

Clinical Development
Biopharma



Learnings and emerging trends in bioanalytical assay development for Biosimilars

Johann Poetzi
Barcelona
November 22, 2019

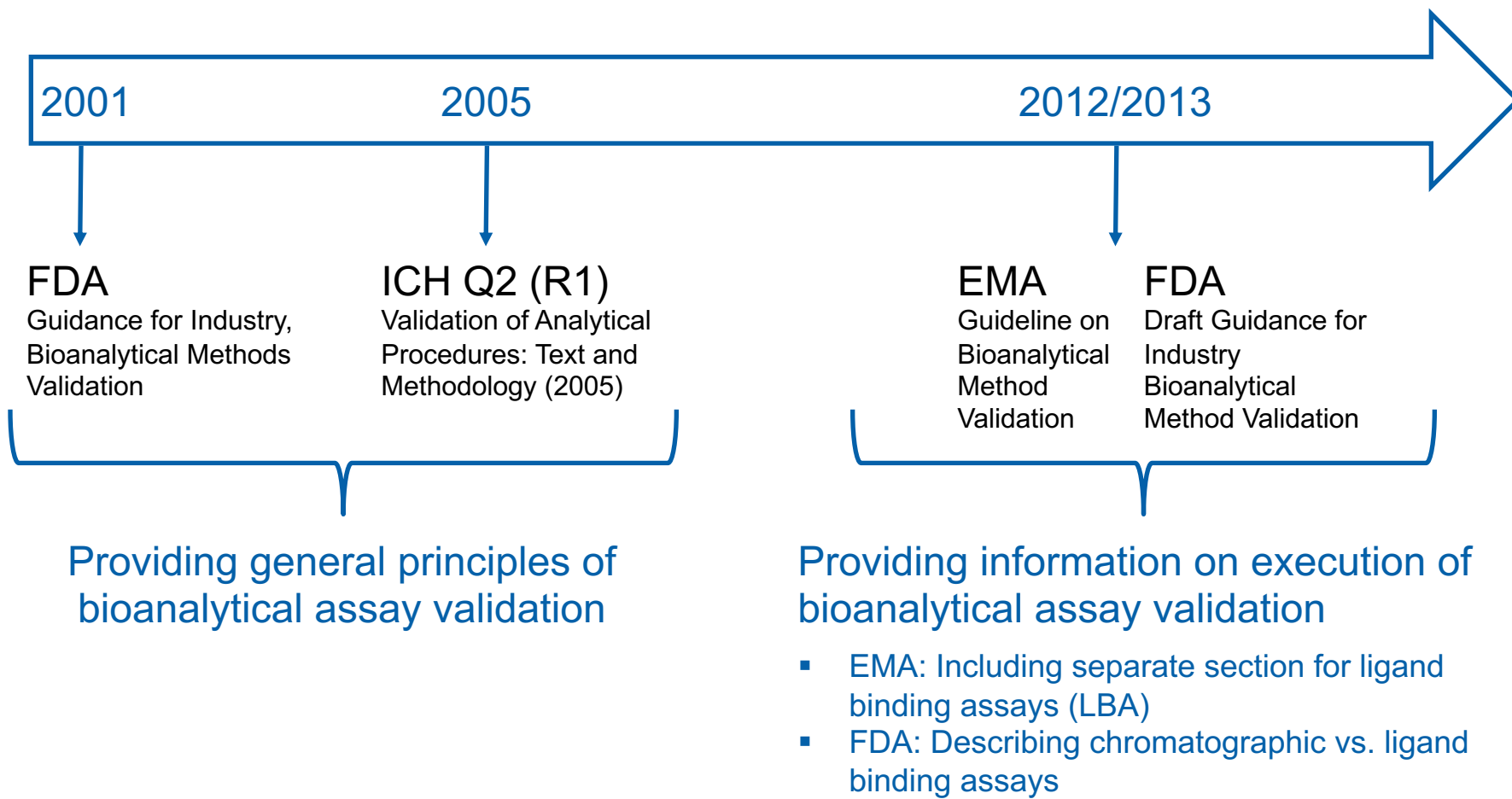
Agenda

1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

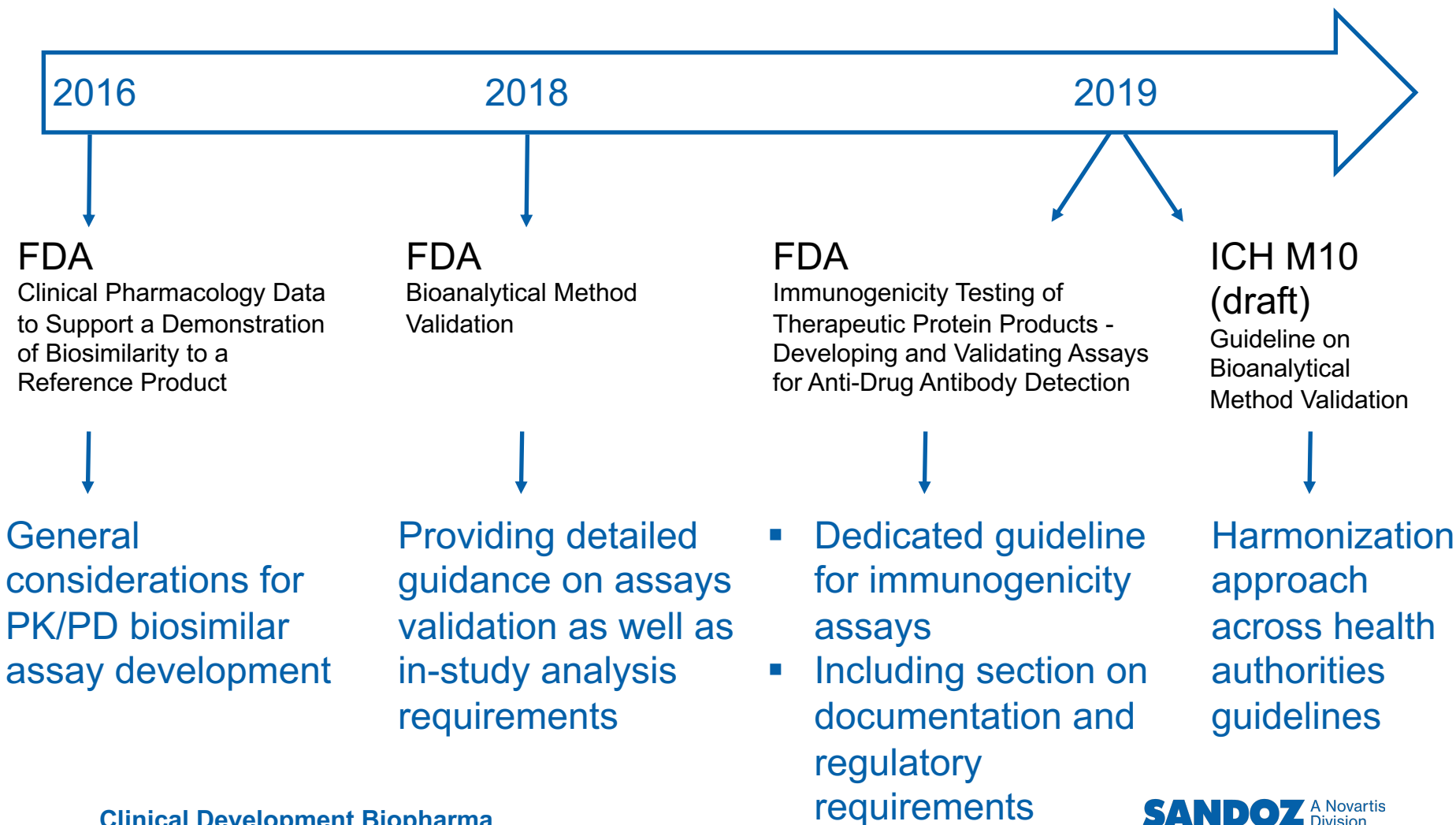
Agenda

1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

Guidelines for bioanalytical method validation have been evolving...



...and include more details on method validation to date...



...while specific information on requirements for biosimilar assay development is still limited

- Guidelines mainly focused on new biological entities (NBEs) - even so they apply for biosimilars as well
- Considerations for biosimilar assay development started to be reflected in recent guidelines
- Guidelines from health authorities beside EMA and FDA to be taken into account as well (e.g. PMDA/MHLW, ANVISA; ...)

