EIP Working Group on Immunogenicity Strategy Update

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on behalf of EIP

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EIP Working Group Membership
20 companies

Project Lead(s):

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Participants :

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- Daniel Kramer, Sanofi
- Harm Buddiger, Genmab
- Sebastian Spindeldreher, ibiologix
- Anita Rudy, Sandoz
- Karien Bloem, Sanquin
- Daniel Splinter, Sanquin
- Asa Marknell-Dewitt, Thermofisher
- Osterlund Karolina, Thermofisher
- Boris Gorovits, Pfizer
- Mantas Malisauskas, Merck
- Lars Ostergaard Pedersen, Lundbeck
- Stefanie Elm, Amgen
- Stephan DeWall, GSK
- Claudio Calonder, Novartis
- Vibha Jawa, MSD
- Huaping Tang, MSD
- Linlin Luo, MSD
- Elena Fernandez, Roche
- Gregor Lotz, Roche
- Martin Schaefer, Roche
- Helene Solberg, Novo Nordisk
- Karin Weldingh, Novo Nordisk
- Martin Ullman, Fresenius Kabi

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Disclaimer

This presentation represents the view of the EIP working group and are not necessarily reflective of the specific views of any member company

Objectives

General feedback on practical experiences with the implementation of the recent IG requirements - different regions – especially regarding HA questions to CTDs / BLAs

- Collecting feedback from team members
- Bring these topics together and identify major points of challenges

Topics in need of further guidance

1) When there is a high risk for serious consequences from ADAs, sponsor should plan for ADA sample collection until ADA return to baseline levels

2) Use of a sensitive PD marker and appropriately designed PK assay in lieu of NAb assay – when justifiable?

3) Assay testing strategy for multi-domain drugs
   - work-out and align on best testing strategy to evaluate domain specificity for multidomain biologics in function of nature of biologic and the immunogenicity risk

Goal: Provide clarification to the community by means of presentations/discussions & publications

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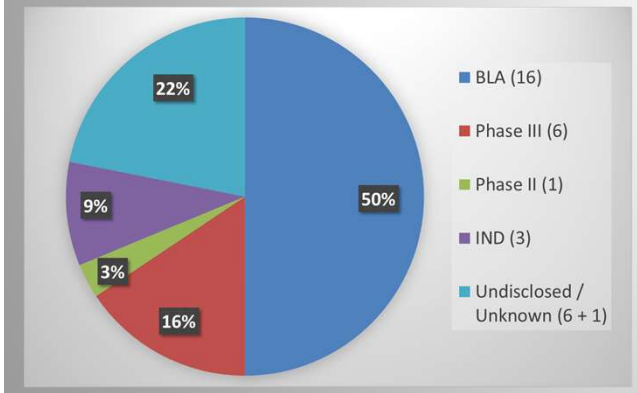
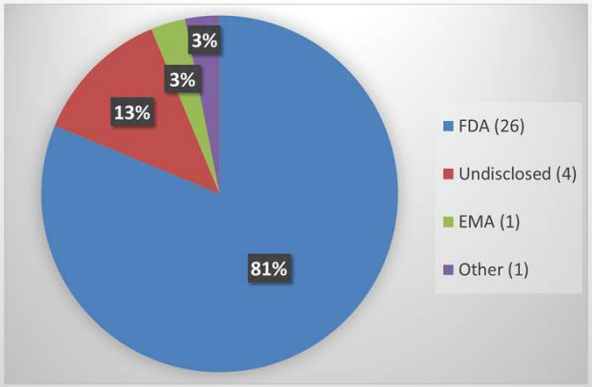
Highlights from HA feedback collection

- May 2018: Feedback from 11 companies & 42 comments
- Living document – annual re-evaluation

