Clinical Development
Biopharma



# Immunogenicity assessment of GP2017: A biosimilar to reference adalimumab

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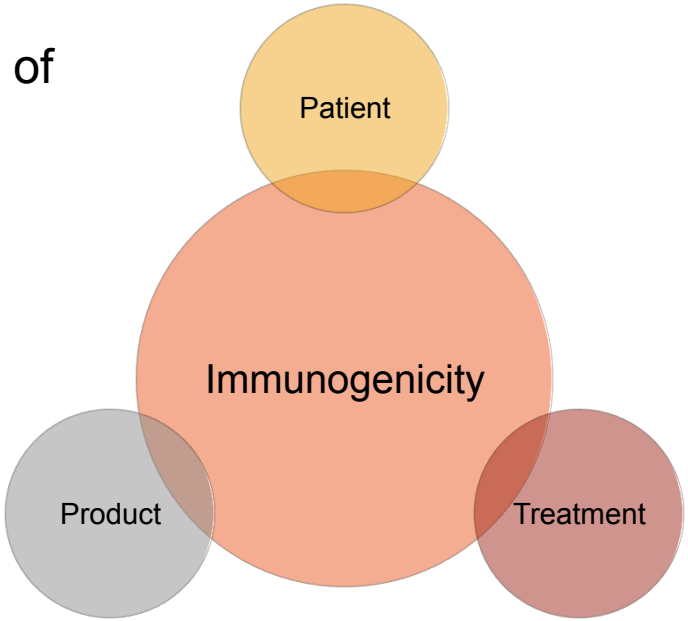
# Agenda

1. Introduction
   - Immunogenicity assessment of biosimilars
2. Immunogenicity assessment of GP2017
   - Immunogenicity results from clinical studies
   - Challenges in bioanalytical method validation
3. Summary

# Immunogenicity may impact clinical safety and efficacy: assessment needed

- Immunogenicity is a potential concern for **all** biopharmaceuticals
  - Might have an impact on safety and efficacy of the molecule
  - Immunogenicity evaluation is essential

- Many factors can influence immunogenicity, e.g.
  - Route of administration
  - Concomitant medication, disease
  - Aggregates, posttranslational modifications

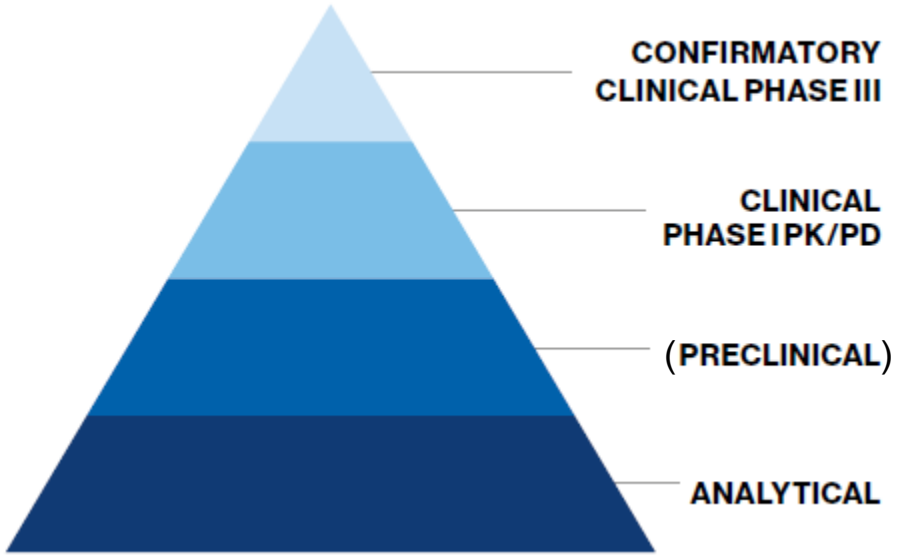


# Immunogenicity assessment of biosimilars: focus on similarity

- Immunogenicity profile of the **molecule per se is already known**
- Focus on confirming that there are **no clinically meaningful differences** between the reference product and the biosimilar
- Head-to-head clinical trials (reference vs. biosimilar) using **state-of-the-art bioanalytical assays**