Need: Harmonization of guidelines on bioanalytical assay validation across health authorities also including specific requirements for biosimilar assay development

Agenda

1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

Why assay development for biosimilars is different

- Comparative nature of clinical studies
 - Biosimilar vs reference product(s) tested head-to-head in clinical setting
 - Specific requirements for bioanalytical strategy and assays (e.g. one vs two assays)
- Blinded sample analysis
 - One assay
 - Determine drug concentrations with one and the same assay irrespective of exposure with biosimilar or reference product
 - Detect immunogenicity derived by biosimilar or originator with one and the same assay
 - Two assays
 - Determine drug concentrations with two PK assays using biosimilar or reference product as calibrators
 - Detect immunogenicity derived by biosimilar or originator with two assays using biosimilar or reference product as capture and detection reagent

Agenda

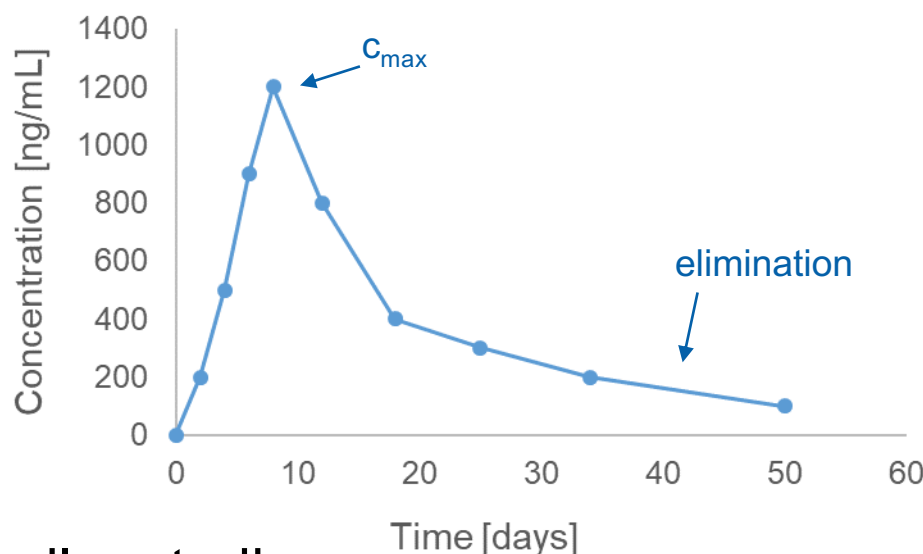
1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

Development of one and the same PK assay for comparative biosimilar studies

- Benefits:
 - Same assay with same characteristics enables sensitive comparison of biosimilar and reference product
 - Limiting sample volume needed from patients compared to 2 assay strategy to ensure blinded analysis
 - In line with FDA guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2016)
- Considerations:
 - Demonstrate suitability of PK assay to quantify biosimilar and reference product(s) the same in method validation
 - Guidelines currently not providing recommendation on testing approach and acceptance criteria to prove suitability of the assay
 - Define extent of drug product batches to be tested, e.g. EU or US sourced drug products

