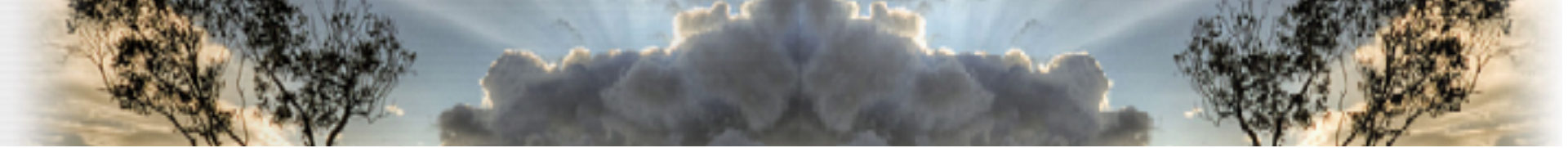


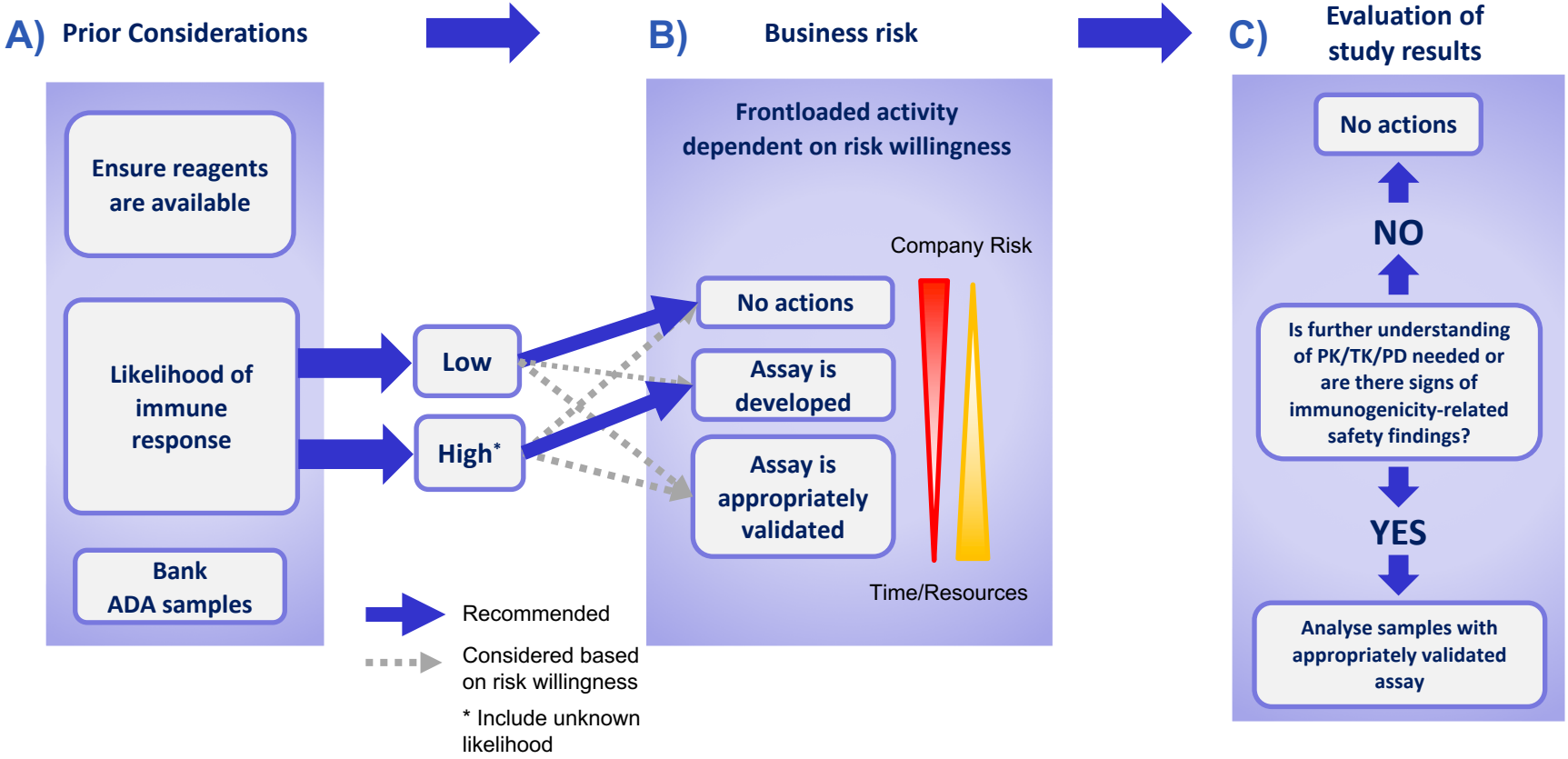
EBF feedback for ADA in non-clinical studies focusing on sampling, communication and evaluation of TK/PK

