical info on expected target/drug concentration upon multiple dosing (modelling approach)

Phase III

- Fully validated assay
- Sufficient drug and target tolerance characteristics as optimal as possible (critical evaluation of clinical data obtained during phase II trials)

Assay development – required assay characteristics

Clinical immunogenicity results

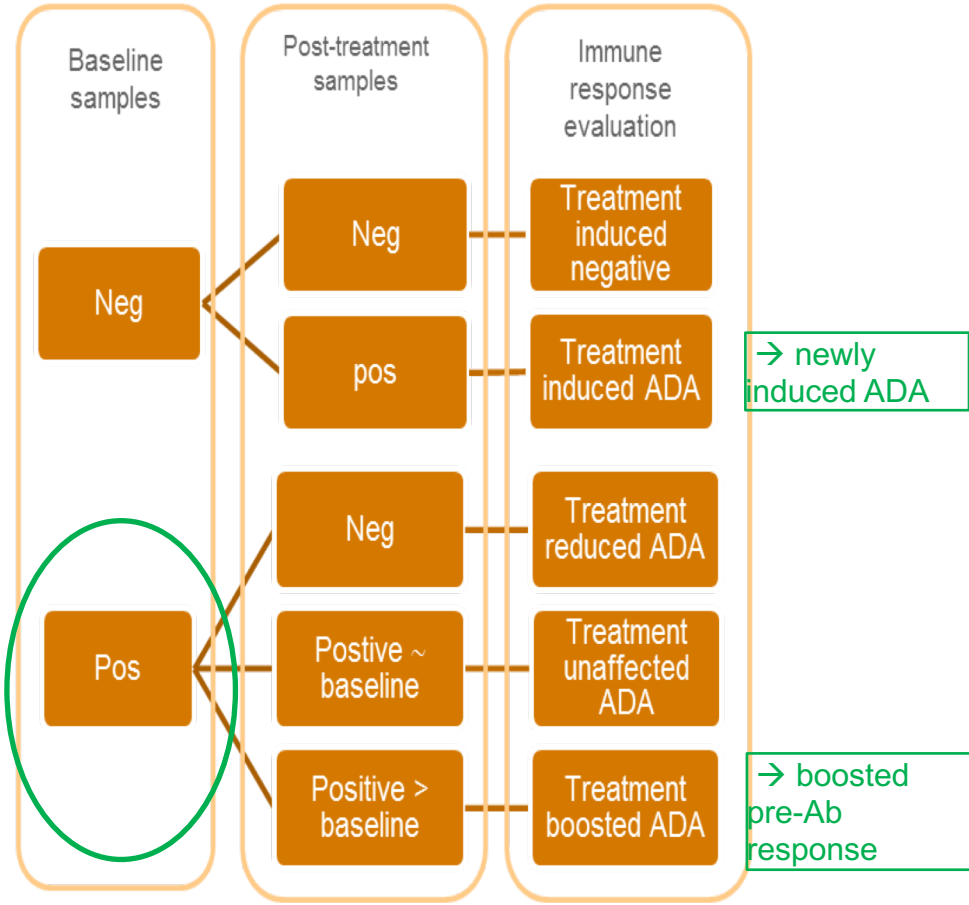
Immunogenicity subject classification

evaluation of clinical impact theoretical examples

Harmonized reporting and subject classification

Based on ABIRISK - *clinical and experimental Immunology 2015*

- Subjects should be classified based on
  - Pre-existing antibody (pre-Ab) status
  - ADA status post-treatment
- Questions to be answered:
  - How many subjects present pre-Ab against the drug?
  - How many subjects develop a newly induced treatment -emergent antibody response?
  - How many subjects develop a boosted antibody response?
- If assay is not sufficiently drug tolerant to allow sensitive detection of ADA under treatment = ADA status is treatment emergent inconclusive