Specific considerations during PK sample analysis in biosimilar studies: ISR

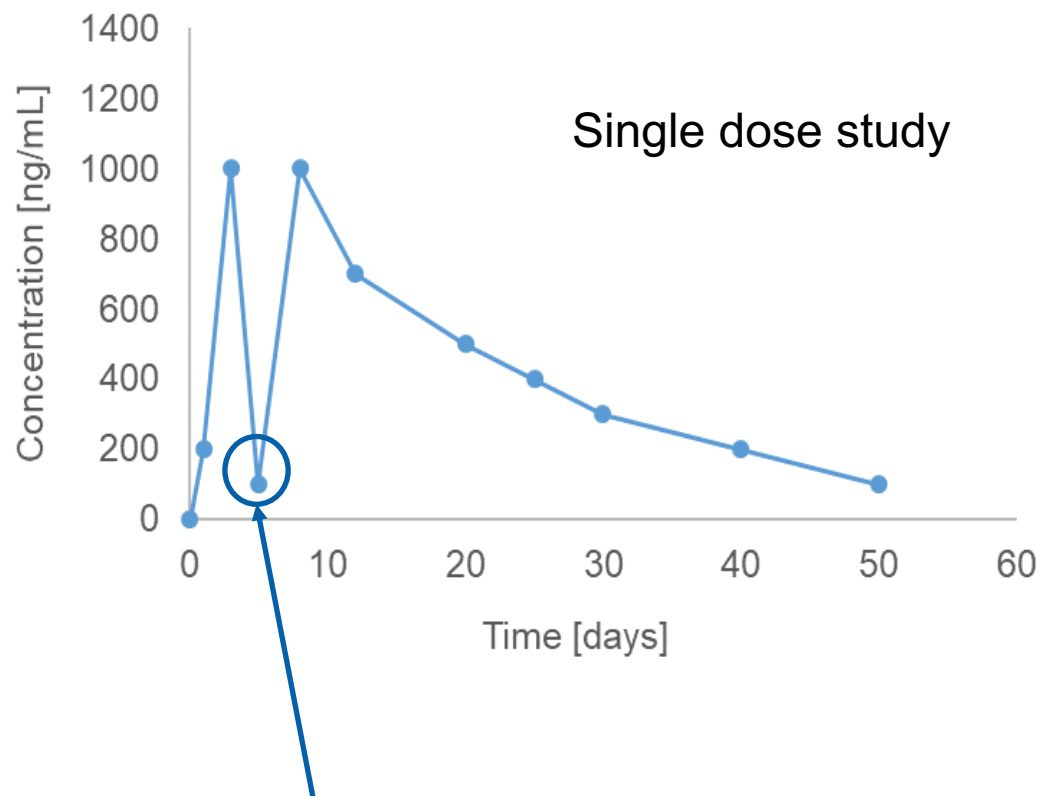
- Incurred sample re-analysis (ISR) per guidance
 - Sample size: 10% reanalysis of the first 1000 samples, and 5% reanalysis of the remaining samples



- ISR in biosimilar studies
 - Blinded sample analysis may lead to unbalanced ISR for biosimilar and reference product exposed healthy volunteers / patients
 - Is it needed to have equal distribution if method was demonstrated to measure biosimilar and reference product the same?

Specific considerations during PK sample analysis in biosimilar studies: Sample Reanalysis

Example



Re-analysis of this sample in biosimilar, i.e. bioequivalence trials?

Specific considerations during PK sample re-analysis in biosimilar studies: HA perspective

- EMA guideline on bioanalytical method validation (2012)
 - *For bioequivalence studies, normally reanalysis of study samples because of a pharmacokinetic reason is not acceptable but might be considered as part of laboratory investigations to identify possible reasons for results considered as abnormal*
- ANVISA RDC Resolution No. 27 (2012)
 - *In relative bioequivalence/bioavailability studies, reanalyses should not be conducted for pharmacokinetic reasons*
- FDA guideline on bioanalytical method validation (2018)
 - *No confirmatory repeats for BE studies*
- ICH M10 (draft): Bioanalytical method validation (2019)
 - *For comparative BA/BE studies, reanalysis of study samples for a PK reason (e.g., a sample concentration does not fit with the expected profile) is not acceptable, as it may bias the study result*

Specific considerations during PK sample re-analysis in biosimilar studies: Sponsor Considerations

- Re-analysis of abnormal results needs to be handled with care in bioequivalence studies and should be prevented
- In case a re-analysis is considered necessary, EMA (2012) recommends to provide:
 - Strong scientific rationale to be provided for re-analysis of abnormal results
 - Reporting of any generated result of the respective sample mandatory
 - Finally accepted value and a justification for the acceptance to be provided
- EMA rationale most reasonable from a Sponsor's perspective

Agenda

1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

Development of PD assays for comparative biosimilar studies

- Benefits:
 - Guideline on general PD biomarker principles for biosimilars available
 - FDA guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2016)
 - A combination of PK and PD similarity can be an important assessment in demonstrating that there are no clinically meaningful differences between the proposed biosimilar product and the reference product
- Considerations:
 - The analytical validity of the PD biomarker assay must be demonstrated to enable highly sensitive comparison of PD effects derived by biosimilar or reference product
 - The sponsor should provide a rationale for the choice of assay and the relevance of the assay to drug activity

Development of PD assays for comparative biosimilar studies

- Considerations

- Evaluation of publications on PD assay validation recommended for own assay development as guidelines from health authorities are not providing detailed recommendation on PD assay development and validation:
- FDA guideline on bioanalytical method validation (2018):
 - *Method validation for PD assays should address the same questions as method validation for drug assays*
 - *The approach used for drug assays should be the starting point for validation of biomarker assays, although the FDA realizes that some characteristics may not apply or that different considerations may need to be addressed*
- EMA guideline on bioanalytical method validation (2012)
 - *Methods used for determining quantitative concentrations of biomarkers used in assessing pharmacodynamic endpoints are out of the scope of this guideline*

