The AAPS Journal (2022) 24: 68
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

Gregor P. Lotz[1] · Karin Benstein[2] · Karien Bloem[3] · Harm Buddiger[4] · Claudio Calonder[5] · Stefanie Elm[6] · Elena Fernandez[7] · Joanne Goodman[8] · Boris Gorovits[9] · Joanna Grudzinska-Goebel[10] · Melody Janssen[11] · Vibha Jawa[12] · Daniel Kramer[2] · Linlin Luo[13] · Mantas Malisauskas[14] · Lydia Michaut[15] · Martin Schäfer[1] · Sebastian Spindeldreher[15] · Martin Ullmann[16] · Karin Nana Weldingh[17] · Arno Kromminga[18,19] · Veerle Snoeck[20]

Received: 18 March 2022 / Accepted: 14 April 2022 / Published online: 12 May 2022

ABSTRACT

The determination of a tailored anti-drug antibody (ADA) testing strategy is based on the immunogenicity risk assessment to allow a correlation of ADAs with changes to pharmacokinetics, efficacy, and safety. The clinical impact of ADA formation refines the immunogenicity risk assessment and defines appropriate risk mitigation strategies. Health agencies request for high-risk biotherapeutics to extend ADA monitoring for patients that developed an ADA response to the drug until ADAs return to baseline levels. However, there is no common understanding in which cases an extension of ADA follow-up sampling beyond the end of study (EOS) defined in the clinical study protocol is required. Here, the Immunogenicity Strategy Working Group of the European Immunogenicity Platform (EIP) provides recommendations on requirements for an extension of ADA follow-up sampling in clinical studies where there is a high risk of serious consequences from ADAs. The importance of ADA evaluation during a treatment-free period is recognized but the decision whether to extend ADA monitoring at a predefined EOS should be based on evaluation of ADA data in the context of corresponding clinical signals. If the clinical data set shows that safety consequences are minor, mitigated, or resolved, further ADA monitoring may not be required despite potentially detectable ADAs above baseline. Extended ADA monitoring should be centered on individual patient benefit.

✉ Gregor P. Lotz
gregor.lotz@roche.com

1 Roche Pharma Research and Early Development, Roche Innovation Center Munich, Penzberg, Germany

2 Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, Frankfurt am Main, Germany

3 Biologics Lab, Sanquin Diagnostic Services, Amsterdam, The Netherlands

4 Genmab B.V., Uppsalalaan 15, Utrecht, The Netherlands

5 Novartis Institutes for BioMedical Research, Basel, Switzerland

6 Amgen Research (Munich) GmbH, Munich, Germany

7 Roche Pharma Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland

8 Integrated Bioanalysis, Clinical Pharmacology and Safety Sciences, AstraZeneca, BioPharmaceuticals R&D, Cambridge, UK

9 Sana Biotechnology, Inc., MA, Cambridge, USA

10 Bayer AG, Drug Metabolism & Pharmacokinetics, Berlin, Germany

11 SciPot Consultancy, Amsterdam, The Netherlands

12 Bristol Myers Squibb, Biotherapeutics and Bioanalysis Non-Clinical Development, Princeton, New Jersey, USA

13 Regulated BA, Merck & Co., Inc., Kenilworth, New Jersey, USA

14 Merck KGaA, Darmstadt, Germany

15 Integrated Biologix, Basel, Switzerland

16 Fresenius Kabi, Eysins, Switzerland

17 Novo Nordisk, Non-clinical & Clinical Assay Sciences, Maaloev, Denmark

18 Kromminga Consulting, Hamburg, Germany

19 Institute for Immunology, Kiel, Germany

20 UCB Biopharma SRL, Translational Biomarkers and Bioanalysis, Braine-l'Alleud, Belgium

KEY WORDS ADA follow-up sampling · clinical trials · extended ADA monitoring · immunogenicity · risk mitigation