pre-existing Ab

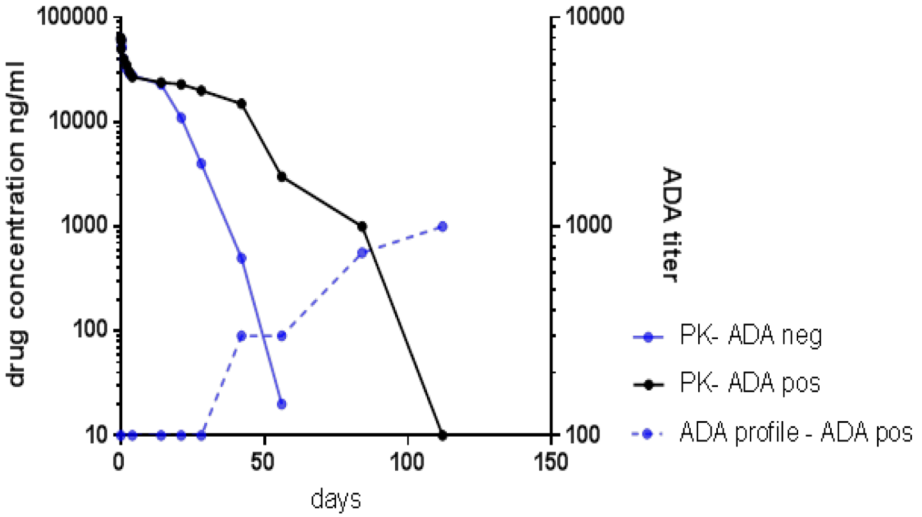
Evaluation of clinical impact

Impact on PK

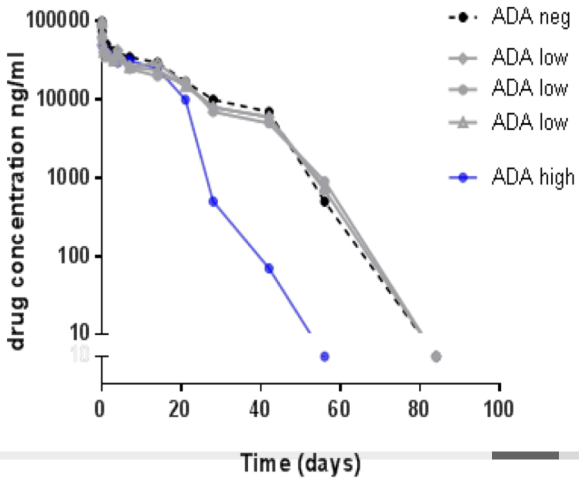
- Can be done **from phase I onwards**
- ADA can reduce PK (clearing ADA) or increase exposure (sustaining ADA)

- **Individual PK/ADA plots to evaluate aberrant PK profiles** (clearing ADA or sustaining ADA)
- If impact is observed – **evaluate titer levels** to define clinical relevant titer level
- Expected to be a robust parameter – PK parameters typically well predicted and consistent between individuals

Individual PK/ADA profiles → PK affected



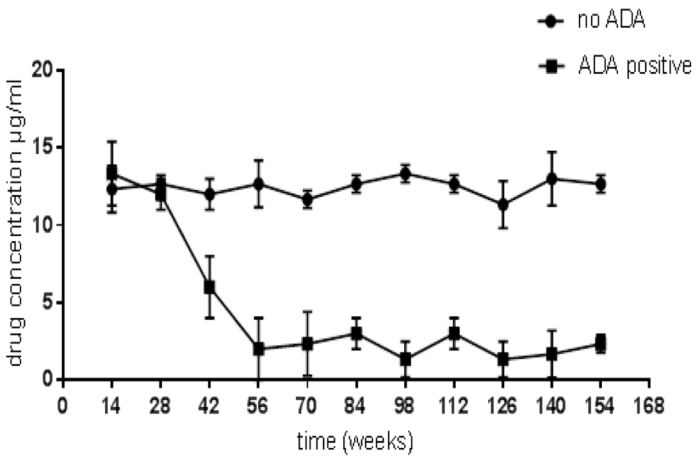
Affected PK in case of high level ADA only and no impact with low ADA titer levels

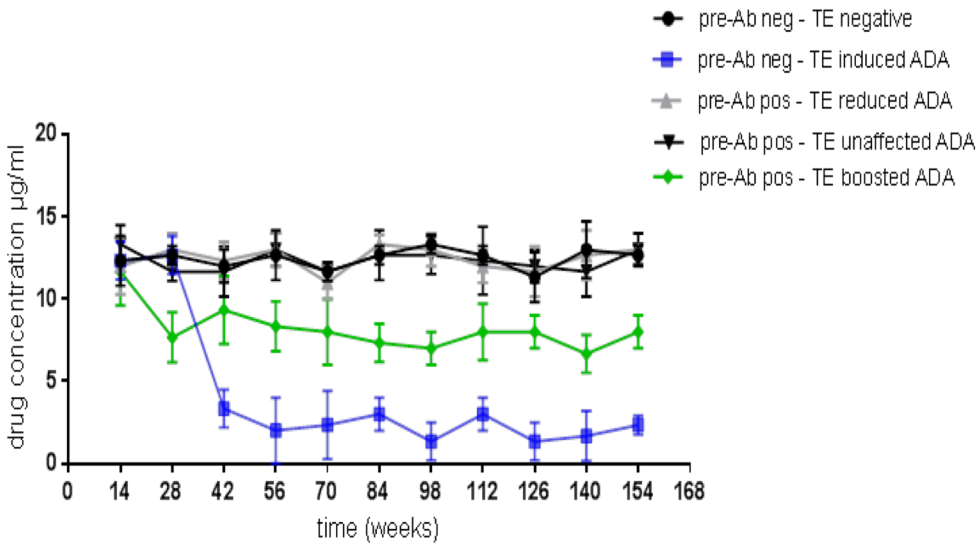


Evaluation of clinical impact

Impact on PK

- Can be done **on population level** – separation of the ADA positive versus the ADA negative subjects (per dose group)
- Can be done **per subject category** to evaluate differences between impact of e.g. newly induced ADA versus boosted ADA responses
- Given the expected high heterogeneity in ADA responses (level, affinity, functionality, e.g.) often the **correlation on individual profiles is more sensitive to detect impact**