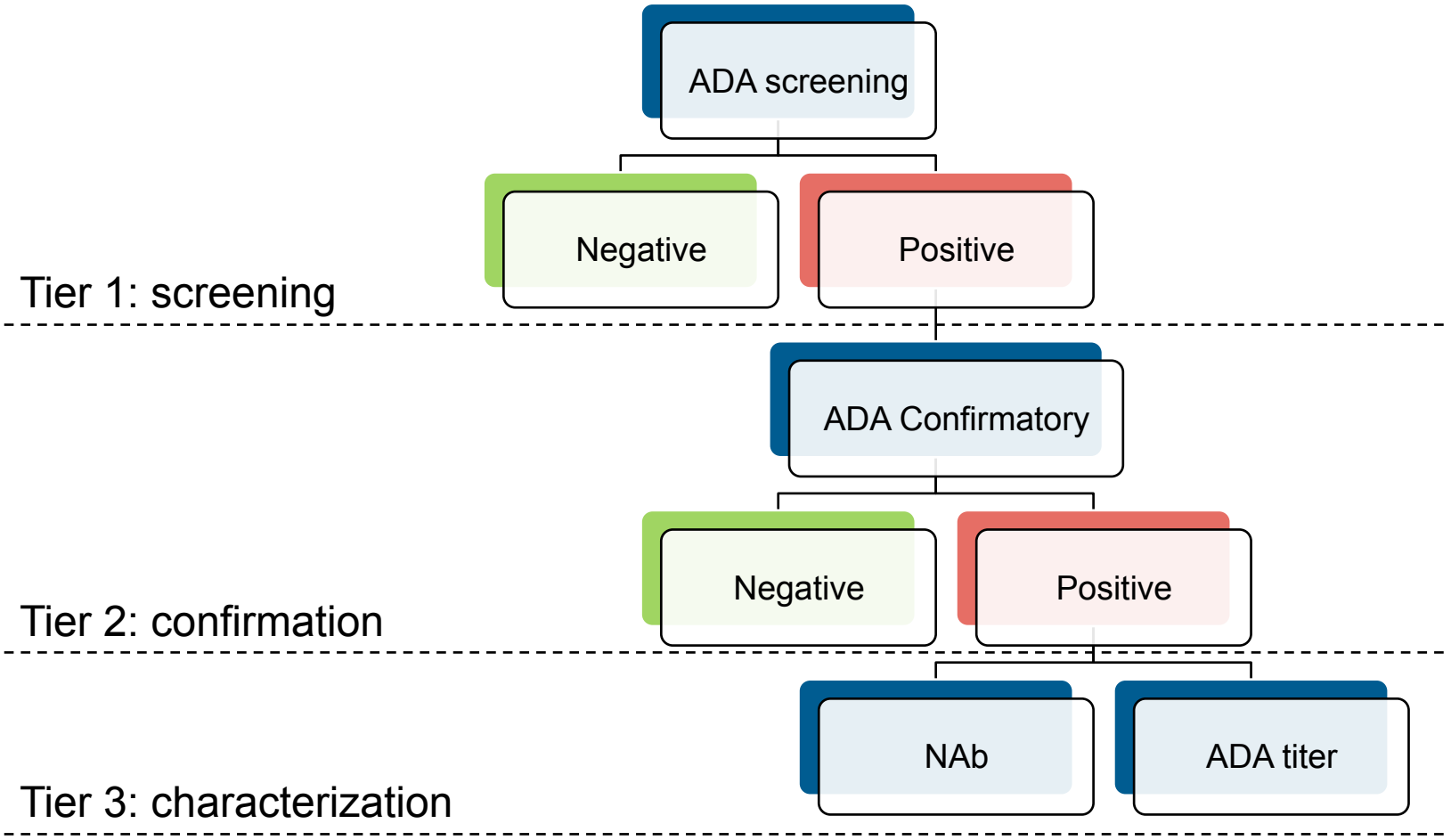
# GP2017 - An approved Sandoz biosimilar to reference adalimumab

- GP2017 is a biosimilar to reference adalimumab
- Up to now GP2017 is approved in US and EU/EEA




- Similar efficacy, safety and immunogenicity demonstrated in confirmatory clinical studies
- Similar PK bioequivalence demonstrated in healthy volunteers
- Comparability demonstrated in comprehensive in vitro studies
- Extensive state of the art characterization demonstrated analytical similarity

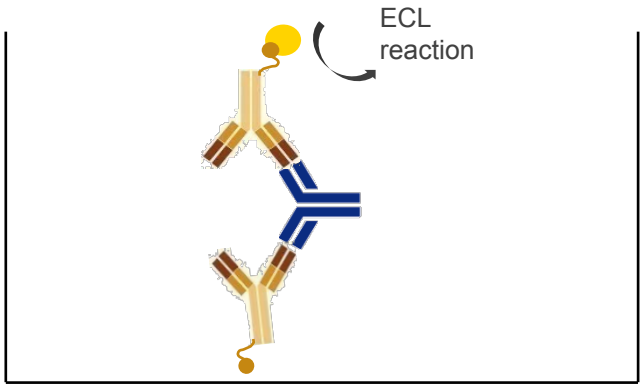
# Immunogenicity of GP2017 was assessed in a multi-tiered approach



# ADA and NAb assay set-up

- State-of-the-art ADA and NAb assays were validated in accordance with current guidelines

