Medicines & Healthcare products Regulatory Agency

Biosimilar Pharmacokinetics Considerations

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Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MHRA or EMA.

Overview:

Biosimilar PK studies considerations including TMDD and batch selection

Regulatory expectations for the bioanalytical methods

PK study design

Statistical comparison

Use of PK modelling to support PK analysis

PK studies

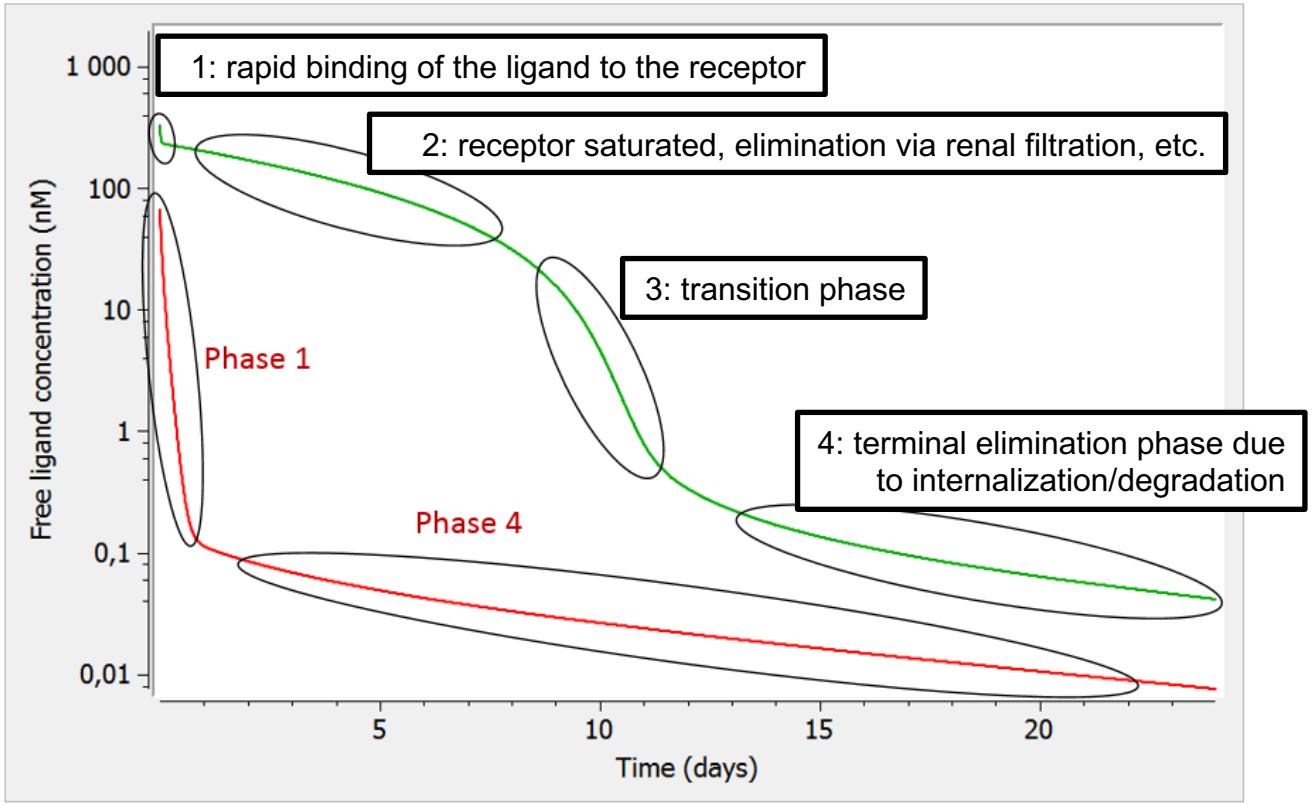
- Standard criteria used for BE studies should be a reasonable basis.
- Reference product as IV and SC: evaluation of SC administration may be sufficient but just should be justified.
- Statistically significant differences in 90% CIs (discussed later)

Parameters		Single Dose	Multiple Dose
Primary	$AUC_{0\text{-}inf}$	✓	
	C_{max}	✓	
	$AUC_{0\text{-}t}$		✓
	$AUC_{0\text{-}T,\ ss}$		✓
Secondary	t_{max}	✓	
	V_d	✓	
	$t_{1/2}$	✓	
	$C_{max,\ ss}$		✓
	$C_{trough,\ ss}$		✓
ADAs		✓	✓

Ref: EMEA/CHMP/BMWP/42832/2005 Rev1

TMDD

- Target mediated drug disposition (clearance): elimination by binding to the target is saturable due to the finite number of targets on the cell surface (or soluble targets in the systemic circulation).
- While comparison of target-mediated clearance is of major importance in the biosimilarity exercise, it may not be feasible in patients due to high variability in target expression, including changes over time.