INTRODUCTION

The evaluation of anti-drug antibody (ADA) detection is a critical step during biotherapeutic drug development. An initial immunogenicity risk assessment (IRA) of the biotherapeutic drug determines the testing strategy for generating sufficient ADA data allowing correlation to changes in pharmacokinetics, efficacy, and safety (1). The understanding of the clinical impact of ADA formation refines the IRA and defines appropriate risk mitigation strategies. Importantly, the ADA sampling schedule should be designed based on the drug IRA. Figure 1 depicts a clinical study design and the arrows indicate ADA samples, which are typically collected to allow evaluation of induced or boosted ADA responses during the drug treatment period and during the subsequent treatment-free period (TFP). The duration of the TFP for a high-risk biotherapeutic should be appropriately tailored to the drug pharmacokinetic features and its corresponding clinical signals but may span five half-lives to assess potential impact of still existing ADAs on safety. The TFP ends with the collection of a safety follow-up (SFU) ADA sample at the end of study (EOS). Data describing ADA levels detected during the clinical trial, consisting of the treatment period and the TFP, can represent an essential part of the filing package that is used to grant marketing authorization. For biotherapeutics with high-risk immunogenicity, there is a clear need to understand how the ADA response could affect the trial subject's safety at EOS.

In their latest guidance, the FDA provides a framework for a suitable evaluation and mitigation strategy of the observed ADA responses during clinical study conduct (2, 3). However, there is limited guidance on the requirement for extension of ADA follow-up (ADA-FU) sampling after the EOS (Fig. 1, in red, extended ADA monitoring period) and common understanding in which cases the extension is required is lacking. Especially the statement in the FDA guideline "when there is a high risk of serious consequences from ADAs, sponsors should plan to collect samples from subjects until ADAs return to baseline level" triggered discussions among the members of the European Immunogenicity Platform (EIP).

The EIP agrees with health authority guidance that ADA evaluation during a dedicated treatment-free period is important to assess the risk caused by immunogenicity and to address the safety consequences associated with ADAs. In cases of ADA-induced adverse events (AEs), strategies should be in place to identify, manage, mitigate, and resolve those events.

However, the EIP recommends that the decision whether to extend ADA monitoring at a predefined EOS should be based on evaluation of ADA data in the context of corresponding safety profile while aiming to provide benefit to the patients. The decision needs to incorporate ADA response correlation with clinical information, including safety and available mitigation strategies. If the clinical data set shows that ADA-induced AEs are absent, resolved, or mitigated, further ADA monitoring is not required despite potential detectable ADAs. A set of defined criteria will help to align with the agency to decide to stop ADA monitoring when there is only little value of gaining more ADA data without strong evidence for safety concern. Consequently, patients are not asked to come over long periods to clinical sites for additional blood draws. Here, the EIP discusses clinical relevance of the "back to baseline" ADA monitoring