Susanne Pihl, on behalf of the EBF

13th EBF Open Symposium
N° 13 From Cyberspace - Staying Connected

http://www.e-b-f..eu

ADA decision-making tree



Agenda

- Considerations for collecting ADA samples and if analysis of the samples are required based on observations in the non-clinical studies
- How to use the ADA results for reporting PK/TK evaluation, if analysed
- Examples

Collection of ADA samples

- According to ICH S6 collect ADA samples for banking and analyse, when required
- Rodents:
  - Limited sample volume and often sparse sampling
  - Collect samples from both main study and PK/TK animals
- Non-rodents:
  - Sufficient volume for collection of full PK/TK profiles in main study animals

- Collection timepoints:
  - Collect ADA samples min predose and at the end of the study
    - For studies with longer duration, the suggestion is to include sample collection during the study as well

Whether to analyse the samples

- Samples should only be analysed if the PK/TK/PD profiles or safety findings indicate a potential impact due to the presence of antibodies aligned with ICH S6
  - If needed for the interpretation

- Important to report back to the lab responsible for ADA analysis, if the analysis is required or not
  - If possible, do the PK/TK/PD and safety evaluation on interim results to reduce the potential delay

Design of non-clinical TK studies

- Studies with full TK profiles:
  - Main study animals will have TK and ADA samples collected

Or

  - Main study animals without TK samples but with ADA samples collected
  - TK animals with full profile and ADA samples collected

- Studies with sparse sampling:
  - Main study animals with TK samples collected as sparse sampling and ADA samples collected

Or

  - Main study animals without TK samples but with ADA samples collected
  - TK animals with sparse sampling and ADA samples collected

Evaluation of TK/PD and safety findings with ADA present – full TK profile available

- Expected TK full profiles for main study animals

- Perform full analysis with and without ADA positive animals
- Exclude the ADA positive animals for the TK evaluation
- Include all animals regardless of ADA status
- Exclude TK data only if impacted by ADA (*a priori* criteria)
- Apply a case-by-case approach

- Consideration:
  - How many animals should be included in the TK exposure used for human exposure ratio?

Evaluation of TK/PD and safety findings with ADA present – Additional challenges

- Sparse sampling:
  - How to remove ADA positive animals as it might lead to unbalanced number of results for each timepoint
  - TK response compose of primary concentrations from few animals

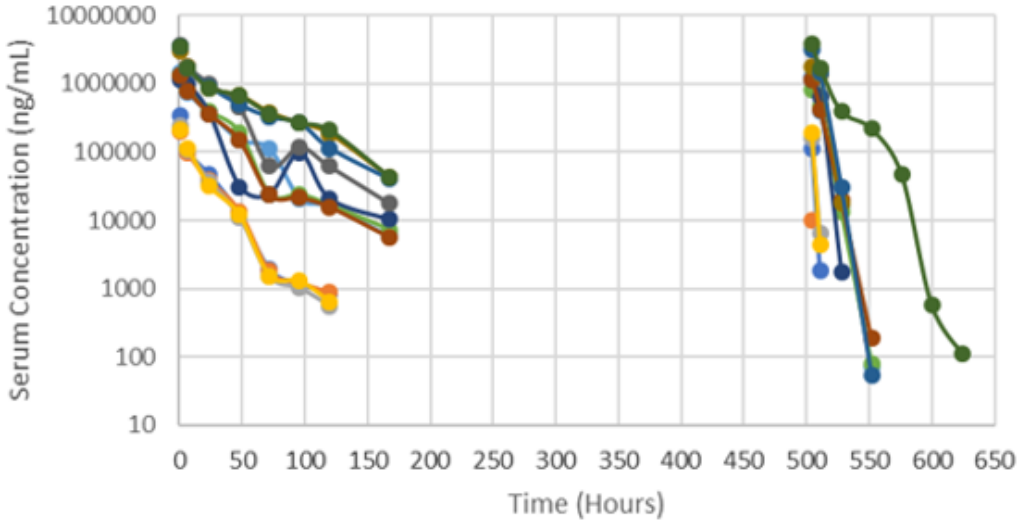
- TK vs main study animals
  - No direct comparison between TK and PD & safety evaluation
  - Important with ADA sampling and analysis of samples in the same manner as for TK animals

Example 1: Monkey DRF study

- A BsAb targeted on an IO therapy for solid tumor

- A multiple dose DRF study was conducted in cynomulgus monkeys
  - (2/gender/dose level) at low, middle and high dose levels
  - Once weekly dosing for total of 5 doses; study was ended 24 hrs after 5th dose
  - PK samples were collected after 1st and 4th doses
  - ADA samples were collected at baseline, Day 15, 22 and 29 pre-dose

