Partial AUCs: tool for development vs regulation

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BioBridges 2022

Content

- History of other metrices for rate of absorption
- Example of Cmax/AUC ratio
- FDA evaluation of partial AUCs
- Practical use of partial AUCs
- EMA guidelines with use of pAUCs
- Examples of pAUCs (regulatory, development)
- Product specific guidance with pAUCs (FDA, EMA)
- Conclusion

History of other metrices for BE assessment in SD studies

- **Ratio of the primary metrics Cmax and AUC** (Cmax/AUC) (Endrenyi 1991)
  - Better reflection of the rate of absorption
  - Good for IR products and SD studies and without plasma concentration time shift
  - Some limitation might be expected for APIs with complex solubility,

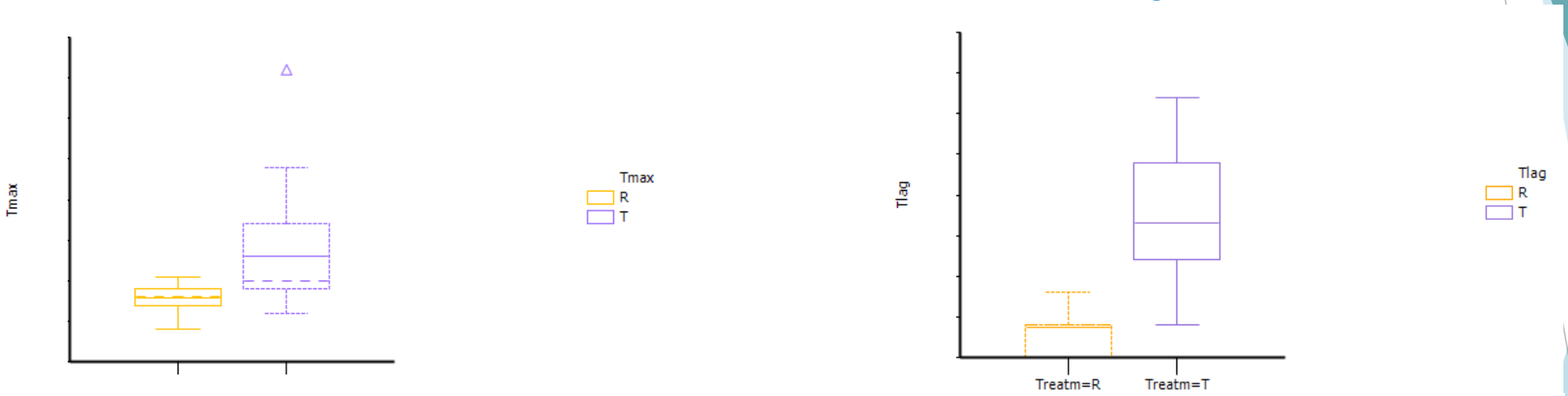
  e.g. low solubility and pH dependent solubility, etc.
- **Partial AUC** - more discriminating than Cmax and/or Tmax in the evaluation of the absorption rate of drugs (Chen 1992)
- **Area under the moment curve** (AUMC) - product concentration and time versus time
- **Apical concentration** (C apical) – mean of concentrations at some level (25-50%) below Cmax (Pollack 1988)
- **Concentration at the end** of the intended dosing interval (Cτ) (Paixao 2012)