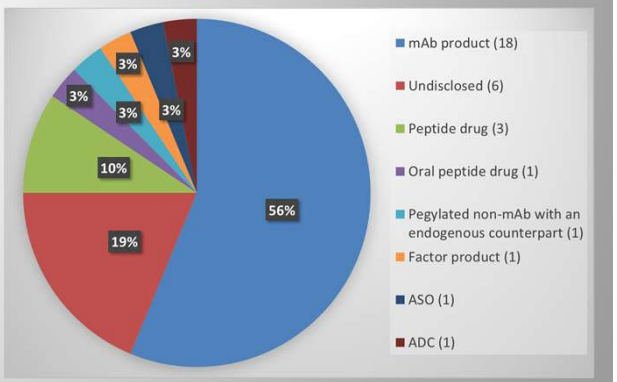
Project Development Stage



Regulatory Agency



Therapeutic product



Highlights from HA feedback collection

- **Comments related to assay validation prior to draft FDA 2016 draft guidance**
  - Confirmatory cutpoint 1% instead 0.1%
  - LPC to be set with sensitivity based on 1% FPR
  - Precision and selectivity (lipemic) evaluation in screening & confirmatory assay
  - Data on robustness of the assay
  - Reporting antibody titers including MRD
- **Drug tolerance**
  - Requested information on drug tolerance levels for ADA levels near the assay sensitivity
  - Demonstrate that the LPC and HPC levels can be detected in presence of drug levels detected in clinical sample
  - Justification for accepted drug tolerance
- **NAb assay**
  - Agency generally recommends the use of a cell based neutralizing assay. If you decide to use a competitive ligand binding assay, the comparison of assay performance is required
  - Rejected proposal to use integrated PK, ADA and target engagement analysis instead of NAb assay → **draft OPINION LETTER #2**
  - Request for 1% FPR in NAb assay instead of 0.1%
  - Request for improved sensitivity and drug tolerance

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Highlights from HA feedback collection

- **Sample collection time points and isotyping**
  - ADA-positive subjects must be followed up until ADA reverted to baseline → draft first OPINION LETTER
  - Comments on sampling time points: d7-d10 needed for IgM and IgG detection
  - Sensitive detection of IgM and IgG, IgA (for oral peptide)
- **Data to be provided**
  - Request for development data for all assays
  - Agency wishes to review all data prior to Ph3 pivotal studies
- **Assay method**
  - Pretreatment step – target bead based depletion step: risk for removal of target-drug-ADA complexes impacting ADA detection
  - Evidence requested that method can detect ADA in low pH when acid method is used

Discussion Topic 1

"When there is a high risk for serious consequences from ADAs, Sponsor should plan to collect samples from subjects until ADAs return to baseline levels"

Further guidance and understanding is warranted

HOW…

- to define high risk for serious consequences from ADA?
- does the ADA data generated beyond the duration of the clinical study help in risk mitigation / management strategies – what is the purpose?
- to define 'baseline levels' & 'return to baseline levels'?
- to define duration of the follow-up?

Discussion Topic 1

"When there is a high risk for serious consequences from ADAs, Sponsor should plan to collect samples from subjects until ADAs return to baseline levels"

Other practical questions such as

- At what stage of clinical development (early phase I/II versus phase III) should further collection of ADA samples be planned for?

- What are the implications on clinical trial execution?

How to define high risk for serious consequences from ADA?

"ADA induced against the therapeutic drug product having high risk for serious **safety** consequences"

- ADA potentially neutralizing the function of an **endogenous counterpart** for which there is no functional redundancy, leading **to clinical manifestations**

  HOWEVER: the presence of an endogenous counterpart does not automatically means the drug should be classified as high risk (functional redundancy)!

- Serious adverse events (MedRA-terms) which are **related to ADA** = immune –related AE (immune related hypersensitivity reactions – may be related to MoA of therapeutic drug compound) (**serious clinical manifestations**)
  - Is life-threatening
  - requires inpatient hospitalization or causes prolongation of existing hospitalization
  - results in persistent or significant disability/incapacity,
  - may have caused a congenital anomaly/birth defect,
  - requires intervention to prevent permanent impairment or damage.

  https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-eve

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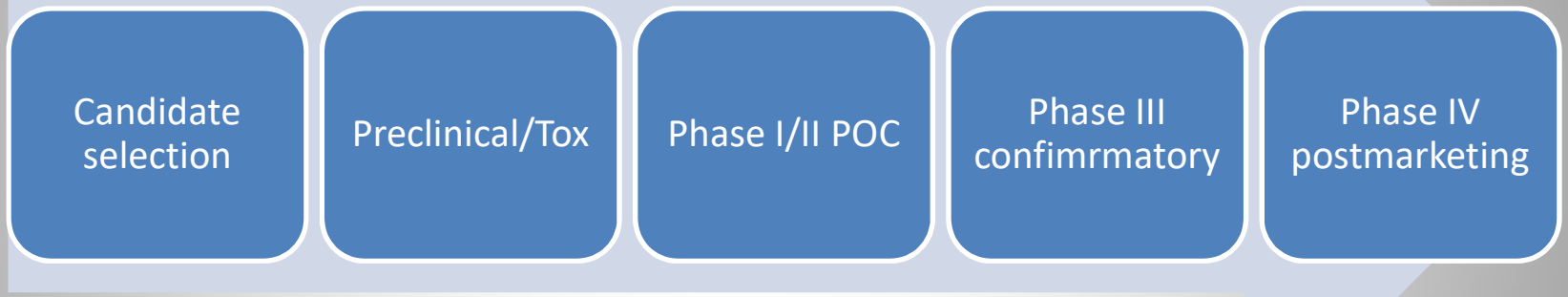
At what stage of clinical development should further collection of ADA samples be planned for?