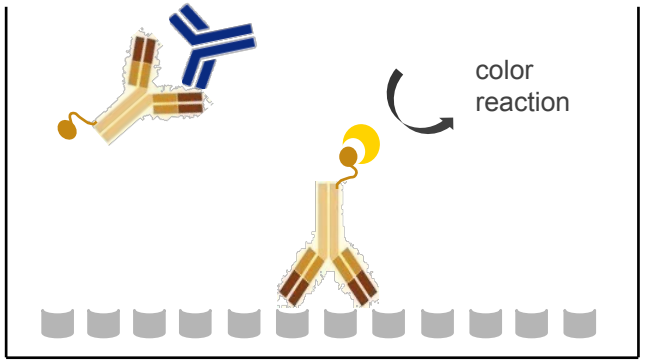
ADA assay




GP2017-biotin/sulfo-tag

ADA

NAb assay




GP2017-biotin

NAb

TNF

# One vs. two assay approach

## 1 Assay

Comparability testing during assay validation to show assay detects ADAs against biosimilar and reference equally

- ↑ Conservative approach: detects reliably antibodies against biosimilar
- ↑ No inter-assay variability
- ↑ Blinded study sample analysis possible
- ↑ Wealth of information on reference immunogenicity available
- ↓ ADAs against immunogenic structures (e.g. carbohydrates) unique for reference not detected

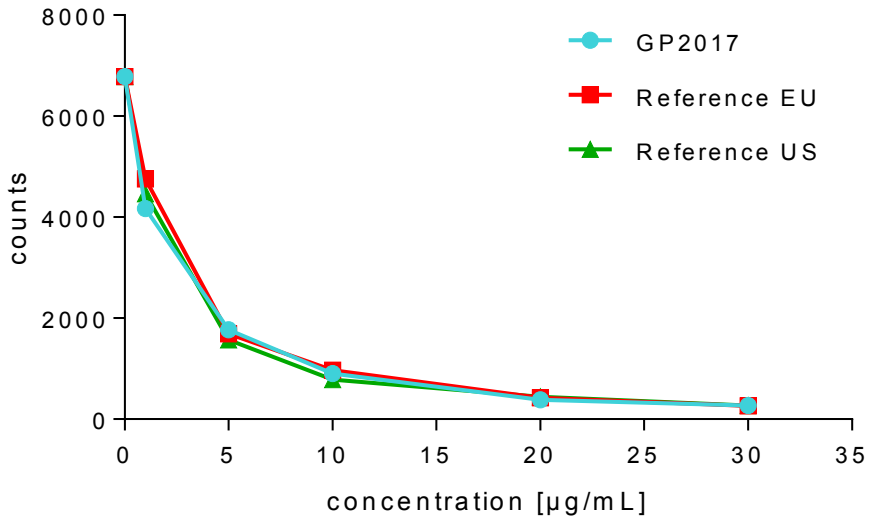
## 2 Assays

Two assays with different properties: different reagents, assay conditions (assay cut-points, sensitivity, stability...)

- ↓ Introduction of additional variability / impact of assay bias on comparative evaluation
- ↓ No blinded study sample analysis possible
- ↓ Data comparison / interpretation more challenging
- ↑ ADAs against potential unique structures of one of the products are detected

# One assay approach is suitable for GP2017 immunogenicity assessment

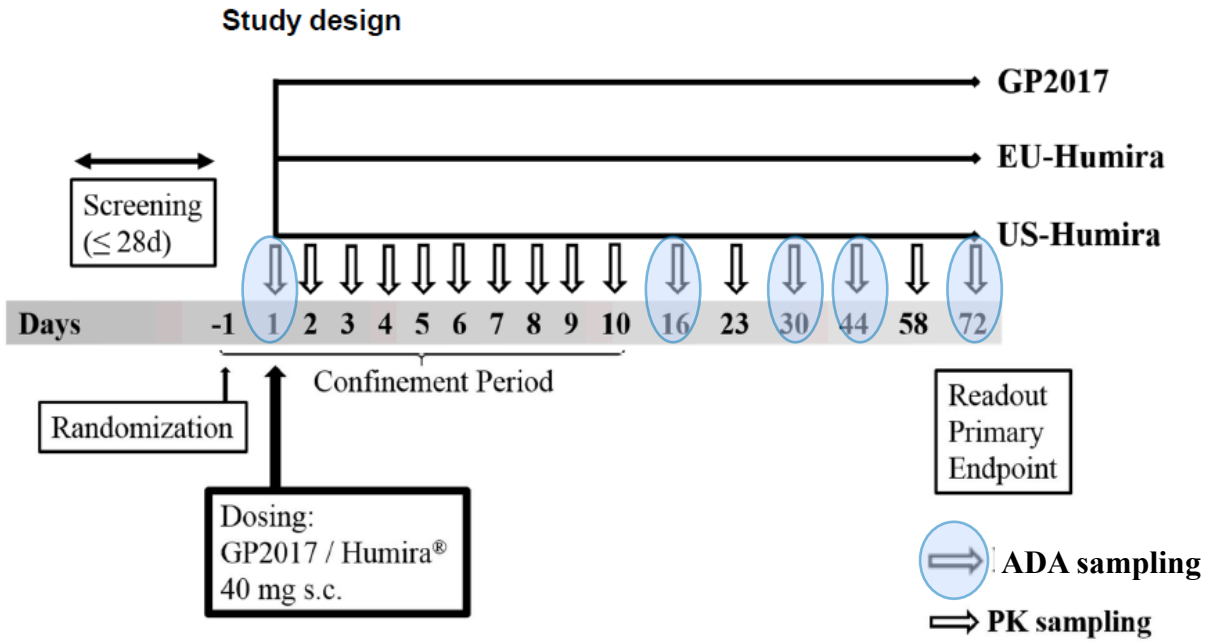
- Specificity demonstrated by immuno-depletion analysis
- Comparable signal inhibition curves




