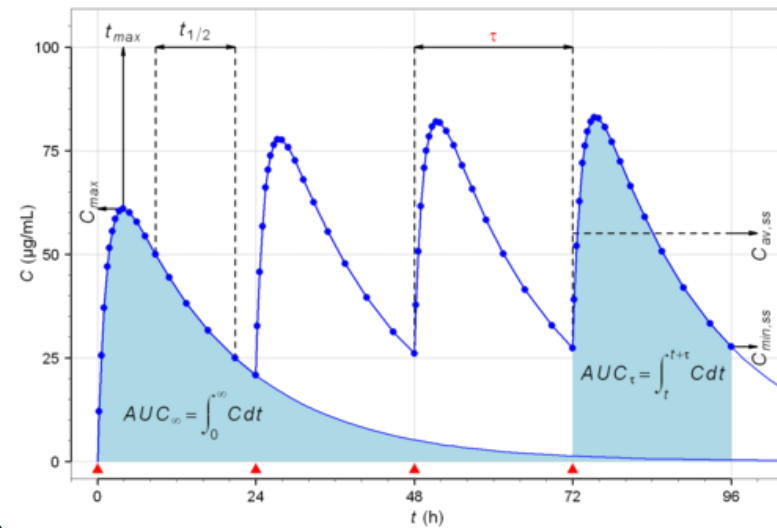


Complex developments: Long Acting Injectables, the role of partial AUCs

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BioBridges,
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This presentation reflects
personal views and opinions and
may not represent official point
of view of Pharmathen

Partial AUCs

- *Why introduced?*

Because in certain cases, AUC and $C_{\max}$ alone may not be adequate to identify formulation differences in early and/or late segments of the dosing interval.

- *How to implement?*

Follow the product specific guideline and/or predefine a **meaningful** cut off point

- *Are there implications?*

Inherited increased variability of *pAUCs* in some cases can lead to complicated or even unfeasible BE study designs

Melatonin product specific guideline

- Background/justification: Partial AUCs should be included as primary pK variables.
- A cut-off of 3 hours results in two approximately equal partial AUCs for both the fasted and the fed study and is thus a reasonable cut-off to characterise the shape of the plasma-concentration time curve and to determine the partial AUCs reliably.
- A different cut-off may be used, in particular for the fed study, if it is pre-specified in the protocol, adequately justified and characterises the shape of the plasma concentration-time curve.
- **The variability may be higher in the fed study, which should be considered in the design of the study.**

pAUCs in ICH M13A guideline

For orally administered IR drug products, BE can generally be demonstrated by measurement of rate and extent of absorption, i.e., C_{max} and AUC(0-t).

However, in some situations, C_{max} and AUC(0- t) may be **insufficient** to adequately assess the BE between two drug products, e.g., **when the early onset of action is clinically relevant.**

In these cases, an additional PK parameter, such as **area under the concentration vs. time curve between two specific time points (pAUC)** or t_{max}, may be applied. In the case of pAUC, it is typically evaluated from the time of drug administration until a predetermined time point **that is related to a clinically relevant pharmacodynamic measure.**

Additional *pAUC* requirements within EMA

For modified-release formulations, inclusion of *pAUC* is needed in case multiple dose studies are waived

In this case bioequivalence needs to be demonstrated for additional parameters representing the shape of the plasma concentration versus time curve in the single dose study (see also section 6.8.2). **An early partialAUC (0 – cut-off t) and a terminal partialAUC (cut-off t - t_{last}), separated by a predefined cut-off time point, e.g. the half of the dosage interval are recommended, unless otherwise scientifically justified.**

For multiphasic modified release products additional parameters to be determined include partialAUC, C_{max} and t_{max} in all phases. **The time point for truncating the partialAUC should be based on the pK profile for the e.g. IR and the MR parts respectively and should be justified and pre-specified in the study protocol.**

[Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms](#)

Product specific guidelines with *pAUC* requirements (EMA)

Product	pAUC in PSGs	Justification
Tadalafil	Tmax or partial AUC	Per ICH M13A
Ibuprofen IR	Tmax or partial AUC.	Per ICH M13A
Paracetamol IR	Tmax or partial AUC.	Per ICH M13A
Methylphenidate MR	Fasting: AUC _{0-3h} , AUC _{3-24h} Fed: AUC _{0-4h} , AUC _{4-24h}	To ensure equivalent onset response
Melatonin PR 2 mg	AUC _{0-3h} and AUC _{3h-t} .	To characterise the shape of the plasma-concentration time curve
Budesonide Gastroresistant caps	AUC _{4-8h} , AUC _{8-24h} [Secondary parameter: AUC _{0-4h}]	Early partial AUC0-4h reflects absorption before site of action. Two late partial AUCs to better characterise the shape of the plasma concentration
Liposomal amphotericin B	AUC _{0-10h} and AUC _{10-tlast}	To characterise distribution and elimination processes of liposomes
PEGylated liposomal doxorubicin	AUC _{0-48h} and AUC _{48-tlast}	To ensure profile comparability of the encapsulated drug
Octreotide acetate depot	AUC _{0-28d} , AUC _{28-56d} [Secondary parameter: AUC _{0-24h}]	To waive the multiple dose study
Lanreotide acetate prolonged release	AUC _{0-168h} , AUC _{168-672h} and AUC _{672h-t}	To waive the multiple dose study