Fed study outcome

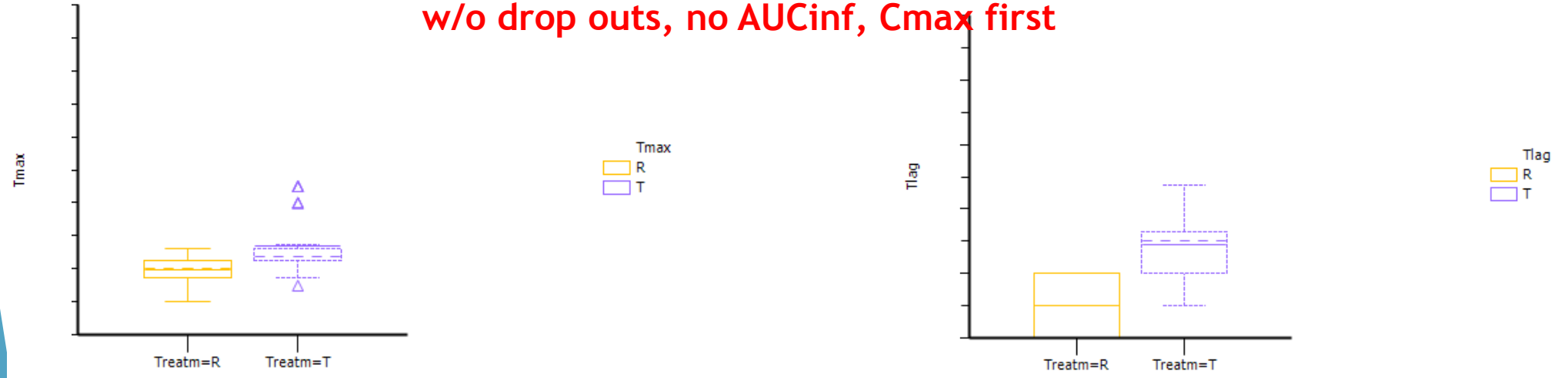
Tmax

w/o drop outs

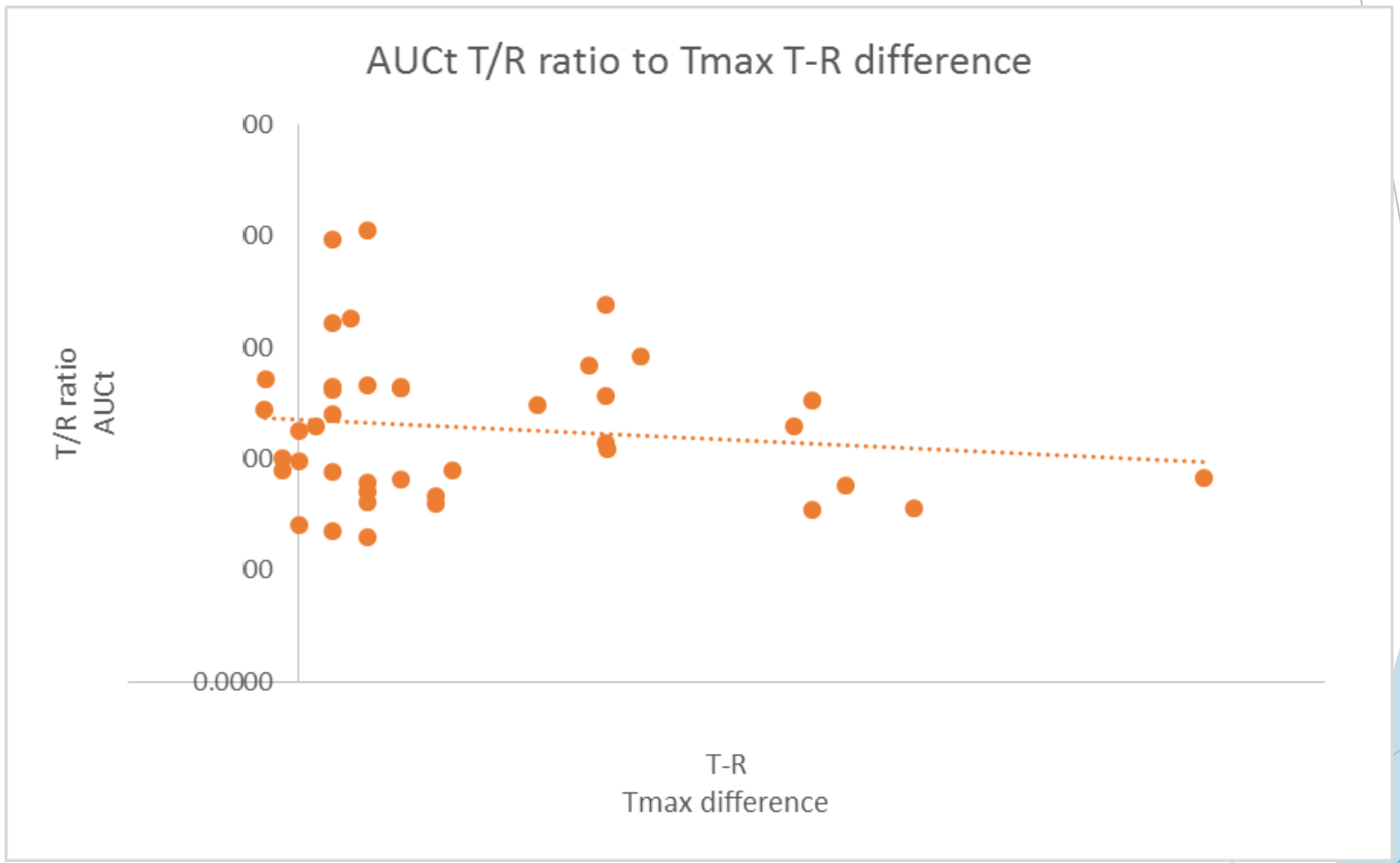
Tlag



w/o drop outs, no AUCinf, Cmax first

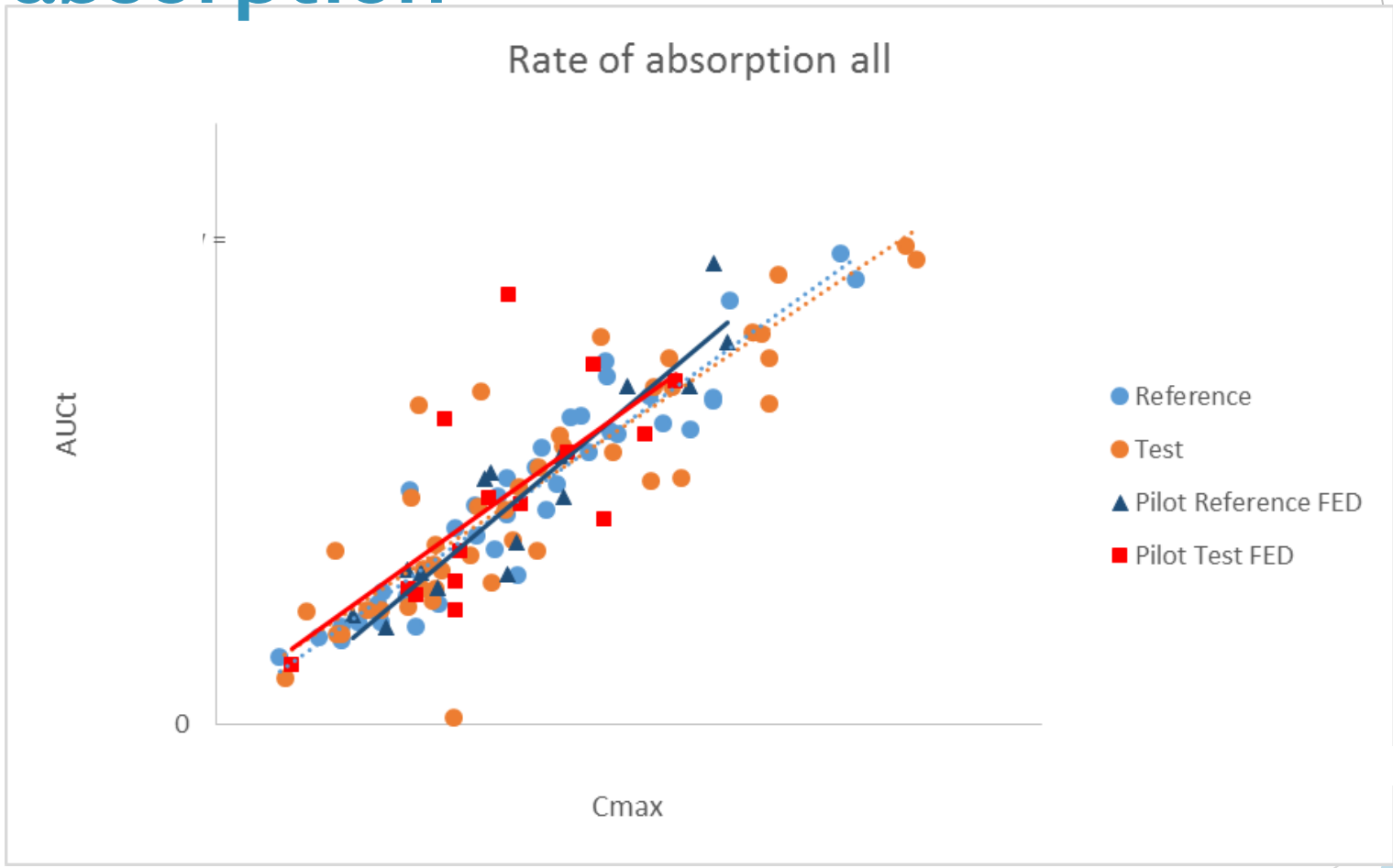


AUCt T/R to T-R difference



- No dependence of T/R ratio on Tmax difference between T and R

Rate of absorption



- Rate of absorption not different between T and R and similar between pilot and pivotal study

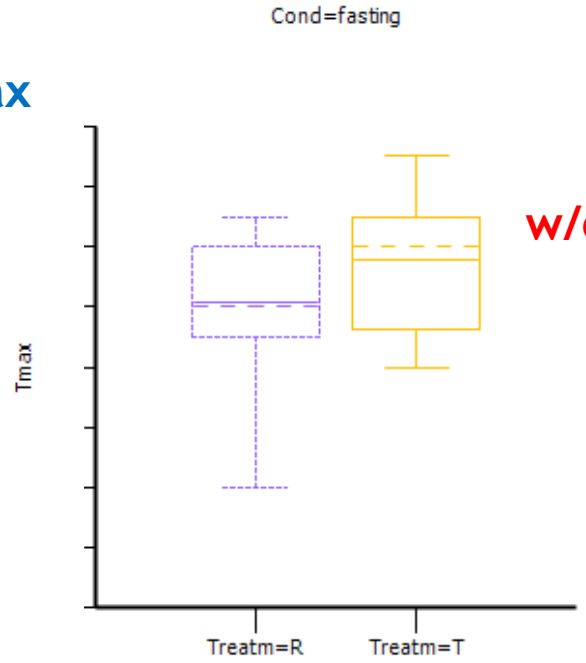
Impact on Rate of absorption Cmax/AUC

BE w/o drop outs			
Dependent	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