Samples containing fixed ADA concentration were spiked with increasing concentrations of GP2017 or reference product.

# PK study to confirm biosimilarity

- Randomized, double-blind, parallel group PK study with three treatment arms to evaluate PK, safety and immunogenicity of GP2017, EU-Reference and US-Reference



# ADA development was similar across all three treatment groups

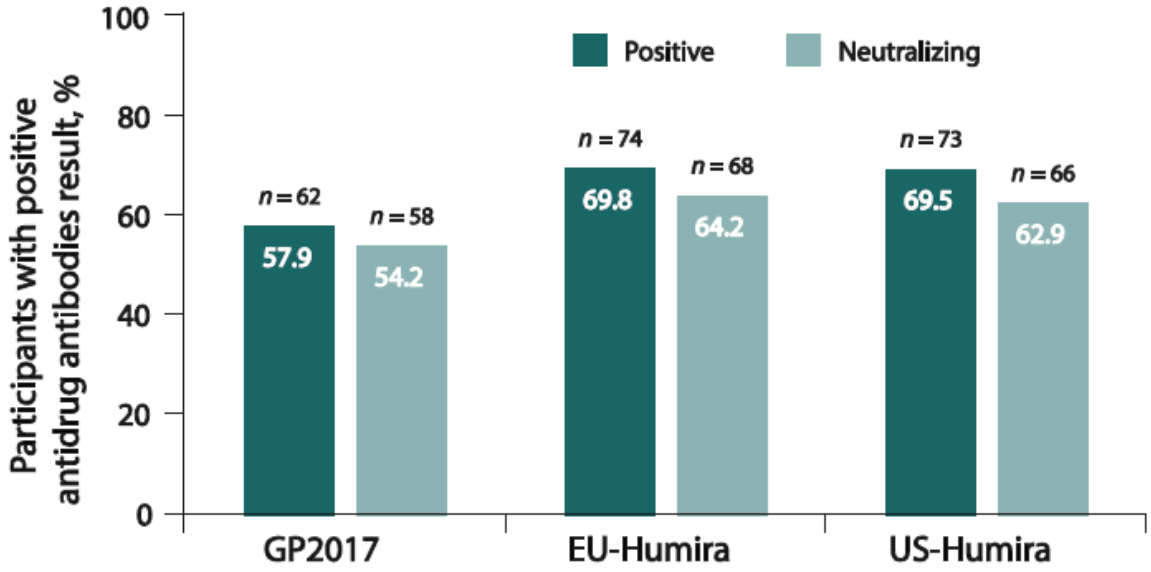
| Visit | ADA status | GP2017 N = 107, *n* (%) | EU-Reference N = 106, *n* (%) | US-Reference N = 105, *n* (%) |
|---|---|---|---|---|
| **Day 1[a]** | **positive** | 2 (1.9) | 3 (2.8) | 4 (3.8) |
| **Day 16** | **positive** | 25 (23.4) | 27 (25.5) | 24 (22.9) |
| **Day 30** | **positive** | 14 (13.1) | 18 (17.0) | 16 (15.2) |
| **Day 44** | **positive** | 19 (17.8) | 25 (23.6) | 27 (25.7) |
| **Day 72** | **positive** | 60 (56.1) | 70 (66.0) | 68 (64.8) |

Immunogenicity data in GP2017 PK similarity studies (safety analysis set).
[a] Day 1 samples were collected pre-dose.

