Health Agency feedback on immunogenicity assays - Results of an EIP survey

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on behalf of the
EIP Immunogenicity Strategy Working Group

EIP Scientific Symposium

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Experience-sharing through survey

32 feedbacks from 11 companies

- > 50% participation rate

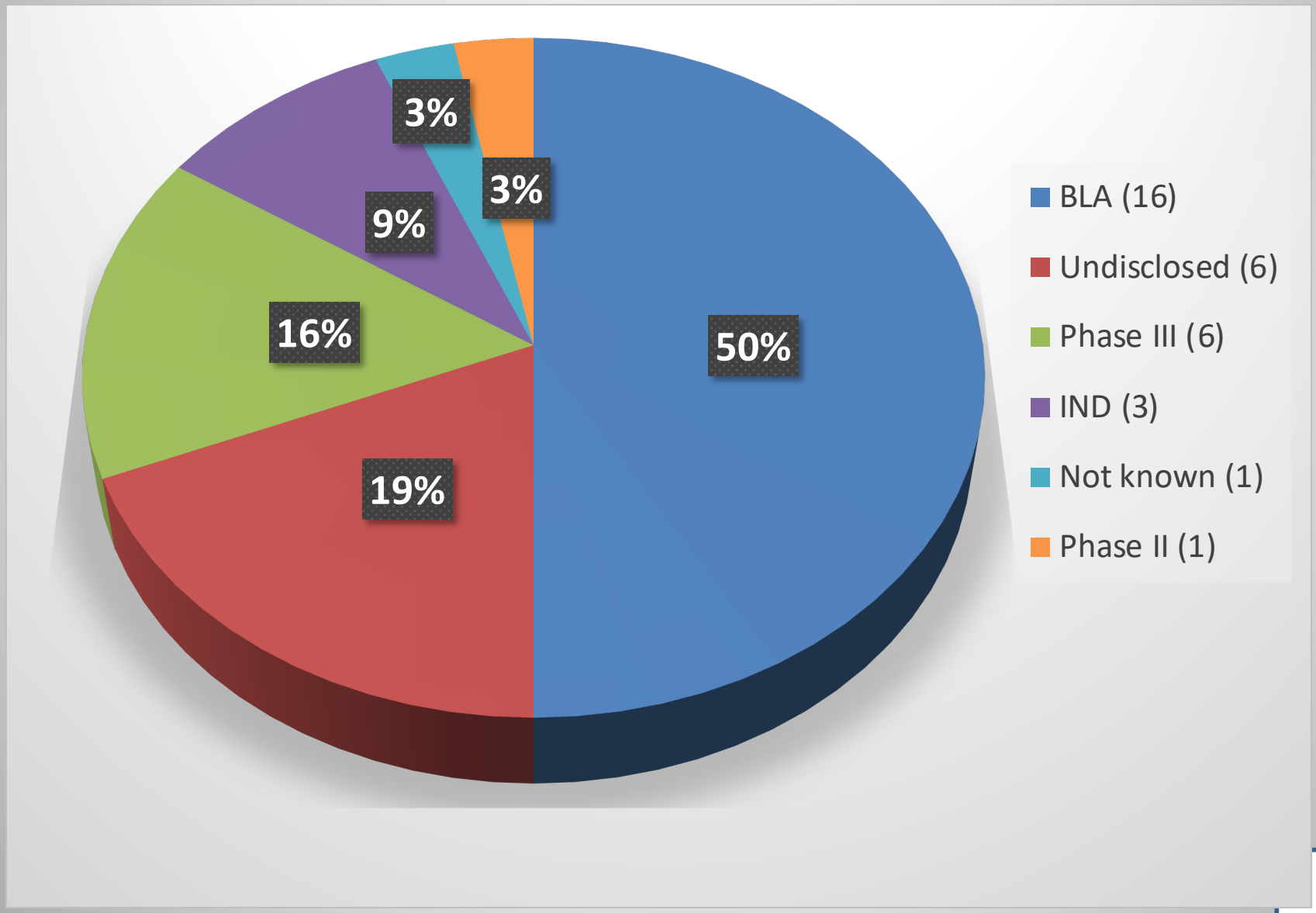
  (19 companies represented in the EIP Immunogenicity Strategy working group)