Ref: Lixoft/Peletier et al 2012

Batch selection

- Representative batches of the biosimilar and innovator product should be used in the comparative PK study and it should be documented how the used batches have been selected.
- When selecting the batches, please consider:
  - Protein content of the batch.
  - Delivered volume, when pre-filled syringes, injection pens, etc. are being used.

Protein content correction

- The protein content of the selected biosimilar and reference product batches should be determined beforehand and analysed using the same analytical method.
- Pre-specified and well justified protein content adjustment can be acceptable, provided that the difference in delivered dose is not reflecting a consistent difference between the biosimilar and reference product.
- Further, proportional adjustment for protein content in case of non-linear pharmacokinetics should be thoroughly discussed.
- Alternative methods to ensure delivery of the same protein dose could be considered.

Delivery of same protein dose

Example: Zessly

As the 90% CI did not cross unity for all 3 PK parameters, an investigation into this observation revealed a difference in drug (protein) content of the vial containing the lyophilisate evidenced by the differences in protein concentration of the reconstituted lyophilisate between the Zessly and EU-authorized Remicade used in study GP11-101.

The difference in protein concentration represents a difference in dose.

EMA guideline allows for content correction where a reference batch with an assay content differing less than 5% from test product cannot be found (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Summary of statistical comparisons of primary pharmacokinetic parameters with protein-content correction (PP set)

Parameters (units)	Adjusted Geometric Means		Ratios (Test/Reference) of Adjusted Geometric Means[a] (%)	90% CIs for Ratios (%)
	Test	Reference		
Zessly (Test versus Remicade-EU (Reference)				
C_{max} (µg/mL)	211.1	208.0	101.48	93.45 – 110.21
AUC_T (µg•hr/mL)	53990	52270	103.29	94.86 – 112.45
AUC_{inf} (µg•hr/mL)	58010	56930	101.91	92.85 – 111.86
Zessly (Test) versus Remicade-US (Reference)				
C_{max} (µg/mL)	211.1	209.4	100.81	92.79 – 109.53
AUC_T (µg•hr/mL)	53990	53240	101.40	93.09 – 110.45
AUC_{inf} (µg•hr/mL)	58010	57540	100.83	91.81 – 110.73
Remicade-EU (Test) versus Remicade-US (Reference)				
C_{max} (µg/mL)	208.0	209.4	99.34	91.61 – 107.72
AUC_T (µg•hr/mL)	52270	53240	98.17	90.31 – 106.73
AUC_{inf} (µg•hr/mL)	56930	57540	98.94	90.29 – 108.41

The protein-content corrected analysis comprised approximately 100.00% comparability between Zessly and EU sourced infliximab with 90% CIs ranging from 93% to 112% for C_{max} , $AUC_{0\text{-}T}$ and $AUC_{0\text{-}inf}$.

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What are the regulatory expectations for the bioanalytical assays?

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Biosimilar Bioanalytical Assays

Expectation : Biosimilar PK profile (Cmax, AUC)

LoQ should not be higher than 5% of Cmax

AUCextrapolated not exceeding 20% in 20% of subjects

Testing strategy with well-designed assays (state-of-the-art, validated)

Sensitive, specific, robust & precise

Biosimilar Bioanalytical Assays (cont.)

- Reference standard should be the same batch used in non-clinical and clinical testing (if not analytical characterisation and bioanalytical evaluation are required)
- A minimum of 6 independent runs of calibration curve should be evaluated during the validation
- The investigation of stability should cover short-term stability at room temperature or sample processing temperature and freeze-thaw stability. In addition, long-term freezer stability should be studied at each temperature at which study samples will be stored (the duration of the stability study should be equal to or higher than the duration of the storage of the clinical samples

Comparative Immunogenicity: Biosimilars

Expectation : ADA profile (incidence, titres, neutralisation, onset and persistence) and clinical impact is similar to the reference product (challenge, limited data)

Testing strategy with well-designed assays (state-of-the-art, validated)

Sensitive, specific, robust & precise

Measure ADA to biosimilar and reference product to a similar extent

PK study design

- Parallel design considering the long half-life ($t_{1/2}$).
- Consider target density for target mediated Cl.
- Consider ADA responses in cross over studies, even beyond washout period due to sensitisation. Therefore parallel design is preferred. Recombinant versions unlikely to enhance ADA responses.
- Consider the washout period for cross over studies considering PD biomarkers
- Examine for balanced groups (after pre-specified exclusions) and if not see whether this could affect the results*.