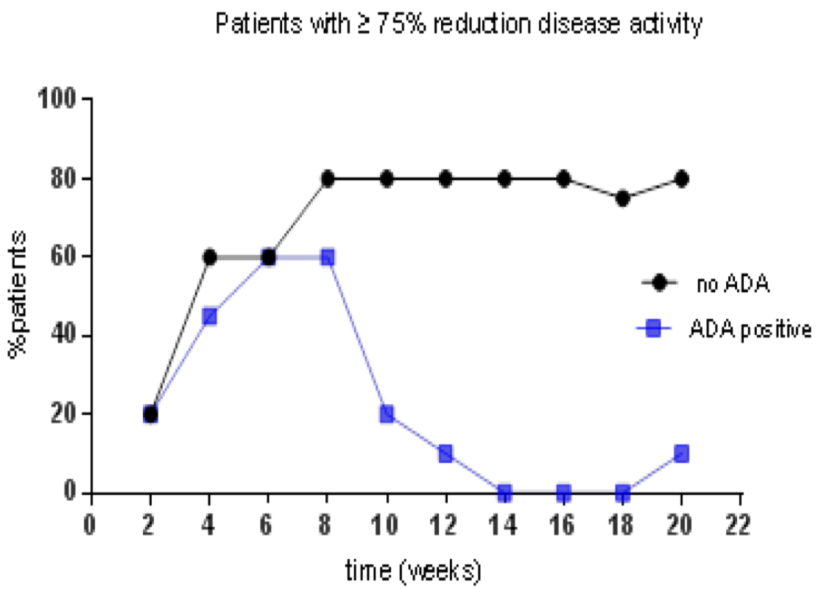


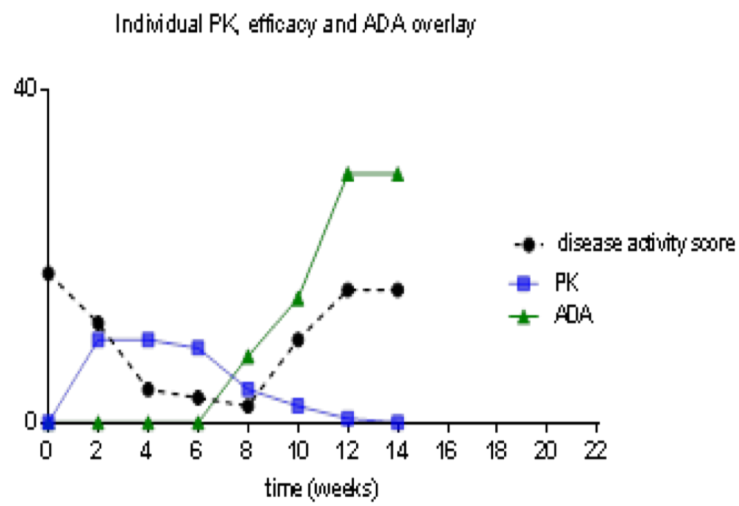
Evaluation of clinical impact

Impact on PD/efficacy

- Can be done from **Phase II onwards, mainly Phase III**
- Essential – well **defined clinical efficacy read-out or PD marker** with clear drug dose response and low variability within the population
- Impact as consequence of altered PK or due to presence of neutralizing antibodies

- **Individual PK/ADA/efficacy plots to evaluate impact**
- If impact is observed – **evaluate titer levels** to define clinical relevant titer level
- Impact expected to be inversely correlated with drug dose level → the higher the dose the more ADA needed to impact