Ln(CmaxAUC_ratio)	97.39	92.09	102.99
BE w/o drop outs, AUC inf subj			
Dependent	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
Ln(CmaxAUC_ratio)	99.00	93.56	104.76
BE w/o drop outs, AUC inf subj and selected subjects			
Dependent	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
Ln(CmaxAUC_ratio)	100.13	94.79	105.78

- Rate of absorption expressed as Cmax/AUCt ratio not affected by subjects exclusion
- Rate of absorption is independent of time

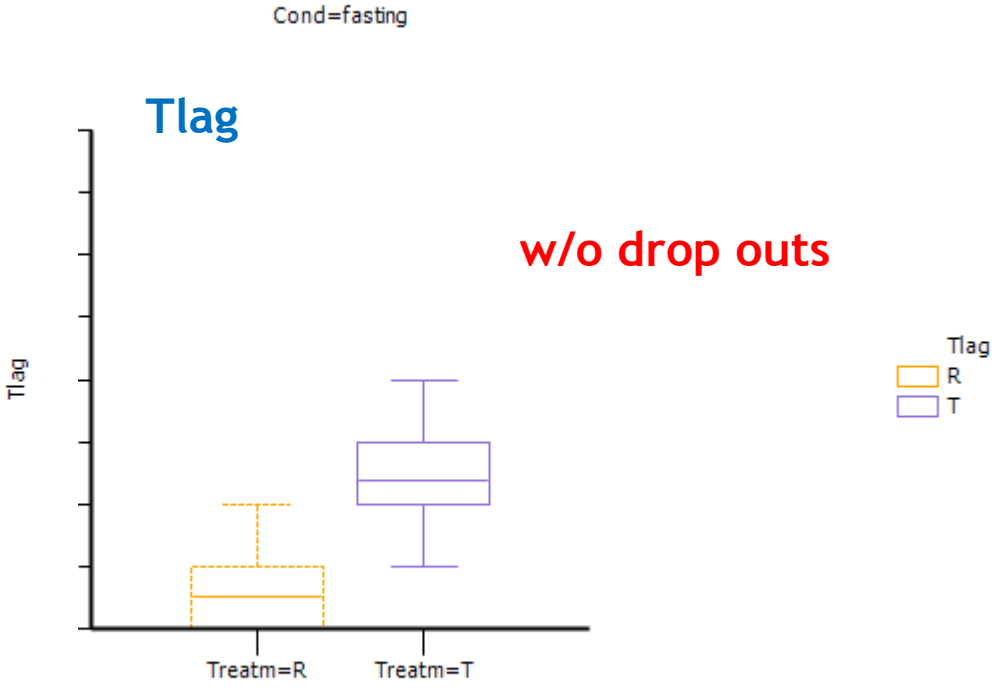
Tmax vs Tlag – fasting study

Tmax



w/o drop outs

Tlag



w/o drop outs

- Does it really matter?