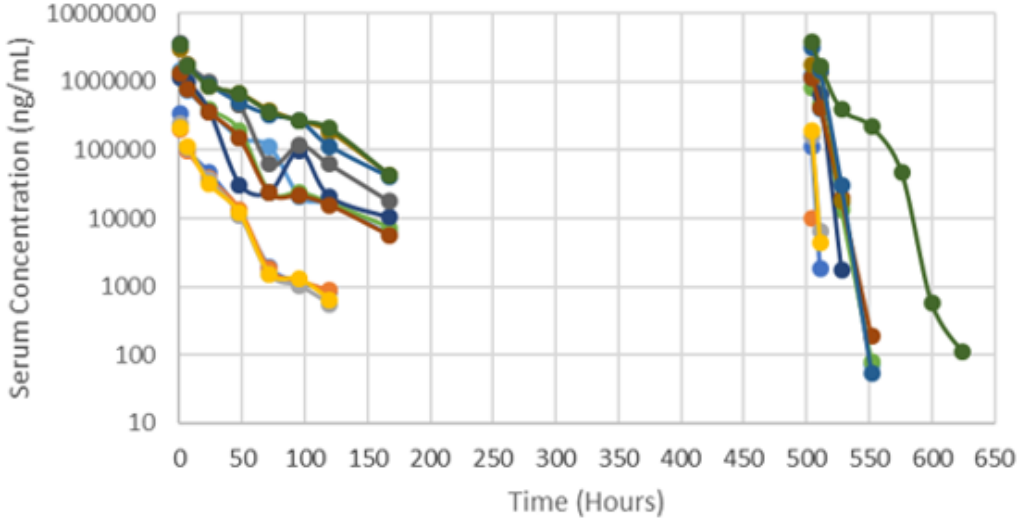
Example 1: Monkey DRF study



Questions:

- Should the samples have been analyzed for ADA?
- How to report PK?
- What to use for exposure ratio?

Example 1: Monkey DRF study



Questions:

- Should the samples have been analyzed for ADA?
- How to report PK?
- What to use for exposure ratio?

Observation and discussion:

- TK exposure level was significantly reduced in most animals
- Samples were analysed for ADA
- TK exposure reduction was most likely due to ADA formation

Overall Summary: ADA data supported the TK analysis. The impact of ADA on TK was clear.

Example 2: 13 week toxicity study in monkey

- Weekly SC administration to 6 animals/gender/group in Group 3 and 4

- Blood samples for TK evaluation were taken from animals after dosing at:

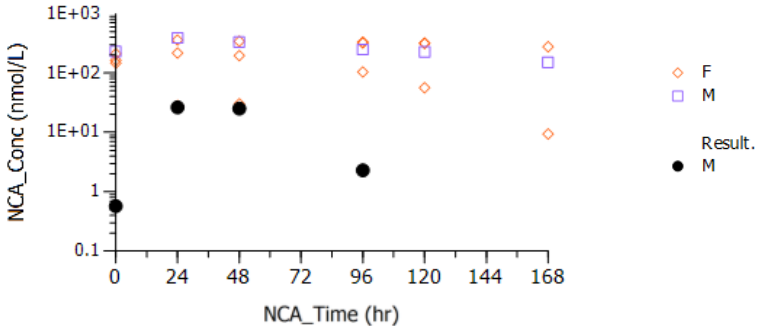
  Day 1 (Week 1), Day 36 (Week 6) and Day 85 (Week 13) at the following nominal time points: Pre-dose and 24, 48, 96, 120 and 168 hours after dose administration

- Sampling for antibodies as below:

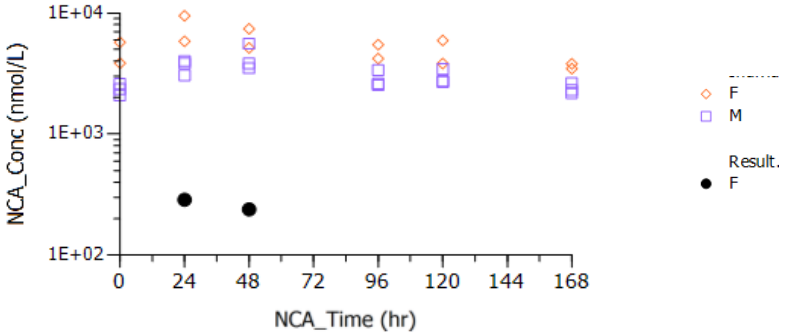
  Pre-treatment, Week 6, Week 13 (+ recovery for group 4)