- Company names anonymized in the results

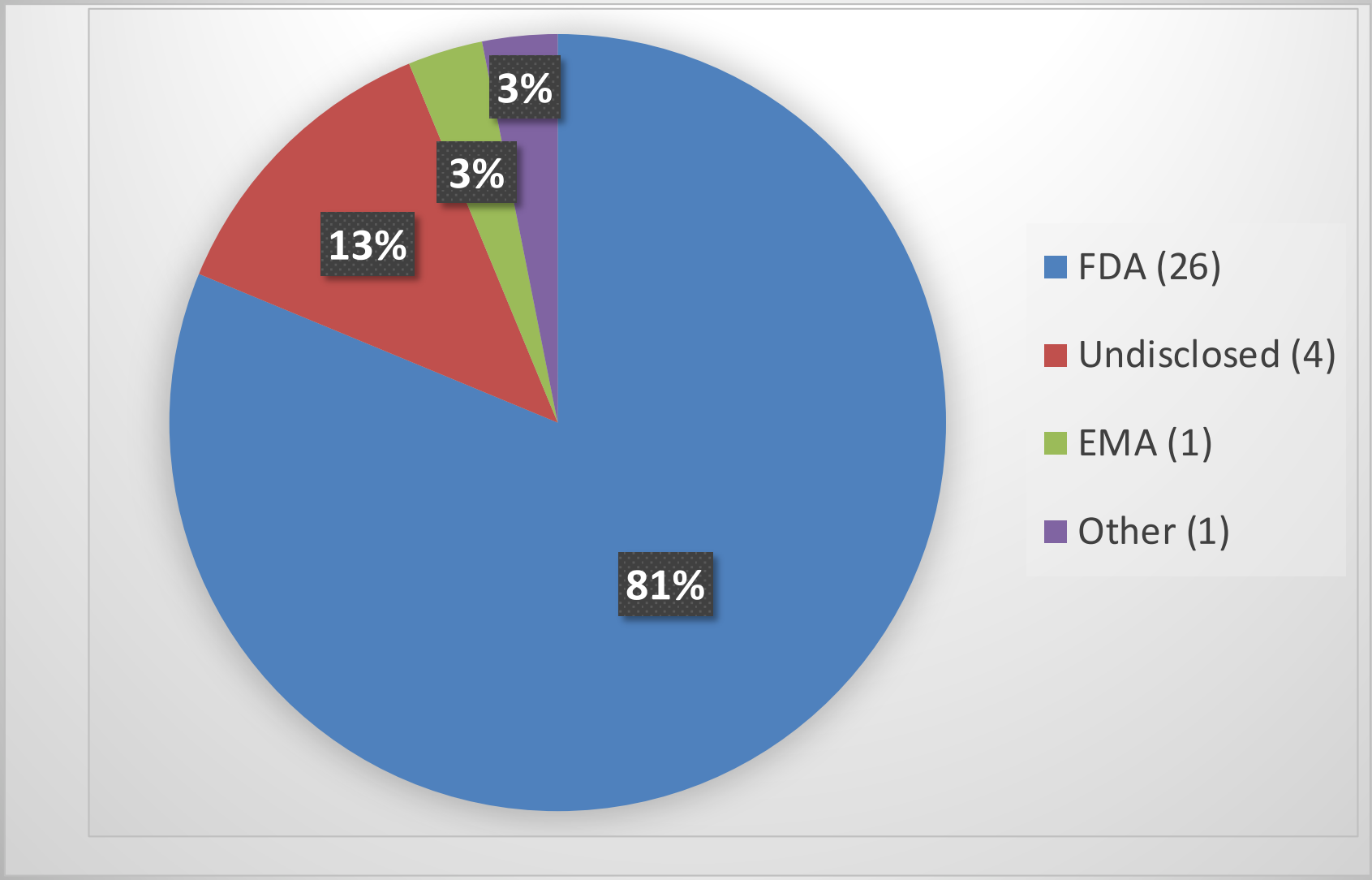
«Non-responder» companies (8):

- Audited by / interacted with HA but did not receive any feedback from authorities?
- No audited by / no interaction with HAs?
- Not allowed to share information?