* Can be addressed by modelling if exclusions are large.

PK study population

- Selected population should be justified.
- Healthy volunteers are acceptable and less variable, but target density could be different.

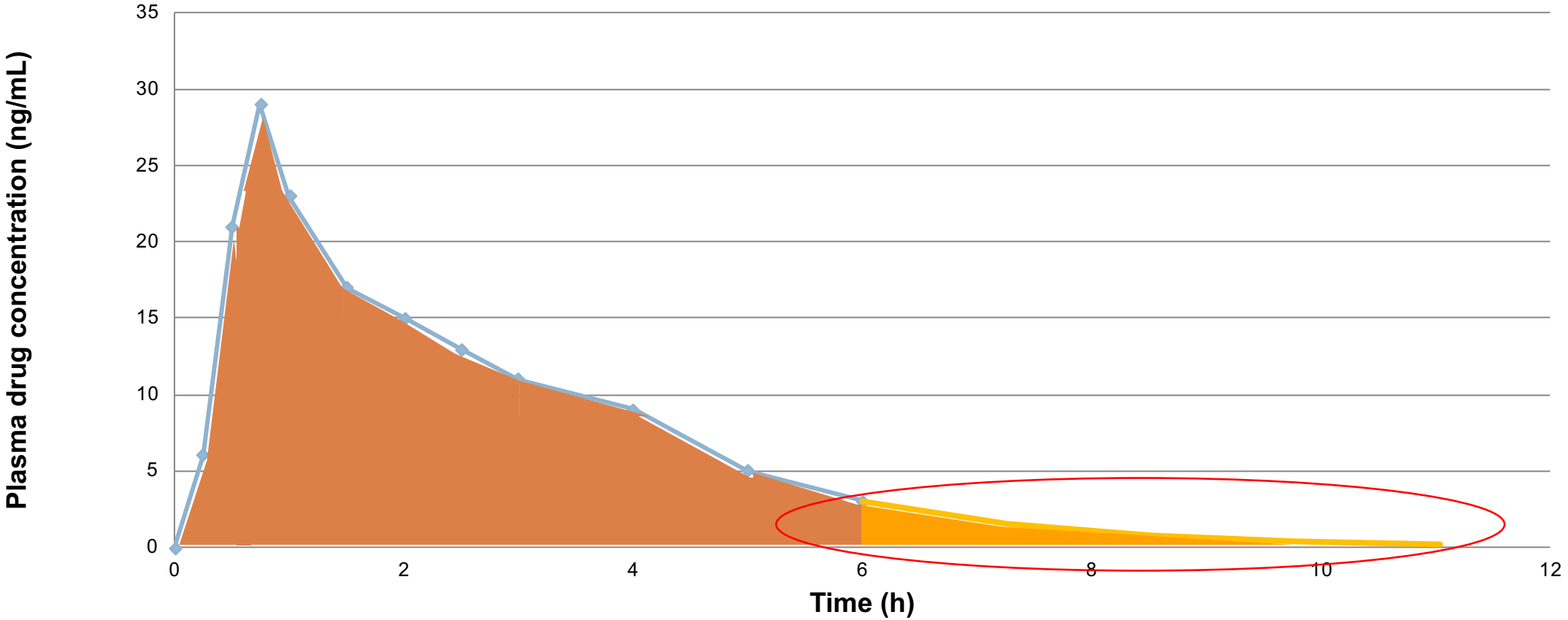
PK dose level

- Important to select the most sensitive dose to investigate target mediated Cl especially when it is higher in patient population.
- A lowest therapeutic dose (before saturation of target) and highest therapeutic dose is recommended.

PK sampling

- Should be long enough to avoid >20% extrapolations in $AUC_{0\text{-}inf}$
- Non-linear Cl could overestimate $AUC_{0\text{-}inf}$ as NCA assumes linear Cl
- 20 X 20 rule applies (>20% in >20% of subjects required discussion for the validity of the study).