The immunogenicity risk evaluation is a 'living' assessment

risk re-assessment during clinical development



Increased knowledge and improved risk assessment regarding impact on efficacy and safety

- ***Definition of high-risk project might evolve during clinical development***
- ***The actual risk of a therapeutic can only be defined at the late stage of clinical development***

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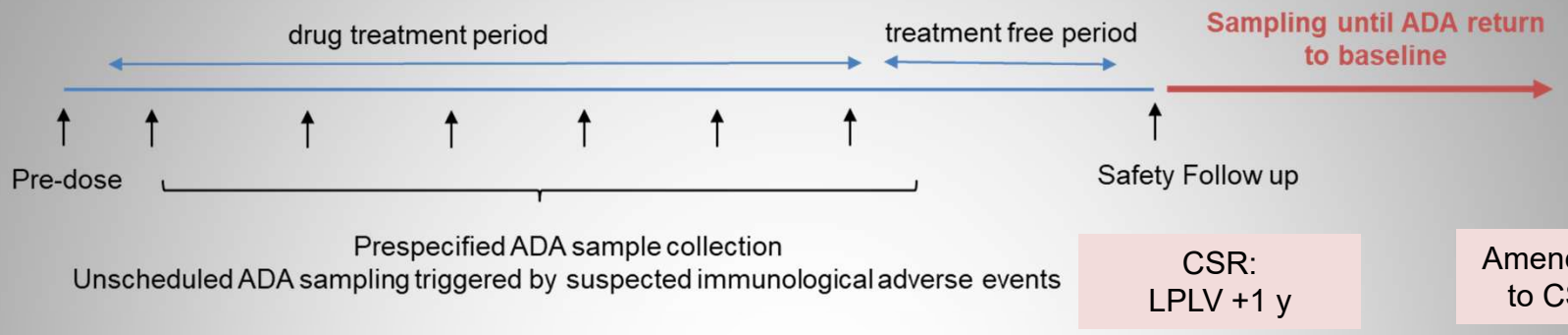
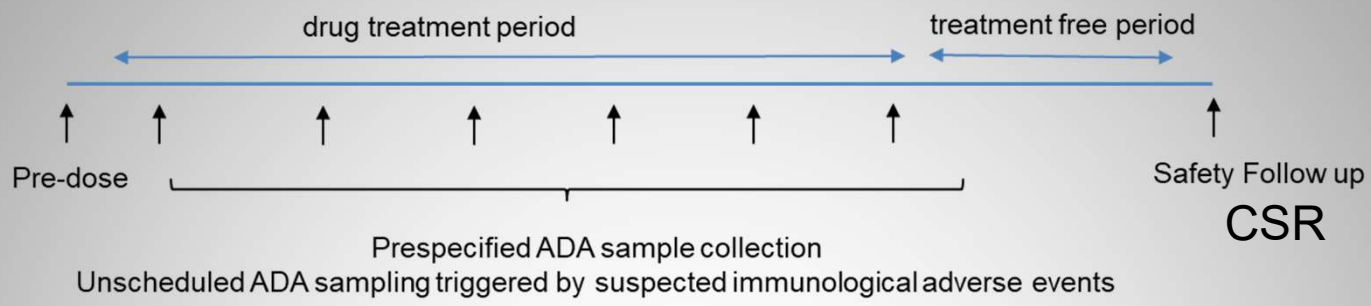
What will we learn from the ADA follow up?



- What can we learn from the ADA follow up?
- How will it help with risk mitigation and management strategies?
- What do we miss if we limit to anticipated clinical study duration?