Example 2: 13 week toxicity study in monkey

Group 2 – Week 6



Group 3 – Week 13

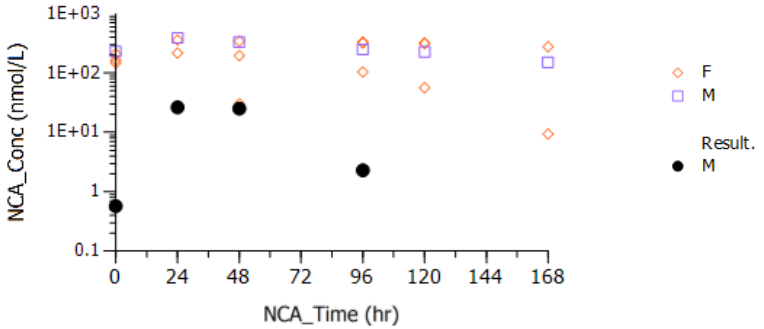


Observations and discussion:

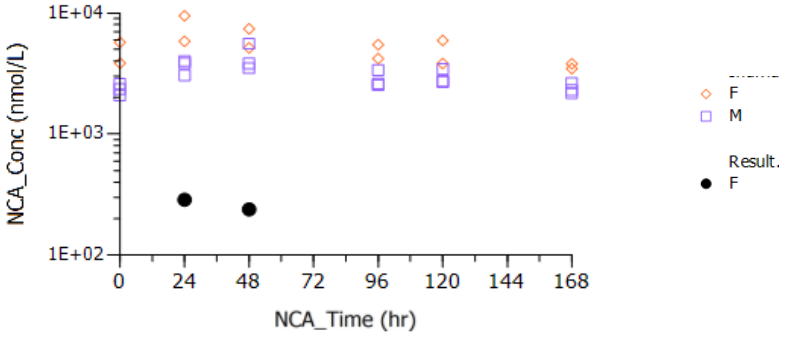
- Several animals with reduced or low exposure after repeated dosing
- Should the samples have been analyzed for ADA?
- How to report TK and calculate human exposure ratio?

Example 2: 13 week toxicity study in monkey

Group 2 – Week 6



Group 3 – Week 13



Observations and discussion:

- Several animals with reduced or low exposure after repeated dosing
- Should the samples have been analyzed for ADA?
- How to report TK and calculate human exposure ratio?

Approach:

- Samples were not analysed for ADA
- The impacted animals were excluded from the start
- Omitting the results did not change the conclusion of the study

Example 3: Study using sparse sampling

	Concentration					
Animal	2 h	4 h	8 h	12 h	16 h	24 h
1	BLQ			BLQ		
2	1			6		
3	1			BLQ		
4		42			8	
5		16			2	
6		2			BLQ	
7			30			4
8			5			BLQ
9			BLQ			BLQ
mean	2	60	35	6	10	4

Evaluation based of TK concentrations:

- Could the TK be impacted by ADA?
  - Increased or decreased exposure?
  - Could ADA have impacted the TK method?

- Should samples be tested for ADA?
  - Is it known from other studies, if ADA is present and the impact on TK, PD and safety
  - Would it impact the decision to go into FHD?

Example 3: Study using sparse sampling

Animal	2 h	4 h	8 h	12 h	16 h	24 h	ADA
1	BLQ			BLQ			Yes
2	2			6			Yes
3	1			BLQ			Yes
4		42			8		No
5		16			1		No
6		2			BLQ		Yes
7			30			3	No
8			6			BLQ	Yes
9			BLQ			BLQ	Yes
Mean (N=3)	1	20	12	2	3	3	NA
Mean ADA neg	NA	29	30	NA	3	3	NA

ADA samples were analysed:
How should the data be reported?

- With and without ADA positive animals?
- If reported for ADA negative animals, the number of animals included at each timepoints varies from 0 to 2
- What TK values should be used for human exposure ratio?
- Representative for the TK animals?
- Any sign of impact of PD or safety based on the ADA response

Conclusion

- 3 animals were the primary driver of the TK response
- TK decreased by the ADA response
- Concern that ADA neg will be unbalanced and only include 4 sampling time points
- Justification needed to document how Sponsor report the data

Summary

- Animals with full TK profile or with sparse TK sampling

- Impact on TK/PD or safety parameters
  - Should ADA samples be analysed?
  - Number of animals with impacted?
  - Decrease or an increase in the TK response?

- Evaluation of TK data:
  - Including (all animals or with and without ADA positive animals)
  - Excluding (all ADA positive animals or only excluding ADA positive animals if impact (*a priori* criteria)
  - Apply a case-by-case approach

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