FDA scientific evaluation of partial AUCs

- FDA evaluation and proposal of pAUCs
- Only in case **input rate is critical to ascertain drug efficacy and/or safety** profile
- Truncating area under the curve at T(max) of reference product (PAUC(r,tmax))

or

- Truncation based on PK/PD relationship or efficacy/safety data
- Higher sensitivity in detecting formulation differences, however more variable
- Reference-scaling approach can be employed for BE evaluation

Pharm Res (2011) 28:1939–1947
DOI 10.1007/s11095-011-0421-x

EXPERT REVIEW

Using Partial Area for Evaluation of Bioavailability and Bioequivalence

Mei-Ling Chen • Barbara Davit • Robert Lionberger • Zakaria Wahba • Hae-Young Ahn • Lawrence X. Yu

Received: 5 November 2010 / Accepted: 4 March 2011 / Published online: 13 April 2011

ABSTRACT Assessment of bioavailability/bioequivalence generally relies on the comparison of rate and extent of drug absorption between products. Rate of absorption is commonly expressed by peak concentration (C_{max}) and time to peak concentration (T_{max}), although these parameters are indirect measures of absorption rate. Recognizing the importance of systemic exposure to drug efficacy and safety, FDA recommended that systemic exposure be better used for bioavailability/bioequivalence assessment. Apart from peak exposure and total exposure, FDA also recommended a new metric for early exposure that is considered necessary when a control of input rate is critical to ascertain drug efficacy and/or safety profile. The early exposure can be measured by truncating the area under the curve at T_{max} of the reference product ($PAUC_{r,tmax}$) or some designated early time after dosing. The choice of truncation is most appropriately based on PK/PD relationship or efficacy/safety data for the drug under examination. Compared with C_{max}, $PAUC_{r,tmax}$ has higher sensitivity in detecting formulation differences and may be more variable. If the metric is highly variable, the reference-scaling approach can be employed for bioequivalence evaluation. The partial area metric is useful in PK/PD characterization as well as in the evaluation of bioavailability, bioequivalence and/or comparability.

KEY WORDS bioavailability/bioequivalence · early exposure · partial area · partial AUC · truncated area

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INTRODUCTION

Regulatory assessment of bioavailability and bioequivalence has relied on the comparison of rate and extent of drug absorption between products (1,2). For systemically acting drugs, this is generally achieved by measuring drug concentrations in an accessible biological fluid, such as plasma or serum, over the time course of a pharmacokinetic study in humans. Derived from the plasma or serum concentration-time profile, the rate of absorption is commonly expressed by C_{max} and T_{max}, whereas the extent of absorption is expressed by the area-under-the-curve to the last quantifiable drug concentration (AUC_t) and/or to time infinity (AUC_∞). To establish bioequivalence, the 90% confidence interval of the geometric mean ratio of the test to reference product has to meet the 80–125% limit for all the aforementioned pharmacokinetic parameters except T_{max} (3) that should be similar for the test and reference product. Statistical comparison is not performed for T_{max} due to the lack of appropriate methods (4).

Strictly speaking, C_{max} and T_{max} are indirect measures for rate of absorption, as 'rate' is defined by a rate constant (ka) or rate profile (5). Direct measures such as rate constant or rate profile are not used for bioequivalence evaluation

Springer

Using partial area for evaluation of bioavailability and bioequivalence.Chen ML, Davit B, Lionberger R, Wahba Z, Ahn HY, Yu LX.Pharm Res. 2011 Aug;28(8):1939-47

Partial AUCs in focus

- ANVISA approved for prolonged release products
- Twenty-four studies in a total of 117 (33.9%) failed on partial AUCs
- Partial AUCs defined as half of the dosage interval for each product
- 76.92% of the studies without significant increase of ICV (CV < 30%) for partial AUCs
- 24 studies that failed the assessment of pAUC, 10 studies (41.67%) had a CV <30%

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Assessment of the impact of partial area under the curve in a bioavailability/bioequivalence study on generic prolonged-release formulations☆

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Keywords:
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ABSTRACT

The requirement for multiple-dose bioequivalence studies for the approval of generic prolonged-release (PR) formulations is not agreed upon by the EMA and FDA. While the EMA requests these studies, the FDA has no specific requirement, nor does ANVISA.

Additional metrics are suggested for the assessment of prolonged-release products, and the partial Area Under the Curve (pAUC) metric has received increasing regulatory recognition.

The objective of this work was to investigate whether the evaluation of the partial AUC in studies assessed by ANVISA can detect differences between 2 prolonged-release formulations that have demonstrated bioequivalence by the usual metrics.

Twenty-four studies in a total of 117, which were already approved by ANVISA considering the usual metrics in the last 14 years, failed to demonstrate bioequivalence for partial AUC, which is related to 33.9% of evaluated PR products.

For 76.92% of the studies, there was no significant increase in the intrasubject variability observed in the partial AUC analysis compared to the usual metrics, with a CV < 30% for both cases, calculated individually for each study, indicating that there is no need to increase the sample size to perform such analysis.

The results of this paper demonstrate that the current criteria for assessing the bioequivalence of some prolonged-release formulations are insufficient and that the evaluation of partial AUC could be useful to assure the therapeutic parity of two products.

1. Introduction

The requirement for multiple-dose bioequivalence studies for the approval of generic prolonged-release (PR) formulations is not agreed upon by the two main regulatory agencies of the world (Paixão, 2012). PR formulations, according to EMA guidelines, are modified-release formulations showing sustained release comparable to that of an immediate-release (IR) formulation administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing methods. Additionally, according to the same guidelines, bioequivalence between two PR formulations should be evaluated based on studies designed to demonstrate that the test formulation exhibits the claimed PR characteristics of the reference (EMA, 2014).