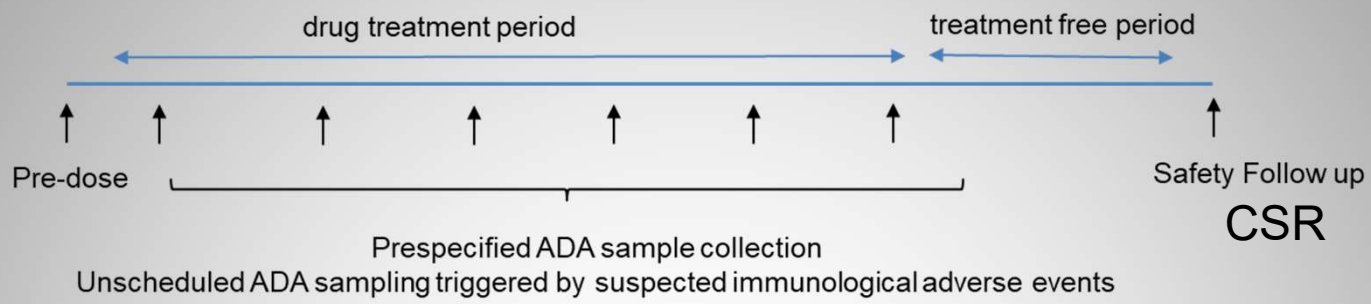
General practice during clinical studies



- **Immunogenicity risk assessment & clinical impact evaluation**
  - ADA results will be correlated with PK, PD, efficacy and safety read-outs
  - Impact of ADA can be different between drug treatment period versus safety follow up due to on-board drug:
    - ADA/NAbs having higher potential to neutralize endogenous counterpart in absence of drug levels
    - Impact of ADA/drug immune complexes might be different due to different drug/ADA ratio's

  = **importance of Safety Follow Up samples**

General practice during clinical studies (cont'ed)



- **Safety risk mitigation and management strategy in place**
  - Specific measures for detection and management of serious adverse events should be in place
  - Unscheduled sampling, triggered by suspected immunologically related adverse events, aims at establishing the clinical relevance of ADA
  - In case of serious AE, the clinical manifestations are being followed up till they are controlled and resolved.

What can we learn from the ADA follow up?
General experiences with ADAs during clinical studies

- Persistence of ADA responses are not uncommon and are often still detected at SFU
- ADA levels are expected to sustaining or decrease over time during treatment free follow up after clinical study
- If no clinical manifestation are observed at SFU, no risk that clinical manifestation will be encountered during further follow up (as no further drug treatment)

  = risk is not expected to increase after clinical study and should not be a rationale for follow up

  = ADA levels will be of non-clinical relevance (if no clinical manifestations are observed at SFU)

What can we learn from ADA follow up?

- Information on the duration/sustainability of the antibody response

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What can we learn from the ADA follow up?
General experiences with ADAs during clinical studies

How will it help with risk mitigation and management strategies?

- Presence or absence of ADA does not de-risk for re-administration or switching to another drug (with potential cross-reactivity of ADA)
- low/no ADA (baseline) responses is not an indicator for absence of immunological memory, which may be triggered by re-administration or switching of drug
- Hence, immunological memory is not necessarily related to durable/detectable ADA responses, and as such will not add value in risk evaluation or mitigation strategies
- If re-administration is warranted, appropriate strategies to detect and manage safety consequences promptly are required and are part of industry's standard practice

CONCLUSION

ADA follow up will not improve risk assessment & mitigation strategy that could justify the patient burden and logistics

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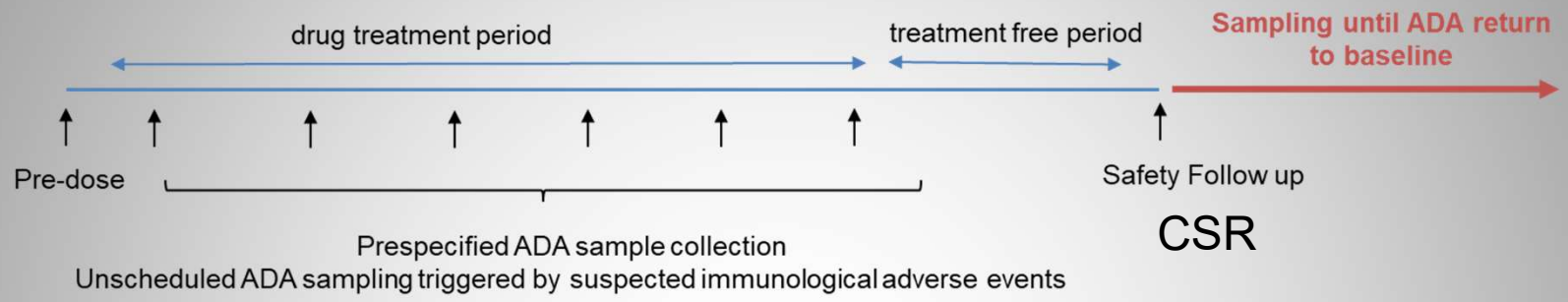
When can we see an added value of collecting data from ADA responses beyond clinical study duration?