*von Richter, O. et al., (2019): GP2017, an adalimumab biosimilar: pharmacokinetic similarity to its reference medicine and pharmacokinetics comparison of different administration methods, Expert Opinion on Biological Therapy*

# Immunogenicity between GP2017 and reference adalimumab is similar

- Immunogenicity is similar, with most ADAs being neutralizing



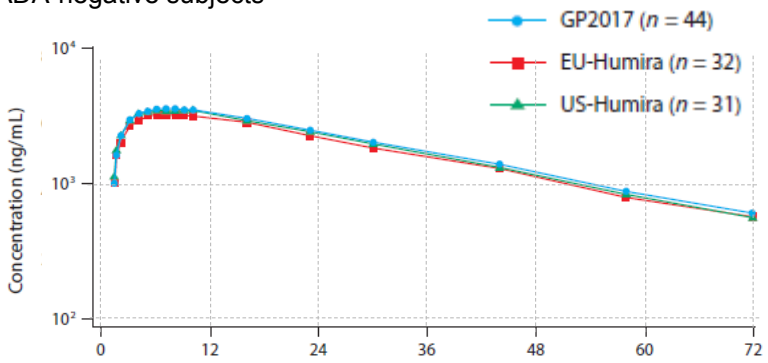

Overall anti-drug antibody detection rates up to day 72 (safety analysis set).

EU/US-Humira, EU-authorized or US-licensed reference adalimumab; GP2017, Sandoz biosimilar adalimumab.

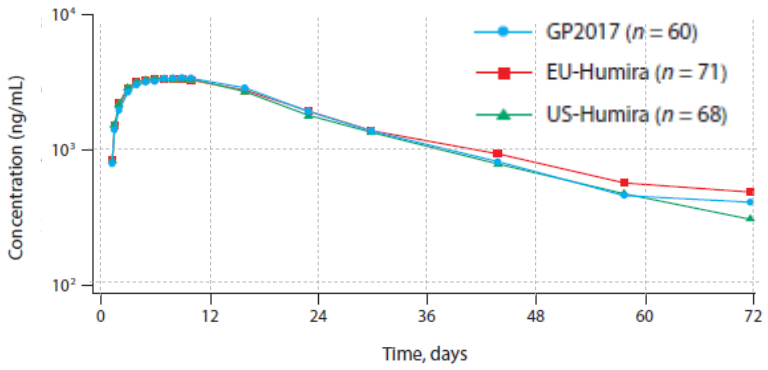
*von Richter, O. et al., (2019): GP2017, an adalimumab biosimilar: pharmacokinetic similarity to its reference medicine and pharmacokinetics comparison of different administration methods, Expert Opinion on Biological Therapy*

# PK between GP2017 and reference adalimumab is similar

(A) ADA-negative subjects




(B) ADA-positive subjects



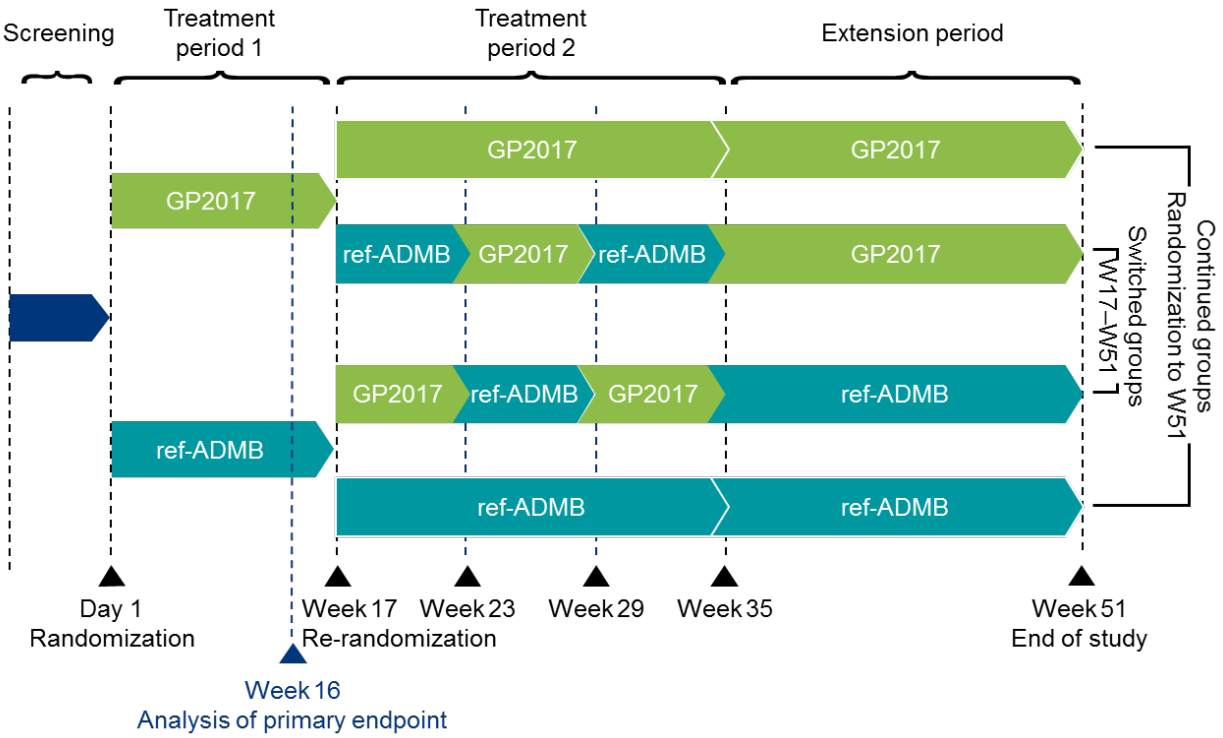

Semi-logarithmic serum concentration–time profiles of ADA-negative (A) versus ADA-positive (B) subjects in the PK similarity study (PK analysis set).