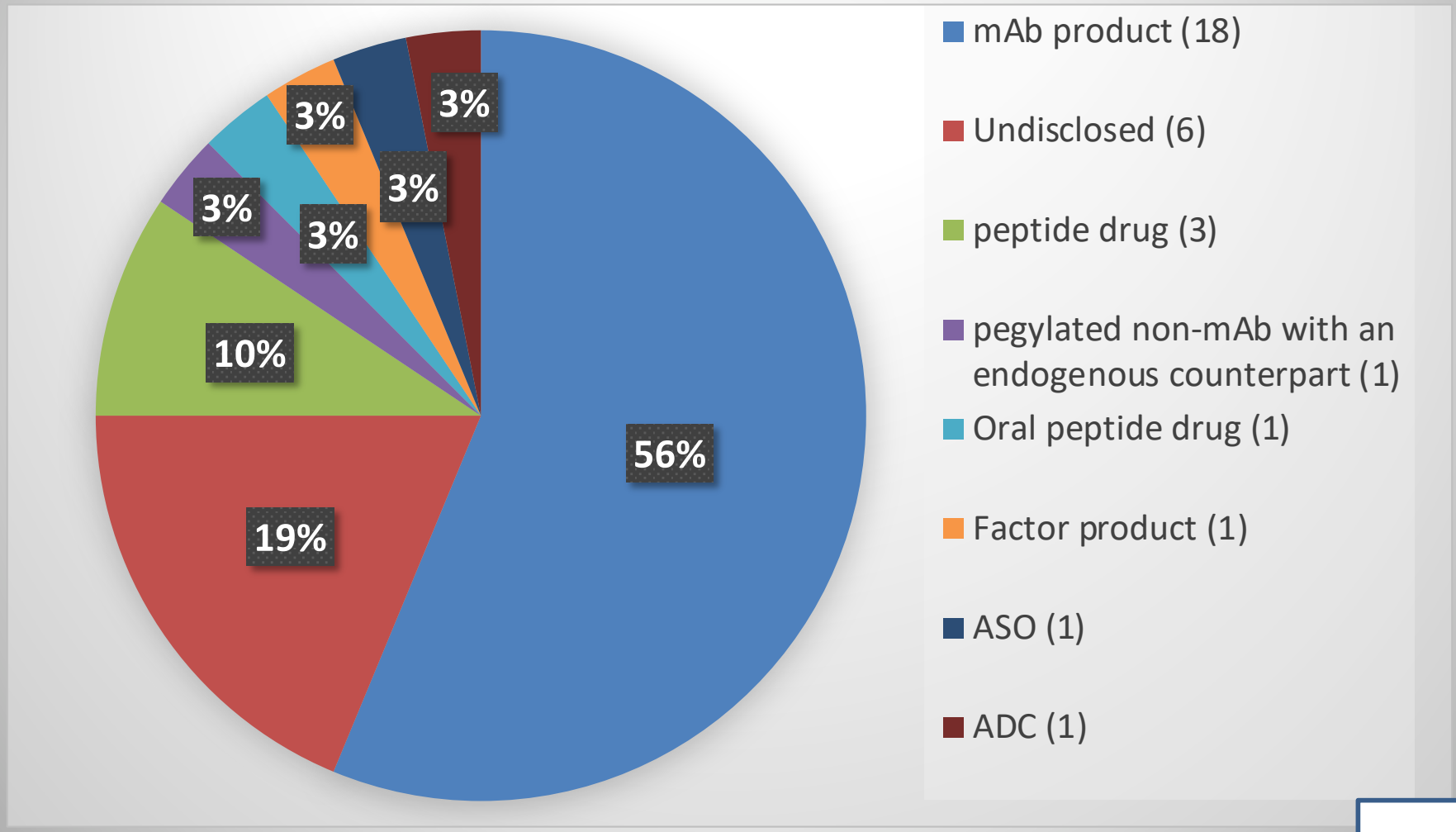
Project development stage (n=32)