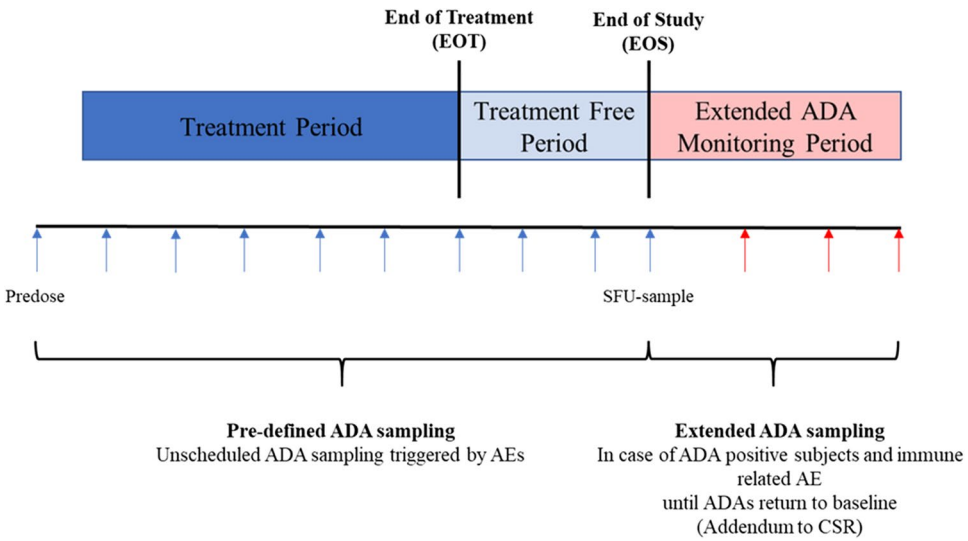

Fig. 1 General schematic ADA sample collection in clinical studies, consisting of ADA sampling during drug treatment period and treatment-free period until End of Study (EOS). In case of a high risk for serious consequences from ADAs, regulators expect to extend sampling for ADA positive subjects beyond EOS until ADA levels return to baseline (Extended ADA Monitoring Period). Arrows indicate ADA sample collection time-points. ADA = Anti-drug antibodies; SFU = Safety Follow-Up; CSR = Clinical Study Report

criterion and provides a simplified criteria-based decision tree as guidance for the requirement of an extended ADA monitoring period.

FROM IMMUNOGENICITY RISK CATEGORY TO ADA-MEDIATED SAFETY MONITORING

A classical immunogenicity high-risk categorization, as defined in the FDA guideline, refers to ADA induction against biotherapeutic drugs bearing a risk of serious safety consequences. Biotherapeutics with a potential to induce immune responses with a limited impact on safety are categorized as low/mid immunogenicity risk (4, 5). As ADA-related high-risk biotherapeutics are defined by their potential impact on patient safety, monitoring of immunogenicity induction received a lot of attention from regulators and the community of practice.

In recent years, concepts for the initial risk assessment have evolved to a more granular level of intrinsic and extrinsic factors of a biotherapeutic drug (6–8). Consequently, a detailed matrix-based risk categorization defines a more tailored immunogenicity testing strategy, which may go beyond the standard three-tiered ADA testing approach for high-risk biotherapeutics. This may consist of a PK/PD testing strategy that includes appropriate safety biomarkers along with thorough ADA sampling. Additional characterization of ADA responses may include use of a neutralizing antibody assay, a cross-reactivity assay to endogenous counterpart, and/or domain characterization assays (9, 10). Such an advanced testing strategy early in clinical development (e.g., phase 1 at multiple ascending dosing (MAD) or phase 2) allows for the generation of a wealth of immunogenicity data which may correlate with ADA-mediated safety consequences and impact appropriate mitigation strategies (11). In addition to the standard safety assessment panel, the selection of biotherapeutic and study-relevant biomarkers that allow correlation between the biotherapeutic-specific biology and potential immune response development might be helpful. This includes monitoring the neutralization of the endogenous counterpart or PD analyses of the mode of action (MoA) or the new modality affected pathways. Often it is challenging to evaluate the exact correlation of ADA induction and safety events in the clinic. The right timing of ADA detection along with safety biomarker analyses is critical. However, temporal correlation of ADA response with onset or duration of clinical AEs and correlation of detected ADA titers with the severity of AEs can be important indicators.

ADAs that can cross-react with an endogenous counterpart, in the absence of a functional redundant pathway, represent an example of a safety-related impact from ADA induction (12–15). Such ADAs may lead to a clinical manifestation by neutralizing the function of the endogenous protein. In such cases, a close monitoring of ADA characteristics, e.g., titer and neutralization potential, and of safety biomarkers related to the biology of the endogenous protein are essential. Monitoring for ADAs during the TFP becomes particularly important because the assay's ability to detect ADA cross-reacting with the endogenous counterpart may increase in the absence of a drug. For those high-risk biotherapeutics, extended ADA monitoring may be required in such cases. On the other hand, there are cases where ADA does not affect the function of the endogenous protein (2, 16) or where supplementary data might deliver sufficient evidence for a redundant physiological role of the endogenous protein and thus, without high safety risk (e.g., by supplemented protein counterpart) to justify a termination of ADA monitoring at EOS (2, 16).