Agenda

1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

Development of one and the same ADA/NAb assay for comparative biosimilar studies

- Benefits:
 - Same assay with same characteristics enables sensitive comparison of biosimilar and reference product
 - Limiting sample volume needed from patients compared to 2 assay strategy to ensure blinded analysis
 - In line with FDA guidance: Immunogenicity Assessment for Therapeutic Protein Products (2014)
- Considerations:
 - Demonstrate suitability of ADA/NAb assay to detect biosimilar and reference product the same in method validation
 - Guidelines currently not providing recommendation on testing approach and acceptance criteria to prove capability of assay to detect both
 - Health authorities in general agree to conservative approach using biosimilar as capture and detection reagent in the one assay format

Specific considerations during immunogenicity evaluation in biosimilar studies

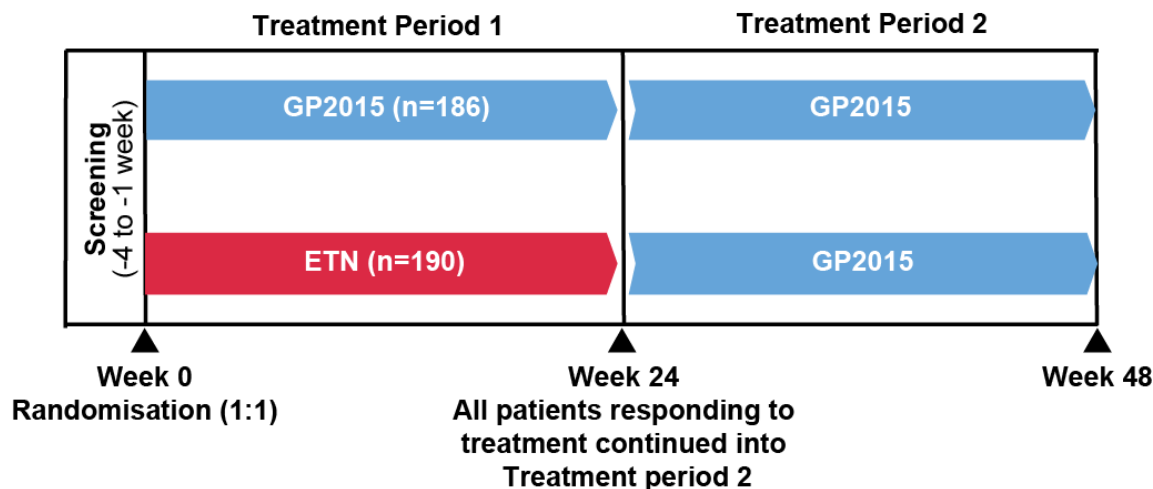
- ADA incidence for the molecule may be different compared to historical data by using highly sensitive and drug tolerant methods enabling the detection of low titer, transient and non-neutralizing antibodies
- Although health authorities are aware of this, public community and physicians may be concerned by increased ADA rates of well established drugs
- Immunogenicity assessment needs to be performed in light of the assay used and considering the totality of data instead of reporting ADA incidence rates alone