In Europe, multiple-dose studies are mandatory for the determination of bioequivalence between innovator and generic PR formulations where accumulation is likely ($AUC_{0,\tau}$ after the first dose covers less than 90% of the mean $AUC_{0,\infty}$) (EMA, 2014). When a low extent of accumulation is expected, bioequivalence needs to be demonstrated for additional parameters representing the shape of the plasma concentration versus time curve in a single-dose study, such as an initial partial Area Under the Curve (pAUC) and a terminal pAUC separated by a predefined time point, which is usually half of the dosage interval (EMA, 2014). On the other hand, the US-FDA does not have these requisites, and there is no special difference between the requirements for a generic IR formulation and a generic PR formulation (Endrenyi and

☆ This manuscript represents the personal opinion of the authors and does not necessarily represent the views or policy of the Brazilian Health Surveillance Agency.

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Practical use of partial AUCs

EMA – MR BES

- SD as a surrogate for MD
  - early pAUC (0 – cut-off t) and a terminal pAUC (cut-off t - tlast), separated by a predefined cut-off time point, e.g. the half of the dosage interval
- Multiphasic modified release products
  - time point for truncating the pAUC based on PK profile e.g. IR and the MR parts, justified and pre-specified
  - widening of the acceptance criteria based on IR gdl for Cmax, Cmax,ss, Cτ,ss, and pAUC
- Note: IR – truncated AUC0-72h (longer than 72 h is therefore not necessary for IR irrespective of the half-life of the drug

EUROPEAN MEDICINES AGENCY
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20 November 2014
EMA/CHMP/EWP/280/96 Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms

Draft Agreed by Pharmacokinetics Working Party	October 2012
Adoption by CHMP for release for consultation	21 February 2013
End of consultation (deadline for comments)	15 September 2013
Agreed by Working Party	23 October 2014
Adoption by Committee	20 November 2014
Date for coming into effect	1 June 2015

This guideline replaces the 'Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation)' (EMA/CPMP/EWP/280/96 Corr*)

Keywords	***Modified release, prolonged release, delayed release, transdermal drug delivery systems (TDDS), bioequivalence, pharmacokinetics, biowaiver, in vitro dissolution, generics, oral, intramuscular and subcutaneous***

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EMA – LALA OIP

3.3 Regarding the evaluation of orally inhaled medicinal products, to what extent do plasma levels reflect bio-availability in the lung? January 2015

- „In case the absorption of the drug in the lung is very quick (e.g., tmax ≤ 5 min) and absorption occurs before the contribution of gastrointestinal absorption is significant (e.g., salbutamol/albuterol, salmeterol), **AUC0-30 min might be acceptable** as a surrogate for efficacy and AUC0-t for safety. Thus, in this case, one study without active charcoal blockade is sufficient.“

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers

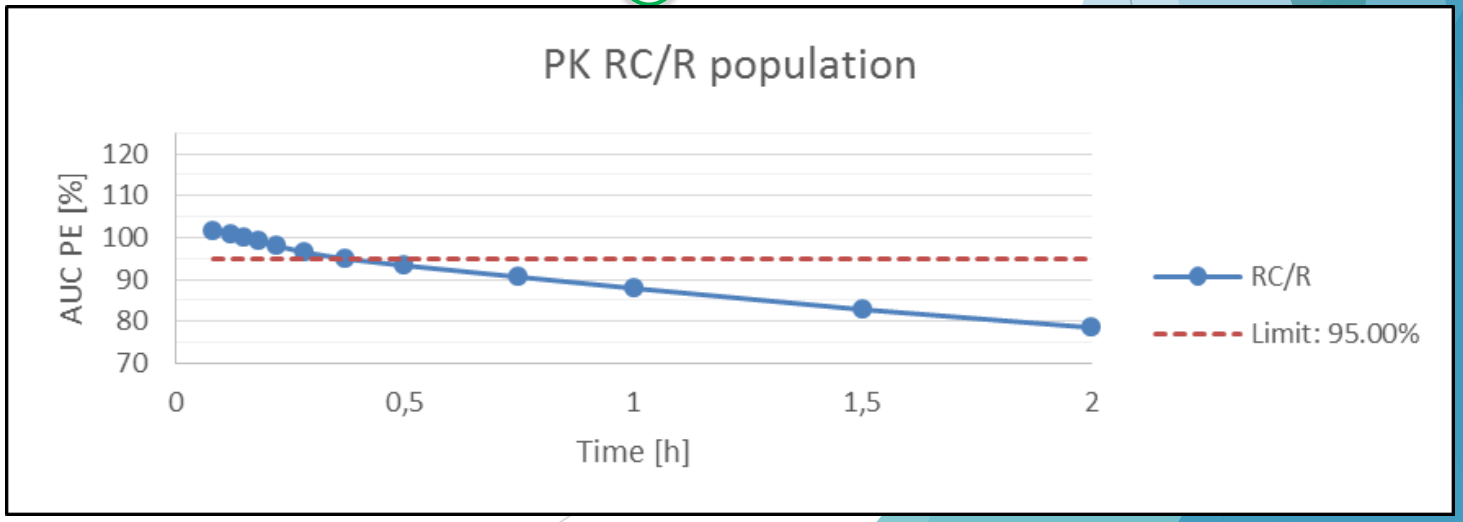
LALA OIP Validation of Truncated AUC

- Comparison reference w/ charcoal (RC) with w/o charcoal (R) of truncated AUC
- Quantification of difference between RC and R: Contribution GIT becoming significant (above 5%) between 0.37 (22min) - 0.5 h, and statistically significant from 0.5 h onwards