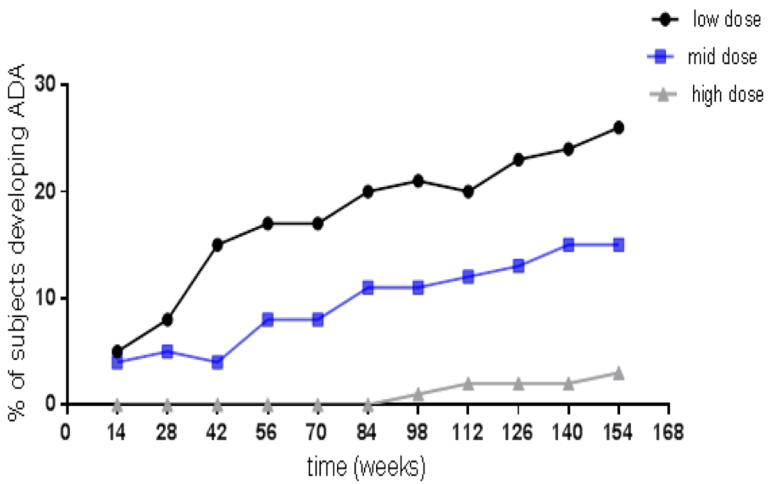




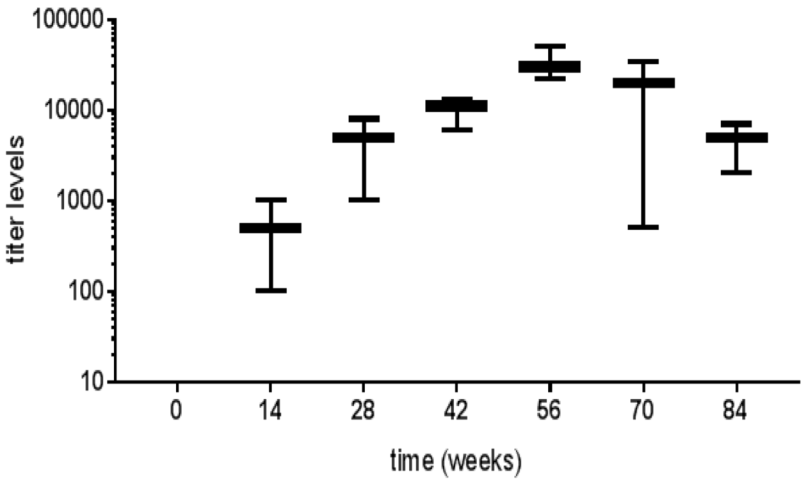
Evaluation of clinical impact

Reporting ADA results – understanding kinetics

- ADA: incidence % of the different subject categories
- Individual and mean ADA titer time profiles – spaghetti plots per dose group
- Onset of ADA: % subjects presenting ADA in function of time



Note: difference in ADA incidence between high and low dose groups might be reflection of higher assay sensitivity in low dose groups (~ drug tolerance)

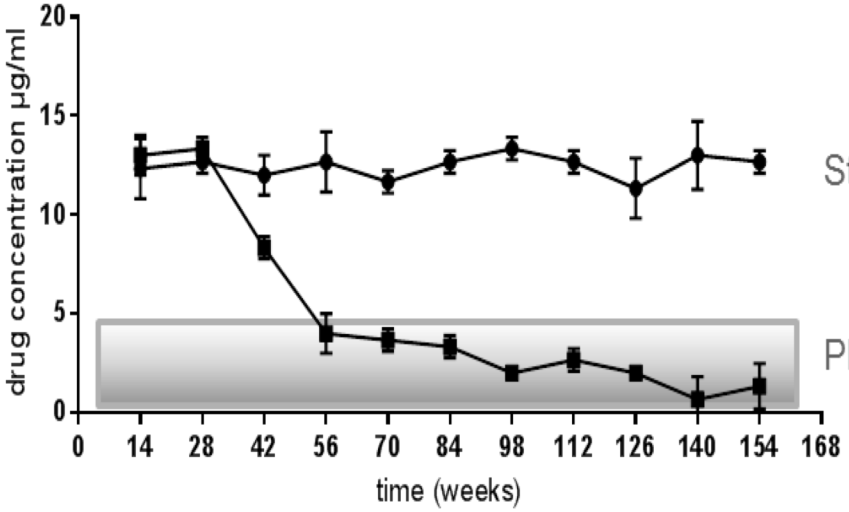


Note: titer levels should be compared within dose groups as titers will be affected by the amount of free drug (~ drug tolerance)

Evaluation of clinical impact

Post-marketing monitoring – towards personalized treatment

- Monitoring PK may be of interest to guide best treatment options for the patient (switch to other biologic) in case immunogenicity impact is mainly on PK (with loss of efficacy as consequence)



Stable drug concentration → linked with sustained efficacy

PK level decreases → resulting in loss of efficacy

Conclusions

- Immunogenicity data should be analysed in context of their relevance to the PK, PD, efficacy of the therapeutic and consequences on safety
- Assay should be fit for purpose, however assays are being developed using positive control antibodies therefore clinical data results should be critically evaluated to confirm assay suitability
- Refinements in ADA assay and testing strategy may be required during clinical development upon availability of new data
- Correlation of ADA data with PK, PD, efficacy and safety parameters should be done on individual level and population level, though the biological variability of the PK, efficacy biomarkers/end-points within the population should be taken into consideration during the evaluation

Acknowlegdments

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Questions?

Thanks!