*Jan Richter, O. et al., (2019): GP2017, an adalimumab biosimilar: pharmacokinetic similarity to its reference medicine and pharmacokinetics comparison of different administration methods, Expert Opinion on Biological Therapy*

- Immunogenicity has an impact on PK
- PK in ADA positive and ADA negative subgroups is demonstrated to be similar

# Confirmatory safety and efficacy study

- Multicenter, randomized, double-blind, comparator-controlled phase III confirmatory study with four study periods




*Blauvelt, A. et al., (2018): Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches, British Journal of Dermatology*

# Immunogenicity between GP2017 and reference adalimumab is similar

- Immunogenicity is similar; most ADAs are neutralizing

| | Treatment period 1 (randomization to week 17) | | Treatment period 2 + extension phase (week 17 to week 51) | | | |
|---|---|---|---|---|---|---|
| | **Reference** (*n* = 234) | **GP2017** (*n* = 231) | **Continued Ref** (*n* = 127) | Ref to GP2017 (*n* = 63) | **Continued GP2017** (*n* = 126) | GP2017 to Ref (*n* = 63) |
| **ADA-positive** | 75/220 **(34.1)** | 81/220 **(36.8)** | 55/122 **(45.1)** | 24/61 (39) | 44/123 **(35.8)** | 28/60 (47) |
| **NAb-positive** | 60/75 **(80)** | 65/81 **(80)** | 47/55 **(85)** | 24/24 (100) | 38/44 **(86)** | 21/28 (75) |

*Values are the antidrug antibody detection rate, n/N (%), safety analysis set*

*Modified from: Blauvelt, A. et al., (2018): Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches, British Journal of Dermatology*

# Efficacy between GP2017 and reference adalimumab is similar

- PASI 75 response at week 16 in ADA positive and ADA negative subgroups is demonstrated to be similar

| ADA status up to week 16 | Endpoint | Treatment group | N | n | Adjusted response rate/ SE (%) |
|---|---|---|---|---|---|
| Negative | PASI 75 response | GP2017 | 149 | 111 | 74.3 / (3.58) |
| | | Reference | 146 | 105 | 72.1/ (3.70) |
| Positive | PASI 75 response | GP2017 | 40 | 17 | 42.8 / (7.72) |
| | | Reference | 38 | 15 | 39.2 / (7.80) |

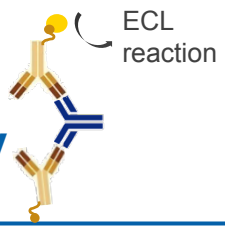
N- Number of patients per treatment group and subgroup, n- Number of patients per treatment group and subgroup achieving PASI 75 response (per protocol set)

Source: Hyrimoz EPAR

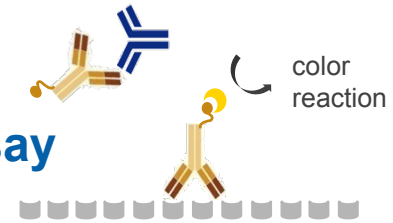
# Immunogenicity results cannot be compared to historical data

- Immunogenicity is similar between GP2017 and reference
- Historical data on immunogenicity vary
  - In published studies with adalimumab the proportion of ADA positive subjects varies strongly
  - Differences in patient groups, co-medication
  - Different assay formats
  - No standardization
  - **Assay sensitivity and drug tolerance improved over time**