Regulatory agency (n=32)



Drug type


56%
19%
10%
3%
3%
3%
3%
3%
mAb product (18)
Undisclosed (6)
peptide drug (3)
pegylated non-mAb with an endogenous counterpart (1)
Oral peptide drug (1)
Factor product (1)
ASO (1)
ADC (1)

Points of challenge (n= 42)

- Assays not meeting guidance requirements: 15
- Drug tolerance: 5
- NAb assays: 5
- Sample collection timepoints: 5
- Data to be provided for review - When and What: 4
- Project-specific questions: 4
- Antibody isotypes: 3
- Result reporting: 1

Assays

- Request for 1% FPR rather than 0.1% in confirmatory assay (6)
- LPC concentration must be established relative to assay sensitivity (4)
- Validate selectivity and specificity in hemolyzed serum in the ADA screening and confirmatory assays
- Determine inter-assay precision of confirmatory controls
- Evaluate prozone effect in the ADA validation
- Evaluate selectivity and specificity for the ADA confirmatory assay
- Method specificity was not demonstrated for the ADA confirmatory assay in method validation

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Drug tolerance

- Requested information on drug tolerance levels for ADA levels near the assay sensitivity
- Demonstrate that LPC and HPC can be detected in presence of drug levels detected in clinical samples
- Justify the acceptability of the Drug Tolerance for the ELISA used in the pivotal studies in context of the expected drug concentrations seen during repeated injection.
- Justification of accepted drug tolerance parameter (concentration)
- Request for additional drug concentrations to be tested

nAb assays

Format and use

- Of note, the agency generally recommends the use of a cell based neutralizing assay. If you decide to use a competitive ligand binding assay to assess neutralizing antibodies, the IND should be updated with a comparison of the cell based and competitive ligand binding assays
- Agreement on use of competitive ligand binding assay - no need for generation of data in cell based Nab assay format
- Rejected proposal to use integrated PK, ADA and target engagement analysis instead of nAb assay

Validation parameters

- Request for 1% FPR in nAb assay
- Request for improved sensitivity and drug tolerance of cell based nAb assay

Sample collection and timepoints

- All subjects must be followed/up until reverted to pre-defined titre
- Follow up until responses have converted to baseline.
- Follow up on positive patients until return to baseline
- Sampling time points: D7-10 needed for IgM and IgG at early time points.
- Sponsor to collect serum samples earlier in future clinical trials to address the levels of IgM specific ADA

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Project-specific questions

- Use of a target bead based depletion step in an ADA assay (risk of removal of target-drug-ADA complexes impacting ADA detection)
- Demonstrate that the ADA assay can detect immune responses to all components of an ADC (e.g., mAb, ADC, linker-payload)
- It is surprising that ADAs have no apparent impact on efficacy despite a clear effect on drug concentration and blood eosinophil level.
- Evidence requested that method can detect antibodies in low pH when acid method used

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Data to be provided for review - When and What

- Agency wish to review all data prior to Ph3 pivotal studies.
- Request for "developmental exercises" for all assays.
- Data on robustness of the assays requested.
- Requirement for adequate storage of all samples under appropriate conditions to allow for additional testing until the agency have reviewed all assays and deem them to be suitable.