- **Primary concern**: patient safety and the understanding of the relationship between the presence of ADA/NAb and the safety consequence

- **In cases of sustained clinical manifestations (observed at SFU)** even beyond the anticipated duration of the clinical study
- In that scenario, following-up ADA response after the study end might **provide info on the relationship between the ADA level and the clinical manifestations**, allowing retrospective evaluation of clinically relevant ADA levels linked to safety consequences

How to define “return to baseline” levels & duration of follow up?

- Persistence of ADA responses are not uncommon
- As seen in many clinical studies, the ADA responses did not necessarily return to baseline levels at the end of the study

- Following up of ADA/NAb till return to baseline levels might not be possible, even if performed for several years
  - several EIP members companies experienced that ADA responses did not return to baseline levels even after several years but:
    - either showed fluctuations around the pre-defined cut-point (“borderline levels”)
    - or plateaued over time and did not reach the baseline level.
  - Presence of memory cells may prevent the return to the pre-dose baseline levels

Can we limit to defined duration of the follow up instead of using the ‘return to baseline’ level criteria? Do we have alternative criteria?

EIP "Immunogeniciy Strategy" WG current proposal – based on the discussion points

- **When would collection of ADA samples beyond clinical study add value? High risk for clinical consequences?**
  - When ADAs are directly linked to negatively impacting patient safety and thus follow up will lead to better risk assessment and mitigation
  - **Further follow up if clinical manifestations are observed at the end of clinical study**
  - As such, we avoid unnecessary delay of drug development for those therapeutic drug products where the information on the duration of the ADA response will not increase patient value
- **Return to baseline and duration of follow up?**
  - In the scenario described above, EIP propose to follow up **ADA till the clinical manifestation resolve and NOT until return to baseline**
  - This allows retrospective evaluation of ADA levels that are of clinical relevance and might help in future risk mitigation strategies

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EIP "ADA Immunogenicity Strategy" WG current proposal – based on the discussion points

- **When? at what stage in clinical development?**

  As the follow-up of ADA beyond the anticipated duration of the clinical study is **limited to cases where clinical manifestations of serious clinical AE are sustained, ADA samples can be collected irrespective of the stage of the clinical development** as subjects are being followed up as industry's standard practice till serious clinical manifestations are resolved.

What is the opinion of the audience?

How can this be implemented?

Be ready for the next big things

Discussion topic 2

"Use of a highly sensitive PD marker and appropriately designed PK assay in lieu of NAb assay"

Further guidance and understanding is warranted

- In which cases can PD and/or PK assays be used instead of NAb assays?
- Best practice to define the clinical impact and conclude on presence of NAb?
- Situations where no NAb assay required irrespective of PK assay/PD marker?

EIP WG considerations

- The immunogenicity risk profile of the therapeutic
- The available assay formats of PK and/or sensitive PD marker
- The clinical design eg. anticipated Ctrough levels, ADA/NAb sampling scheme
- Biological variability in the PK and PD markers

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"Use of a sensitive PD marker and appropriately designed PK assay in lieu of NAb assay"

- **Only applicable for low risk projects?**
  - No direct link with potential safety consequence
  - No endogenous counterpart (no functional redundancy and thus linked with potential safety consequence)

- **High risk projects?**
  - NAb assay reflective of mode of action
  - Ensure detection of NAb in timely manner before impact is observed on PK, PD, efficacy and safety
  - Can PK assay and PD assay be designed that are indicative for very low levels of NAb and can be used for high risk projects?

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- Joining the EIP working group?
- Questions or suggestions?
- Contact
  - Veerle Snoeck
  - Lydia Michaut
  - Jo Goodman
  - Melody Jansen

Thank you!!