Infusion-related reactions (IRR) and anaphylaxis occurring at the time of drug administration may or may not be linked to the presence of ADAs. In case of serious hypersensitivity responses, further characterization is recommended to elucidate the underlying mechanism to further substantiate whether there is a link with ADA development.

One potential underlying mechanism of ADA-mediated serious AEs is the formation of ADA-drug immune complexes (17). Related clinical safety signals are dependent on the concentration of ADA-drug complexes, which may trigger effector function-based immune responses (18). Early identification and monitoring of those AEs during the drug treatment period is critical due to a possible increase of ADA-drug complex levels. Although these immune-stimulating ADA-drug complexes mainly form in the presence of high drug and ADA concentrations (18), it would also be important to monitor ADAs during the TFP to see the effect of the changes in drug concentrations, with potential different effects on the immune system (17, 18). Hypersensitivity responses secondary to immune complex formation that usually occur days after the drug is administered may justify advanced ADA monitoring. However, the drug treatment period is considered the most critical phase for generating data required to understand ADA-induced hypersensitivity reactions due to immune complex formation. In combination with a robust TFP design, enough data should be available at the EOS to consider the need for an extension of ADA monitoring.

Such hypersensitivity responses related to ADA complex formation and/or related to cross-reactivity of the ADA with an endogenous protein (in the absence of functional redundancy) associated with neutralization of its key physiological function are two examples viewed as serious ADA-induced safety events that may require extension of ADA monitoring. Monitoring for presence and nature of ADAs and clinical safety data during treatment and treatment-free period will provide data determining whether an extension

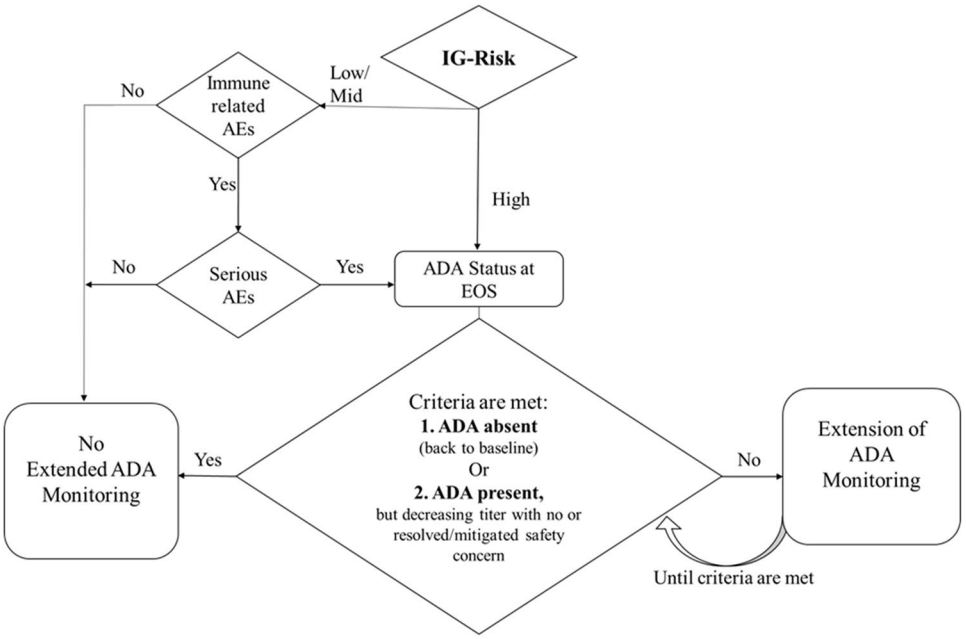

Fig. 2 The EIP provides a simplified decision tree of general recommendations to guide decisions around potential extension of ADA monitoring in case of high risk for serious consequences. When at the End of Study (EOS), ADAs are either i) absent or ii) still detectable but ADA titers are decreasing, and safety concerns are either absent or resolved/mitigated then no extension of ADA monitoring is required. IG = Immunogenicity; AEs = adverse events; EOS = End of Study

of the ADA analyses as part of SFU is needed. In some cases, regulatory authorities might request an extension of the ADA monitoring beyond the planned EOS, even when there is no evidence of critical clinical manifestations related to an impact of endogenous protein function. The EIP recommends discussing with the regulatory authorities early on as the situations vary case-by-case.