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Antibody isotypes

- Document that assay can detect IgA ADA
- Must sensitively detect IgG and IgM
- Sensitivity of IgE assay for hypersensitivity samples
- Report antibody titers including the MRD

Topic for further discussion

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https://doi.org/10.1208/s12248-022-00712-2

COMMENTARY

When to Extend Monitoring of Anti-drug Antibodies for High-risk Biotherapeutics in Clinical Trials: an Opinion from the European Immunogenicity Platform

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General schematic ADA sample collection in clinical studies

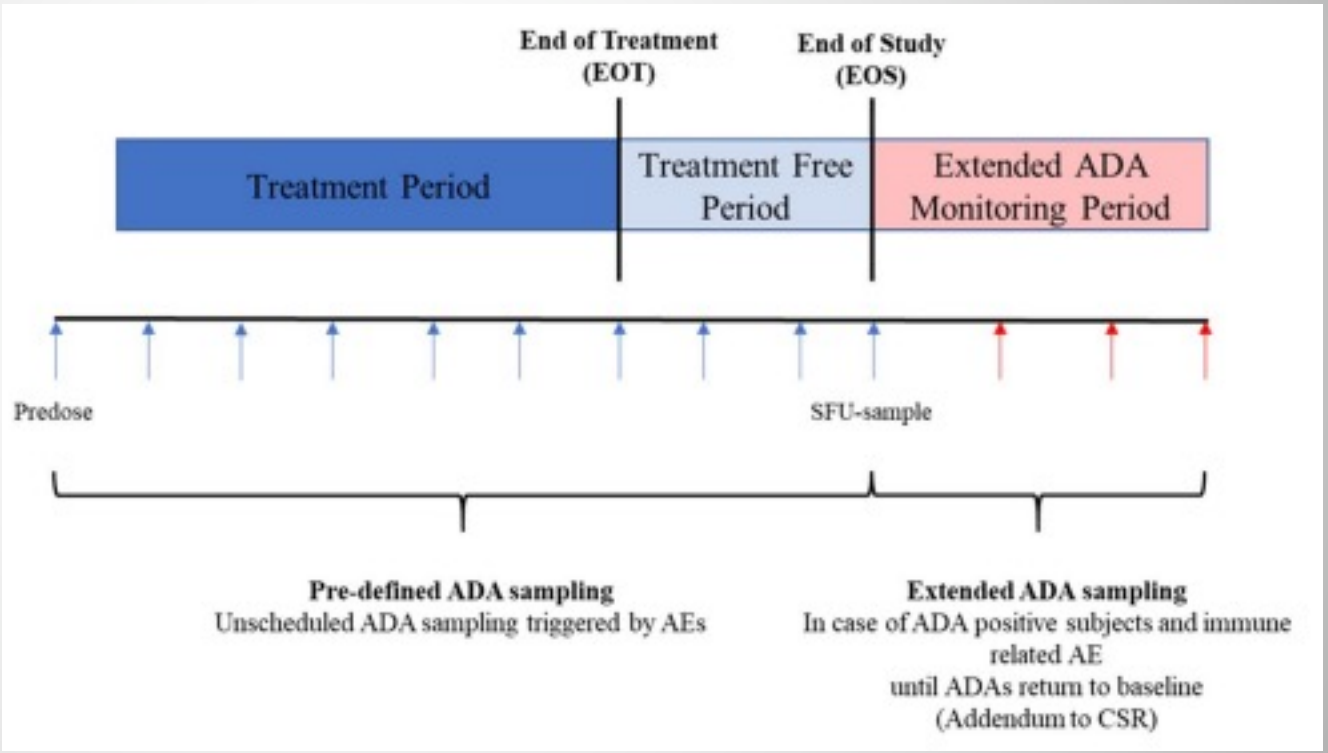
ADA sampling during:
- drug treatment period
- treatment-free period

-> until end of study.