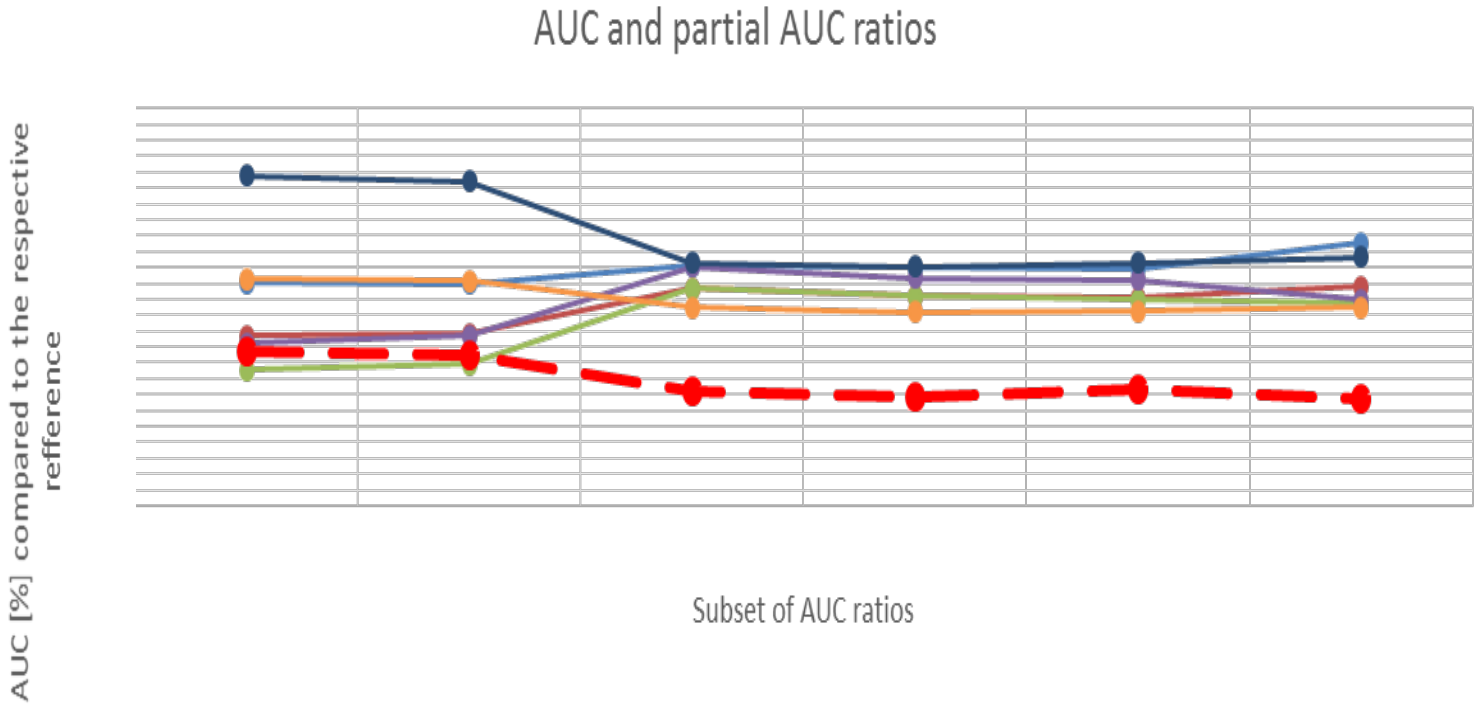
Formulation Dependent		Ln(AUC0.08)	Ln(AUC0.12)	Ln(AUC0.15)	Ln(AUC0.18)	Ln(AUC0.22)	Ln(AUC0.28)	Ln(AUC0.37)	Ln(AUC0.5)	Ln(AUC0.75)	Ln(AUC1)	Ln(AUC1.5)	Ln(AUC2)
RC/R	Time	0.08	0.12	0.15	0.18	0.22	0.28	0.37	0.5	0.75	1	1.5	2
	Ratio_%Ref_	101.70	100.89	100.05	99.18	98.13	96.66	94.93	93.31	90.66	87.84	82.84	78.43
	CI_90_Lower	93.68	93.79	93.34	92.75	91.98	90.77	89.26	87.84	85.47	82.88	78.28	74.19
	CI_90_Upper	110.40	108.52	107.24	106.06	104.70	102.94	100.97	99.12	96.16	93.09	87.67	82.91
	CV[%]	32.56	28.77	27.32	26.35	25.43	24.69	24.17	23.68	23.07	22.73	22.16	21.74

PK data corrected by 0.9492

- Proposal: truncated AUC0 – 0.5h (30min) well within EMA PK QndA



Impact of particles and GI tract absorption



- Evolution of pAUC over the time
- Charcoal study identified in red

IVIVC: AUC 0-20min

Full dataset

X L/min					
Reference		Test			
	R2		R2_total		R2_P1-P2
Stage 7	0,9999	FPD ≤5µm*/DD	0,6469	Stage 3	0,9906
<0,34 µm	0,9988	Presep	0,5727	FPD ≤5µm*	0,9904
ED	0,9911	MOC	0,5714	< 2,82 µm	0,9731
Throat	0,9756	FPD ≤3µm/DD	0,5236	FPD ≤5µm*/DD	0,9694
MOC	0,9699	Throat	0,5051	< 4,46 µm	0,9466
< 0,55 µm	0,9617	<0,34 µm	0,3304	Stage 5	0,9437
< 0,94 µm	0,9426	DD (NGI)	0,2616	FPD ≤3µm	0,9357
Stage 6	0,9412	ED	0,2403	< 0,94 µm	0,9325
Stage 5	0,9337	Stage 5	0,2160	< 1,66 µm	0,9266
FPD ≤3µm/DD	0,9219	< 8,06 µm	0,2086	FPD ≤3µm/DD	0,9248