RECOMMENDATIONS TO DETERMINE CRITERIA FOR ADDITIONAL ADA-FU SAMPLING

Understanding the potential correlation between ADA response and impact on safety, as well as the availability of appropriately tailored strategies to mitigate clinical manifestations, forms the basis for defining the criteria to decide whether an extension of an ADA-FU is required or not. It may be reasonable to extend the TFP in cases when insufficient clinical information is generated at the EOS. This may be the case when remaining high ADA titers are linked to acute safety signals, which were neither resolved nor could be mitigated. An extension of ADA monitoring along with relevant safety assessment is in such cases considered essential (Fig. 2). If the ADA titers are stable or decreasing in the absence of clinical safety signals and with a defined mitigation plan in place, a decision towards a termination of an extension of ADA monitoring is justified.

To avoid the risk that insufficient clinical information is generated at the EOS, the EIP recommends the following practical points to consider for drugs categorized as high immunogenicity risk. ADA sampling schedule described in Clinical Study protocol should be appropriately designed to allow for evaluation of ADA response with clinical signals during the drug treatment period and the TFP. The sample collection schedule should allow for a potential extension of ADA sampling after the planned EOS, the so-called *extended ADA monitoring period* (Fig. 1), which can be added as an addendum to the Clinical Study report for drugs categorized as high immunogenicity risk. In such a case, the company may plan for a two-stage sampling period. The first stage will cover the study period until the "EOS/SFU" (TP and TFP) and follow a conventional but robust study design regarding time points of ADA sample collection. This may constitute a frequent sampling at multiple time points, including pre-dose, pre-administration time point (ideally Ctrough time point) during the treatment period and at certain time intervals during TFP (Interval sampling is recommended in case of high risk of immunogenicity) until the SFU time point at the EOS (Fig. 1, blue line). The second stage will allow some trial subjects to enter the ADA-FU period based on predefined criteria as depicted in Fig. 2. This will generate an appropriate and adequate data set to refine the IRA, which drives the testing and mitigation strategy needed during subsequent clinical studies (Fig. 1, redline, extended ADA monitoring period). It is highly recommended to add to the sampling schedule a process that allows for an efficient collection of unscheduled samples, triggered by IRR and/or suspected immunologically related AEs. Other important considerations are (a) combined collection of PK and ADA samples to check for potential drug interference in the ADA detection (except for the extension period after the SFU when drug levels are

very low or absent) and to be able to correlate presence of ADA with change in PK and (b) enabling the use of ADA samples for an advanced immunogenicity analysis including ADA characterization (e.g., assess domain specificity, neutralizing activity characterization, ADA isotyping). An appropriate ADA sampling schedule allows evaluation of the potential association of the ADA response and clinically observed safety events and therefore to understand the clinical relevance of immunogenicity response to safety signals. This understanding is the prerequisite for establishing a data-driven mitigation strategy to manage, control, or potentially resolve an ADA-mediated event. It is the sponsor's responsibility to determine whether sufficient immunogenicity relevant data are available at the EOS and whether an extension of ADA-FU sampling is required or an appropriate mitigation strategy has to be put in place during the ADA monitoring period.