AUC calculation



- AUC calculation – linear trapezoidal method.
- At least **three** to **four samples** are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant.
- AUCextra < 20% of $AUC_{0\text{-inf}}$.

Statistical comparison

Analysis method

ANOVA for crossover trials

ANCOVA for parallel group trials – adjusting for pre-specified baseline covariates (not post-baseline covariates such as ADA formation)

If study compares both EU & US reference compared to test – remember to include only directly relevant data in each analysis e.g. for comparison on test with EU reference, data from US reference should be excluded.

Acceptance criteria

Ideally should be justified using PK/PD argumentation – failing this 80-125% can be used but could cause problems later.

Statistical comparison

Statistically significant difference

If CIs fall inside well justified acceptance limits – then all important differences have been excluded and study is positive. A statistically significant difference between products would not be an issue.

If limits are not fully justified then confidence intervals which are close to the boundary will require further justification, especially if the point estimate is away from 1.00. This can include some (but not all) cases where there is a statistically significant treatment difference, but is not restricted to such cases.

Modelling

Can PK modelling be used?

Types of modelling:

- Population PK (PopPK) modelling: ‘top-down’, empiric approach, utilises all available pharmacokinetic information, and builds a model that fits the data.
- Physiologically-Based Pharmacokinetic (PBPK) modelling: ‘bottom-up’, based on physiological knowledge/systems.
- PK/PD modelling can be supportive if there is a need for clinical comparability data based on PD surrogates or clinical endpoints but is not currently adequate as a stand-alone analysis for biosimilarity.

Case study: Zessly (infliximab)

- Bind to sTNF and mTNF
- population PK model based on one clinical study used to describe PK of Zessly and Remicade in patients with rheumatoid arthritis.
- Objective to evaluate potential covariates on CL and V
- 2 compartment model with linear elimination
- Similar CL, V1, V2 for Zessly and Remicade

"Taking into consideration that the population PK model is of low impact in supporting biosimilarity, it has not received close Regulatory scrutiny. However, the use of popPK approach to support PK similarity and to add to the totality of evidence is acceptable. "

Limitations of the PK study

- Compared to conventional BE approach for small molecules, comparative PK study cannot be used to outweigh substantial differences in quality, nonclinical or efficacy and safety studies.
- The results of the PK investigations should always be interpreted and weighed in the context of all other data.
- The extent to which potential differences in disposition between biosimilar and reference product could occur depends on the nature of the molecular differences between both products. It is therefore important to consider also the quality characteristics and data on binding properties when judging the likelihood of potential pharmacokinetic differences.

On the other hand…Case study: Teriparatide

- Recombinant 1-34 N-terminal fragment of endogenous human parathyroid hormone rhPTH(1-34)
- Treatment of osteoporosis
- Test: RGB-10. Reference: Forsteo
- One comparative (2 stage) PK Study in 54 healthy women. PD but no efficacy or safety.

	LSMs				
Parameters	**Treatment A (RGB-10)**	**Treatment B (Forsteo®)**	**GMR%**	**94.12% CI**	**Intra-subject CV%**
C_{max} (pg/mL)	83.192	90.179	92.25	85.51 - 99.52	19.37
$AUC_{0\text{-}tlast}$ (pg*hr/mL)	92.443	100.857	91.66	85.20 - 98.60	18.63
$AUC_{0\text{-}inf}$ (pg*hr/mL)	103.886	115.657	89.82	83.75 - 96.33	17.48
$t_{½}$ (hr)	0.654	0.715	91.39	83.28 - 100.29	23.38

Subjects 2, 22 and 54 were excluded from statistical analyses. Geometric least-squares means (LSMs) are calculated by exponentiating treatment LSMs derived from ANOVA. Geometric mean ratio (GMR)=100 * (test/reference); intra-subject CV was calculated as 100 x square root(exp[residual variance]-1).

$AUC_{0\text{-}inf}$: area under concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$: area under concentration-time curve from time zero to last quantifiable concentration; CI: confidence interval; C_{max}: maximum concentration; $t_{½}$: terminal half-life; t_{last}: time at last measurable concentration

statistically significant differences in 90% CIs need to be explained and justified

Conclusions and Questions

For more information: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers#7.-biosimilars-section