Y L/min					
Reference		Test			
	R2		R2_total		R2_P1-P2
MMAD	0,9985	< 10,033 µm	0,8948	FPD ≤3µm*/DD	0,9154
FPD ≤3µm*/DD	0,9959	< 5,507 µm	0,8186	FPD ≤5µm*/DD	0,8883
< 1,165 µm	0,9939	Stage 3	0,6633	Stage 3	0,8774
FPD ≤3µm*	0,9935	MOC	0,6000	Stage 4	0,8695
Stage 6	0,9902	<0,446 µm	0,5795	FPD ≤5µm*	0,8674
< 0,701 µm	0,9833	Stage 7	0,5398	< 3,454 µm	0,8671
FPD ≤5µm*/DD	0,9794	FPD ≤3µm*/DD	0,5180	< 5,507 µm	0,8590
Stage 5	0,9757	FPD ≤5µm*/DD	0,5006	< 2,008 µm	0,8553
< 2,008 µm	0,9729	< 1,165 µm	0,4932	FPD ≤3µm*	0,8549
FPD ≤5µm*	0,9684	< 0,701 µm	0,4756	< 10,033 µm	0,8456

- No common correlation parameters for systemic absorption identified
- Confirmed for data set w/o o
- No correlation for other flows

IVIVC: AUC 20min-24h

Full dataset

X L/min						Y L/min					
Reference		Test				Reference		Test			
	R2		R2_total		R2_P1-P2		R2		R2_total		R2_P1-P2
DD (NGI)	0,9863	MOC	0,7094	Throat	0,4798	Stage 3	0,9664	< 10,033 µm	0,5172	Stage 2	0,2670
Stage 3	0,9412	Stage 1	0,4583	DD (NGI)	0,4252	Presep	0,8752	Throat	0,4597	Stage 5	0,2541
< 8,06 µm	0,8754	<0,34 µm	0,2384	ED	0,3654	ED	0,7944	Stage 1	0,3390	ED	0,2470
< 4,46 µm	0,8557	FPD ≤5µm*/DD	0,2156	Stage 5	0,3598	MOC	0,7875	< 5,507 µm	0,3235	Stage 4	0,1697
FPD ≤5µm*	0,7364	Presep	0,1972	< 2,82 µm	0,3563	Stage 2	0,4739	Stage 2	0,2418	FPD ≤3µm*	0,1626
Presep	0,7218	FPD ≤3µm/DD	0,1870	Stage 4	0,3546	Throat	0,4159	Stage 5	0,1858	< 2,008 µm	0,1611
< 2,82 µm	0,6980	Throat	0,1800	FPD ≤3µm	0,3513	<0,446 µm	0,3758	Stage 3	0,1553	FPD ≤5µm*	0,1596
Stage 4	0,6218	< 8,06 µm	0,1648	Stage 3	0,3502	< 0,701 µm	0,3160	< 1,165 µm	0,1389	FPD ≤3µm*/DD	0,1584
FPD ≤5µm*/DD	0,6006	< 0,55 µm	0,1057	FPD ≤5µm*	0,3484	Stage 6	0,2877	Presep	0,1343	MMAD	0,1573
FPD ≤3µm	0,5770	< 0,94 µm	0,1036	< 1,66 µm	0,3454	MMAD	0,1722	ED	0,1170	< 3,454 µm	0,1555

- No common correlation parameters for systemic absorption identified
- Confirmed for data set w/o o
- No correlation for other flows

IVIVC: AUC 0-20min ratios

Full dataset

X L/min				Y L/min			
Test/Reference				Test/Reference			
	R2_total		R2_P1-P2		R2_total		R2_P1-P2
FPD ≤3µm*/DD	0,7936	< 2,82 µm	0,9531	< 10,033 µm	0,8946	FPD ≤5µm*/DD	0,9561
FPD ≤5µm*/DD	0,7634	FPD ≤5µm*	0,9449	< 5,507 µm	0,8853	< 5,507 µm	0,8785
MOC	0,7374	Stage 5	0,9360	< 1,165 µm	0,8092	< 3,454 µm	0,8165
Throat	0,5807	FPD ≤3µm*	0,9284	<0,446 µm	0,7506	Stage 4	0,8049
Presep	0,5769	< 0,94 µm	0,9174	< 0,701 µm	0,7455	< 2,008 µm	0,7889
Stage 4	0,5150	< 1,66 µm	0,9161	FPD ≤3µm*/DD	0,7243	< 10,033 µm	0,7887
< 1,66 µm	0,4922	Stage 4	0,9129	Stage 6	0,7045	< 1,165 µm	0,7603
Stage 5	0,4797	FPD ≤3µm*/DD	0,9020	FPD ≤3µm*	0,6951	FPD ≤3µm*/DD	0,7530
FPD ≤3µm*	0,4795	FPD ≤5µm*/DD	0,8788	FPD ≤5µm*/DD	0,6835	Stage 3	0,6755
ED	0,4611	< 0,55 µm	0,8594	FPD ≤5µm*	0,6812	FPD ≤5µm*	0,6623

- Identified correlation parameters – ratios T/R for Y L/min
- < 5.507 µm
- < 10.033 µm

EMA – LALA GIT

4.3.3. Products acting locally in the intestine

- Partial AUC assessment can help to distinguish absorption caused by an early release and absorption from
- Reference to - Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1
  - Partial AUCs (early and late partial AUCs as defined by predefined, well justified cut-off points) should be used as primary PK endpoint in both SD and MD studies under fed and fasting conditions
  - Comparison of drug levels in faeces may be necessary in certain cases

EUROPEAN MEDICINES AGENCY
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18 October 2018
CPMP/EWP/239/95 Rev. 1, Corr.1*
Committee for Medicinal Products for Human Use (CHMP)

Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract†

Draft agreed by Gastroenterology Working Party and Quality Working Party	October 2016
Draft agreed by Pharmacokinetics Working Party	February 2017
Adopted by CHMP for release for consultation	23 March 2017
Start of public consultation	1 April 2017
End of consultation (deadline for comments)	30 September 2017
Agreed by PKWP	June 2018
Adopted by CHMP	18 October 2018
Date of coming into effect	1 May 2019

†This guideline is an addendum to the 'Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents' (CPMP/EWP/239/95).