There is an overall agreement in the EIP community that in cases where there is a high risk for serious clinical safety consequences related to the immune response induction, special ADA testing and mitigation plans should be included in the clinical protocol. These testing and mitigation plans may include, but should not be limited to the following:

Access to validated ADA detection from phase I clinical evaluation onwards and ADA characterization assays from MAD or phase 2 onwards (ADA characterization at SAD is not recommended)
Tailored and advanced analytical testing strategy for ADA and for appropriate safety biomarkers to detect and investigate clinical AEs in a timely manner
Robust ADA sampling in drug treatment and treatment-free period with 2-stage ADA sampling schedule management, e.g., first stage robust sampling design until SFU at EOS and with a second stage adaptive sampling design to potentially enter a subsequent follow-up period
Specific language in the clinical protocol should be considered to allow for a fast adaptation, including changes in the sampling schedule and potential extension of ADA sampling and testing frequency, thereby avoiding time-consuming amendments.
Based on ADA and safety risk assessment (safety biomarker), adequate management of any clinical manifestations, if these occur
Implementation of an adequate mitigation strategy

With these criteria considered, sponsors should be in a comfortable position to gain relevant clinical information and to decide at the SFU whether the risks associated with ADA responses are sufficiently understood and controlled or whether further ADA-FU sampling and analysis are needed. Similarly, a detailed and extended ADA testing strategy plan may be required for biotherapeutics that were initially categorized as low/mid immunogenicity risk but demonstrated ability to induce ADA-mediated serious AEs in the clinic (Fig. 2). In these scenarios, regulatory authorities might request an extension of ADA monitoring. The EIP recommends contacting the regulatory authorities early on to discuss the specific cases.

PATIENT BENEFIT AND CLINICAL RELEVANCE OF "BACK TO BASELINE" CRITERION

As the patients' health is paramount, prolongation of follow-up ADA sampling, requiring additional clinical site visits and blood draws, should be thoroughly justified based on the need to gain critical clinical information. If, after the completion of clinical study, patients decide to seek other treatment options, ongoing requirements for extended ADA monitoring will add an unnecessary burden and reduce patient compliance. For that reason, extension of ADA monitoring without treatment options (e.g., exclusion to participate to a different clinical study with an investigation drug) might not be ethically justified. The decision whether to extend ADA monitoring should be always patient centered, including whether the additional data will benefit study patients or future regulatory decisions of drug approval.

The FDA recommends, "continued testing until ADAs reach baseline" as the decision criterion for ending the ADA-FU sampling. The EIP questions whether it is always useful to follow the return of ADA signals to baseline level. In some cases, where the ADA response is strongly associated with AEs/IRR, the absence of ADA signal might become necessary and the "back to baseline" criterion may indeed serve as the correct clinical threshold. Here, the EIP recommends monitoring ADAs during the TFP until the EOS to generate an ADA negative result as an important criterion to decide whether additional ADA-FU sampling becomes necessary. In the case of pre-treatment positive trial subjects, a titer equal to or below a predefined ADA titer baseline in the pre-treatment samples can be used. Criteria for defining if ADA baseline levels in pre-treatment positive trial subjects are treatment boosted upon drug administration have been previously described (19, 20) and could be similarly applied. A robust mitigation plan should also be in place to manage safety signals.

For other cases, ADA evaluations during clinical studies have revealed that long-term, persistent ADA responses are a common observation and ADA titers might remain constant over several months or even years. ADA responses may not return to baseline during the extended ADA monitoring period but either (i) fluctuate around the assay cut-point ("borderline positive levels"), or (ii) plateau over time above the cut-point. In these cases, patients are asked to come back over long periods, often without benefit and evidence of

safety concern. The ADA response and its magnitude should not be considered an isolated criterion but in the context of the corresponding clinical observations. Therefore, the ADA titer should not be the only criterion to prolong ADA monitoring. Sustained or decreasing ADA titers (e.g., two dilution factors change in titer decrease (19)) observed in the treatment-free period, in the absence of clinical safety concerns, reduce the potential risk that serious safety consequences may be encountered or induced later in time in the absence of additional drug administration. When a robust clinical data set is showing that safety consequences are minor, mitigated, or resolved, a decision of not following up with extended ADA sampling is justified, even where detectable ADA levels are above the baseline. Thus, biotherapeutics initially categorized as high immunogenicity risk may be reclassified to a data-driven mid or low-risk category. Although this is in line with health authority life cycle management approach of the IRA based on reassessment upon availability of new clinical data, the EIP recommends a close consultation with the regulatory authorities to align on adaptive strategies for further clinical studies.