# ADA and NAb assay with high sensitivity and drug tolerance used for immunogenicity assessment of GP2017



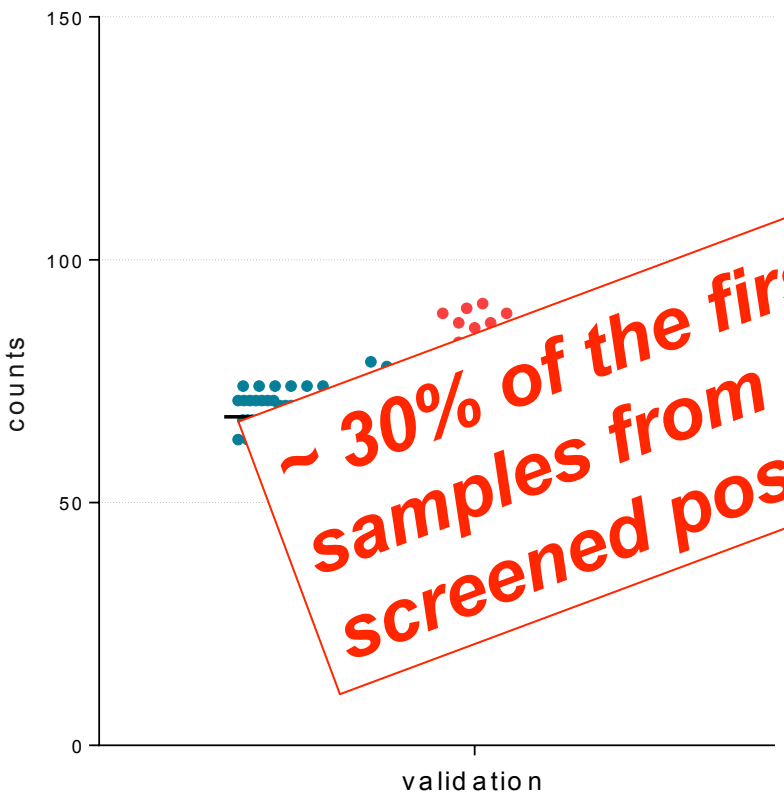

**ADA assay**




**NAb assay**

| | | |
|---|---|---|
| Matrix | Validated for different matrices | Validated for different matrices |
| Assay type | ECL based assay<br>2-fold acid dissociation | ELISA based CLB assay<br>2-fold acid dissociation |
| Sensitivity | ~30 ng/mL | ~100 ng/mL |
| Drug tolerance | At least 40µg/mL | At least 40µg/mL |
| Cut-point | Floating screening<br>Fixed confirmatory | Fixed |

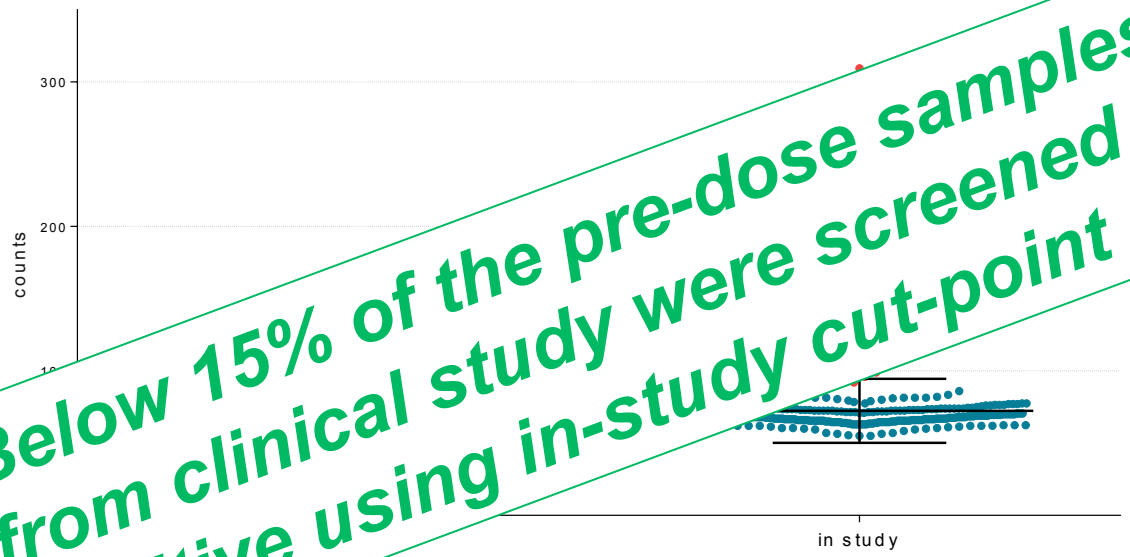
# Challenges in ADA assay development – screening cut-point




- The assay cut-point i… el of response tha… ble respo… e
  …sing
  …ilable sera
  …r exclusion (according to Shankar et al, 2008)
- Floating cut-point factor was determined
- Very low signals

**~ 30% of the first ~300 pre-dose samples from clinical study were screened positive**

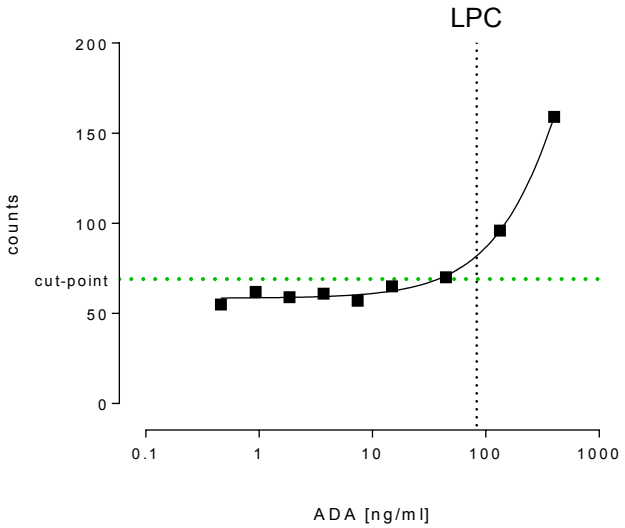
# In-study cut-point was determined and used for further analysis