Extended ADA Monitoring Period:

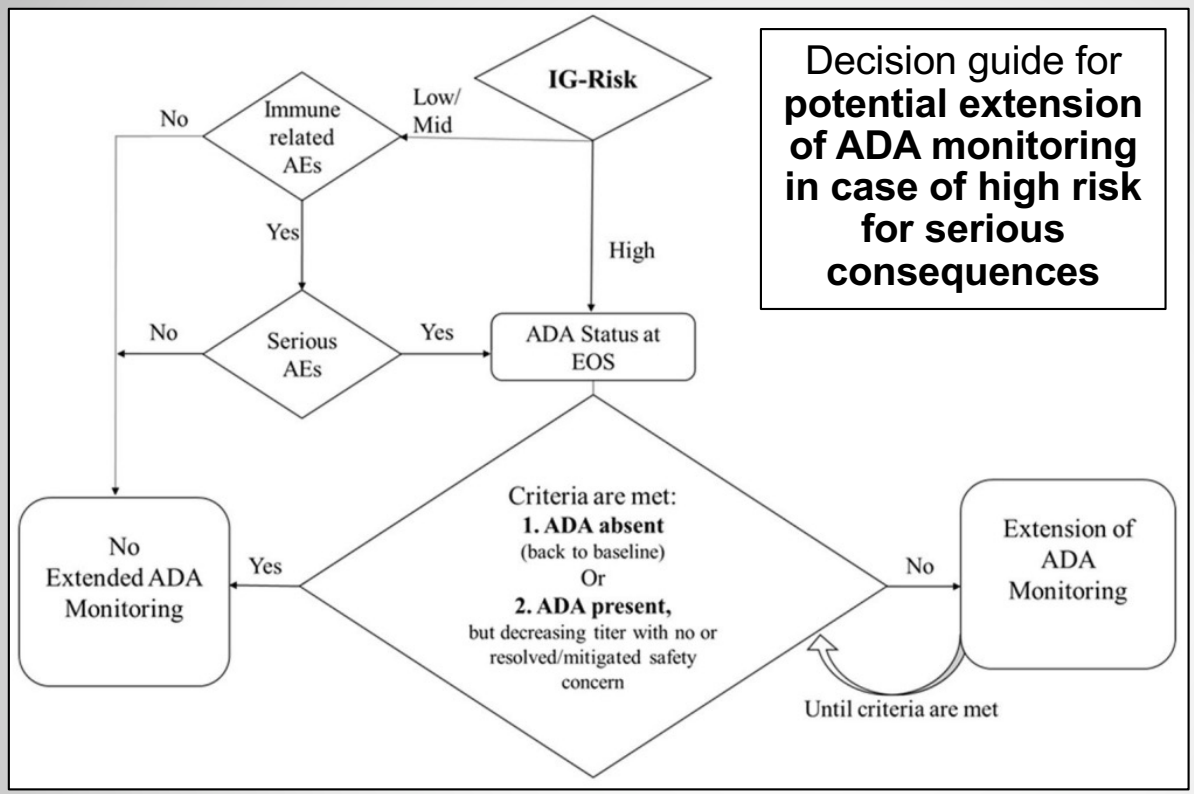
In case of a high risk for serious consequences from ADAs, regulators expect to extend sampling for ADA positive subjects beyond EOS until ADA levels return to baseline

Arrows indicate collection time-points



ADA=Anti-drug antibodies; SFU=Safety Follow-Up; CSR=Clinical Study Report
AE=adverse event; EOS=End of Study

EIP Opinion



ADA=Anti-drug antibodies; SFU=Safety Follow-Up; AE=adverse event; EOS=End of Study

At EOS, when ADAs, are either absent or still detectable but ADA titers are decreasing, and safety concerns are either absent or resolved/mitigated then no extension of ADA monitoring is required.

ADA extended monitoring should be based on evaluation of ADA data in the context of corresponding clinical signals:
If the clinical data shows that safety consequences are minor, mitigated, or resolved, then further ADA monitoring may not be required despite potentially detectable ADAs above baseline.

Thank you

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Member company representives:

UCB
MedImmune / AZ
BioAgilytix
Abzena
Amgen
Boehringer Ingelheim
Covance
Genmab
GSK
Lundbeck
Merck
Novartis
NovoNordisk
Pfizer
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Sandoz
Sanofi
Sanquin
Thermofisher