*On page 4, section 3 EC regulations No. 1084/2003 and No. 1085/2003 have been replaced with (EC) No. 1234/2008.

Keywords	***Therapeutic equivalence, gastrointestinal, mouth, throat, locally applied and locally acting, in vitro, pharmacokinetic, equivalence, bioequivalence, guideline, CHMP***

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LALA - locally in the mouth and/or throat

- BE demonstrated among different dosage forms acting in mouth and throat
- Non-inferiority demonstrated using clinical efficacy study

Variable	Test product mg	% of reference value	90% CI	
$Ln(AUC_{2h})$	Dosage form B	99,90	88,50	112,76
$Ln(AUC_{2h})$	Dosage form C	84,05	74,47	94,87
$Ln(AUC_{1h})$	Dosage form B	94,73	81,35	110,30
$Ln(AUC_{1h})$	Dosage form C	66,12	56,78	76,99

- Some differences exist for pAUCs
- Differences of pAUCs more pronounced in case of absorption before GIT contribution

Variable	Test product mg	% of reference value	90% CI	
$Ln(AUC_{0.25h})$	Dosage form B	58,52	43,00	79,66
$Ln(AUC_{0.25h})$	Dosage form C	25,07	18,42	34,12
$Ln(AUC_{0.5h})$	Dosage form B	80,57	65,32	99,37
$Ln(AUC_{0.5h})$	Dosage form C	45,48	36,87	56,10

- Overall efficacy not in question – non-inferiority demonstrated
- Onset of action, correlation of PK/PD?

FDA - Product specific guidelines - pAUCs

FDA recommendations for pAUCs based on clinical relevance

- **Zolpidem**, Extended Release Tablets
  - SD fasting: AUC0-1.5 h, AUC1.5 h-t
  - Evaluation of the drug bioavailability responsible for the sleep onset and sleep maintenance phases
- **Methylphenidate Hydrochloride**, multiphasic modified-release formulation – IR/SR combination,
  - SD fasting: AUC0-3 (onset Tmax IR), AUC3-7 (school Tmax MR, AUC7-12 (effect duration – homework)
  - SD fed: AUC0-4, AUC4-8, AUC8-12,
- **Oxycodone** Extended Release Tablet, Capsule
  - SAFETY abuse by insufflation: Fasting, comparative nasal pharmacokinetic (PK) study with physically manipulated drug products
  - AUC0-3 hours and AUC0-4 hours as supporting data on top of the “traditional“ metrics

Note: only pAUC listed, other requirements listed in respective gdls

EMA - Product specific guidelines - pAUCs

- **Lanreotide acetate** LAI - draft
  - Waiver of MD: AUC0-t, AUC0-∞, Cmax, Cτ (concentration at the end of the dosing interval, i.e. day 28), **AUC0-168h, AUC168-672h and AUC672h-t**
- **Liposomal amphotericin B,** powder for dispersion for infusion – draft
  - partial AUCs (e.g. *liposomal amphotericin B*: AUC0-10h and AUC10-tlast; *non-liposomal amphotericin B*: AUC0-24h and AUC24-tlast)
- **Etonogestrel and ethinylestradiol** vaginal delivery system
  - AUC0-21days (approved dosing), AUC0-28days (efficacy maintained - risk mitigation)
- **Octreotide acetate** depot powder
  - Waiver of MD: AUC0-28days (dosing), AUC28-56d, Secondary AUC0-24h, Tlag, Cmax partial AUCs, Cmax initial release
- **Pegylated liposomal doxorubicin**
  - SD: additionally AUC0-48h, AUC48-last for encapsulated drug to ensure profile comparability

Note: only pAUC listed, other requirements listed in respective gdls

MR Long-acting Injectable

- Substantial FDA a EMA differences for demonstration of BE
- FDA requirements based on clear clinical justification vs EMA?

MD data - BE data set			
Dependent	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
Ln(Cmax)	94,95	87,49	103,05
Ln(Clast)	100,70	92,91	109,14
Ln(AUClast)	94,29	87,75	101,33
Ln(AUC0-72h)	91,31	84,35	98,83
Ln(AUC72-tau)	94,74	88,13	101,85
Ln(AUC0-7days)	90,32	83,69	97,49
Ln(AUC7-tau)	95,89	89,15	103,14
Ln(AUC0_Tmax)	90,15	83,51	97,32
Ln(AUCTmax_tau)	95,61	88,90	102,83
Ln(AUCfirst half)	91,74	85,24	98,75
Ln(AUCsecond half)	97,32	90,51	104,65

- DREAM - Harmonization of requirements for complex developments, e.g. in case of biosimilars

Conclusion - pAUCs

Development aspects

- Powerful tool for product performance evaluation
- Evaluation of rate of absorption of IR
- Evaluation of site specific absorption in case of LALA products
- Description of multiphasic release IR/SR formulations

Regulatory aspects

- **Use on case-by-case basis – ONLY if clinically relevant and justified**
- Truncation based on PK/PD relationship or efficacy/safety data for the drug under examination
- Higher sensitivity in detecting formulation differences and may be more variable
- Reference-scaling approach can be employed for BE evaluation

Thank you for your attention!

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