A data-driven link to clinical signals is even more of an advantage as the absence of ADA responses does not necessarily de-risk for a future drug re-administration. Potential immunologic memory can be activated by repeated drug administration or by switching to another drug, even when ADAs have returned to baseline levels beforehand. For that reason, a preventative or mitigation strategy should be in place if any retreatment is considered. Furthermore, patients, in which a previous ADA response to a high-risk therapeutic protein has been observed, may potentially experience a boost in response during periods of severe illness or severe tissue injury in which inflammation is prominent. Although considered rare occasions, in these cases an additional evaluation of ADA might be needed to adjust the IRA accordingly (only possible if patients are still enrolled in the study) and to link ADA data to clinical safety signal. Here, a consultation with the health authorities is recommended.

CONCLUSION

ADA monitoring should be focused on the understanding of the potential correlation between ADA response and the impact on clinical safety and available mitigation strategies. ADA response and its level should not be considered in isolation or clinical manifestation per se and require evaluation in the context with the corresponding clinical signals. If the clinical data set shows that safety consequences are minor, mitigated, or resolved, further ADA monitoring is not required. Extended ADA monitoring should be centered on individual patient benefit.

Acknowledgements Bengt Hoepken (UCB Pharma).

Declarations

Disclaimer The views and conclusions presented in this manuscript are those of the Immunogenicity Strategy Working Group of the European Immunogenicity Platform (EIP) and do not necessarily reflect the representative affiliation or individual company's position of the authors on the subject.

Funding No external funding was received for this work.

Contribution statements
- Conception of manuscript: EIP working group (all authors)
- Manuscript design and writing: GPL, BG, MU, AK, VS
- Manuscript reviewing and editing: all authors
- All authors read and agreed to the final version of the manuscript.

Conflict of interest G. P. L. is an employee of Roche Diagnostics GmbH, there is no conflict of interest
K.B. is an employee of Sanofi-Aventis Deutschland GmbH, there is no conflict of interest
K. Bloem is an employee of Sanquin Diagnostic Services, there is no conflict of interest
H.B. is an employee of Genmab, there is no conflict of interest
C.C. is an employee of Novartis Pharma AG, there is no conflict of interest
S.E. is an employee of Amgen Research (Munich) GmbH, there is no conflict of interest
E.F. was an employee of Roche, there is no conflict of interest
J. G. is an employee of AstraZeneca, there is no conflict of interest
B.G. is an employee of Sana Biotechnology, there is no conflict of interest
J.G-G. is an employee of Bayer AG, there is no conflict of interest
M.J. is a consultant and owner of SciPot Consultancy and has no conflict of interest.
VJ is an employee of Bristol Myers Squibb, there is no conflict of interest
D.K. is an employee of Sanofi Aventis Deutschland GmbH, there is no conflict of interest
Linlin is an employee of Merck & Co. Inc, there is no conflict of interest
M.M. was an employee of Merck Healthcare KGaA, there is no conflict of interest
L.M. was a consultant for Integrated Biologix GmbH and has no conflict of interest.
M.S. is an employee of Roche Diagnostics GmbH, there is no conflict of interest
S.S. is a consultant and co-owner of Integrated Biologix GmbH and has no conflict of interest
M.U. is an employee of Fresenius-Kabi, there is no conflict of interest.
K. N. W. is an employee of Novo Nordisk A/S, there is no conflict of interest
A.K. is an independent consultant and faculty member of the University of Kiel, Germany. No conflict of interest.
V.S. is an employee of UCB Biopharma SRL, there is no conflict of interest

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