Below 15% of the pre-dose samples from clinical study were screened positive using in-study cut-point

- Highe[illegible]se sample variability
- Slightly higher in-study cut-point determined

# Challenges in ADA assay development - LPC

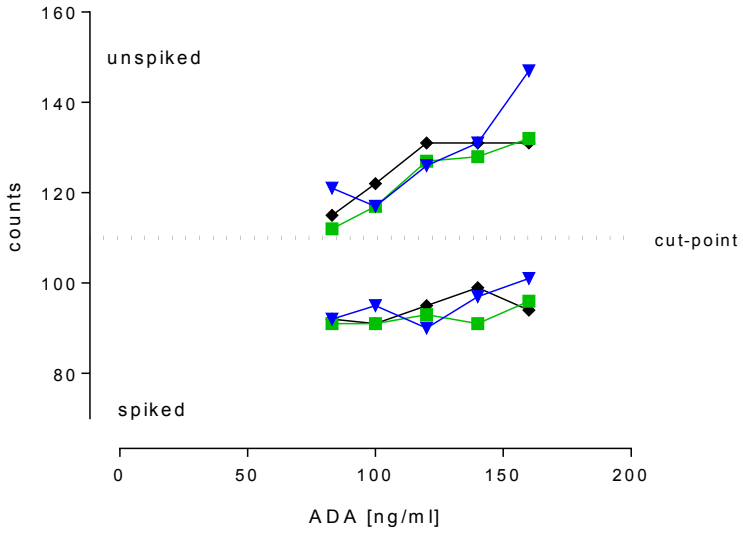


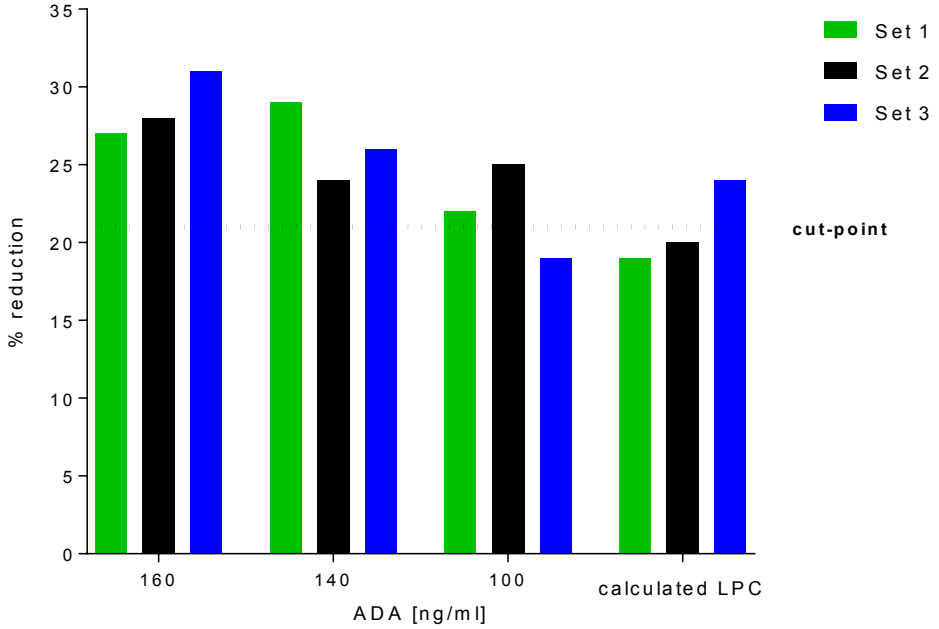

Samples spiked with increasing ADA concentrations were analyzed in the ADA assay.

- LPC: low positive control set to fail in 1% of assay runs
- Calculated LPC below 100 ng/mL was successfully validated

# Confirmatory LPC in routine analysis

- LPC above screening cut-point, but LPC could not be confirmed reproducibly
- Confirmatory LPC had to be adapted to a higher concentration



# Summary

- Immunogenicity assessment is crucial for **all** biopharmaceuticals
- Similar immunogenicity of GP2017 (approved in EU/EEA and US) to the reference adalimumab was demonstrated
- Sandoz used highly sensitive and highly drug tolerant state-of-the-art assays to determine immunogenicity of GP2017
- Proper cut-point and LPC determination are important for immunogenicity assessment and may be challenging

# Acknowledgement

GP2017 Global Team

Clinical Bioanalytics Oberhaching

# Thank you

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