Agenda

1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

Immunogenicity evaluation: case study

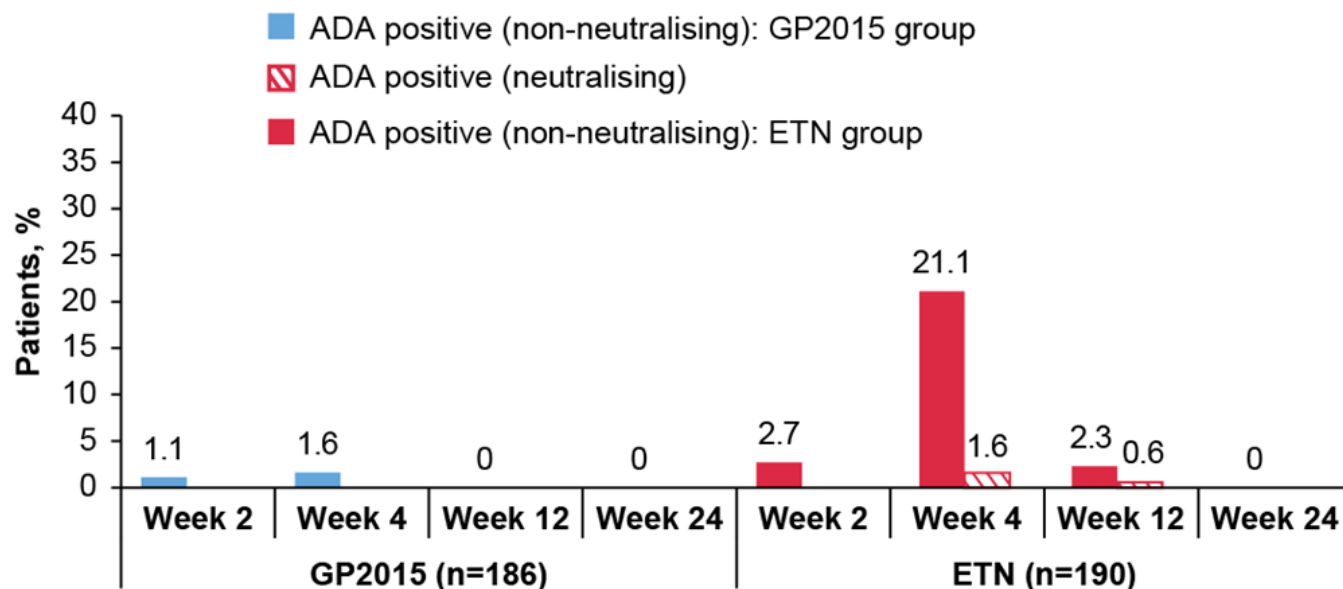
- **Study:** Efficacy, safety and immunogenicity of GP2015, an etanercept biosimilar, compared with the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative phase III, randomised, double-blind EQUIRA study (Matucci-Cerinic M et al.; 2018)



- **Treatment:** 50 mg GP2015 or reference product subcutaneously, once weekly, for 24 weeks
- **Bioanalytical method for binding ADAs:**
 - Bridging electrochemiluminescence assay including acid dissociation steps
 - Screening / confirmatory assay false positive rate: 5% / 1%
 - Assay sensitivity: <100 ng/mL
 - Drug tolerance: 50 µg/mL for biosimilar and reference (> highest drug concentration level in study)

Immunogenicity evaluation: case study

- **Historical immunogenicity data:** ADA incidence: 0% - 5%; no neutralizing antibodies.



- **Immunogenicity assessment:**
 - Very low titer of all measured ADAs near the assay detection limit
 - All ADA/NAb responses were transient
 - None of the patients had detectable ADA or NAb levels at week 24
 - A correlation of immunogenicity outcome to efficacy or patients' safety was not observed
 - Immunogenicity of biosimilar GP2015 and reference product considered as similar

Immunogenicity evaluation: case study

- Conclusion of immunogenicity assessment:
 - GP2015 demonstrated a similar efficacy and a comparable safety and immunogenicity profile with reference product
 - Assay comprising a high sensitivity and drug tolerance enables the detection of low titer and transient ADAs even during the drug treatment phase
 - In biosimilar trials, ADA sampling schedule is usually high frequent in order to monitor immunogenicity closely to enable the detection of transient ADA responses
 - Beside the evaluation of ADA/NAb incidence, a correlation of immunogenicity outcome to efficacy or patients' safety was not observed, indicating that detected ADAs were not clinically relevant

Agenda

1. Evolving guidelines within last decade
2. Why assay development for biosimilars is different
3. Considerations in biosimilar assay development and sample analysis
 - a) PK
 - b) PD
 - c) Immunogenicity
4. Immunogenicity evaluation: case study
5. Summary

Summary

- Guidelines on bioanalytical method validation have been evolving in the last decade and provide more details on health authorities expectations compared to the past
- Specific requirements for biosimilar assay development and validation started to be discussed in guidelines but is still limited
- Harmonized bioanalytical guidelines also including considerations on particular needs for biosimilar assay development desirable
- Blinded sample analysis in comparative biosimilar clinical trials elicits considerations to be factored in when analyzing clinical study samples
- Results of generated immunogenicity data need to be interpreted in light of the assays used and the totality of data
- Evaluation on clinical relevance of detected anti-drug antibodies essential - especially when discussing immunogenicity data in public community

Thank you