Additional *pAUC* requirements within FDA

When the early onset of action is clinically relevant or for certain products in which the different phases of release correspond to a clinical effect (ie on case-by-case basis)

[Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under](#)

Long-acting injectables PSG with *pAUC* requirements

Leuprolide	Octreotide	Norethindrone acetate Injectable depot
Exenatide	Naltrexone	Afamelanotide Subcutaneous Implant
Buprenorphine	Triptorelin pamoate	Goserelin Acetate Implant

... but is the inclusion of partial AUCs in bioequivalence studies always justified or in some cases, the drawbacks can outweigh the benefits?



LAIs: Breaking Standard Rules

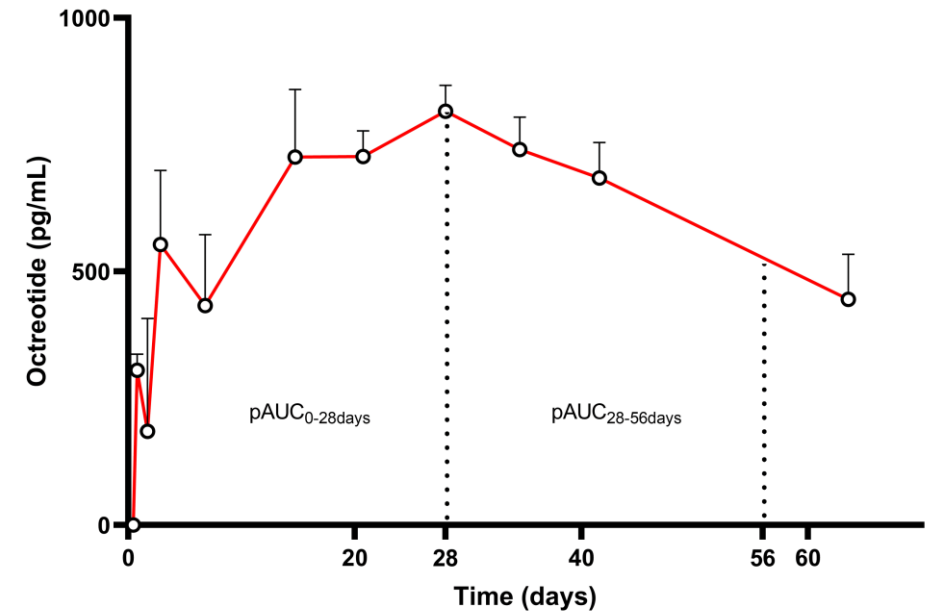
Administered over
long-time intervals
(1, 3, 6 months)

Have complex
multiphasic PK
profiles

Not always clear
pK/pD
relationships.

Case study: Octreotide LAI

- Extended-release injectable suspension, administered **once per month** intramuscularly
- Used for the treatment of acromegaly and neuroendocrine tumors (GEP-NETs)
- EMA's and FDA's PSGs are similar, recommending a **single dose parallel** pk study in healthy volunteers, with primary endpoints being AUC_t , $AUC_{0-\infty}$, C_{max} , plus **pAUC_{0-28d}**, **pAUC_{28-56d}**
- EMA's recommends also C_t as a primary parameters and AUC_{0-24h} , t_{lag} , C_{max} per partial AUC and C_{max} initial release, as secondary parameters



Case study: Octreotide LAI

❑ Three main release phases

- the initial release of surface-adsorbed octreotide (burst phase),
- the polymer erosion phase (release happens through pore diffusion, biodegradation, osmotic swelling, and ionic interactions) and
- the terminal erosion phase which leads to complete drug release through the full biodegradation of the polymer

❑ pK/pD is established

- ❑ Based on pK modeling, sub-populations exists in the population pK curve. In this case, the more the pAUCs the more the random variability with limited clinical relevance

	Intersubject variability
AUC_t	34,6%
$AUC_{0-\infty}$	34%
$pAUC_{0-28d}$	46,6%
$pAUC_{28-56d}$	36,9%

Public assessment report CZ/H/0802/003

Octreotide LAI: pK study design considerations

Parallel study design*

	95%	92%	90%
30%	76	112	156
35%	102	148	208
40%	130	190	266
45%	160	236	332
47%	174	256	358

duration of clinical part ~2,5months/subject

Crossover study design*

	95%	92%	90%
20%	19	27	37
25%	28	40	56
30%	39	56	79
35%	52	75	105

a. duration of clinical part ~7months/subject

b. is it safe to administer twice in healthy?

c. are those numbers feasible for patients in an orphan indication?

d. is it acceptable to wash out patients?

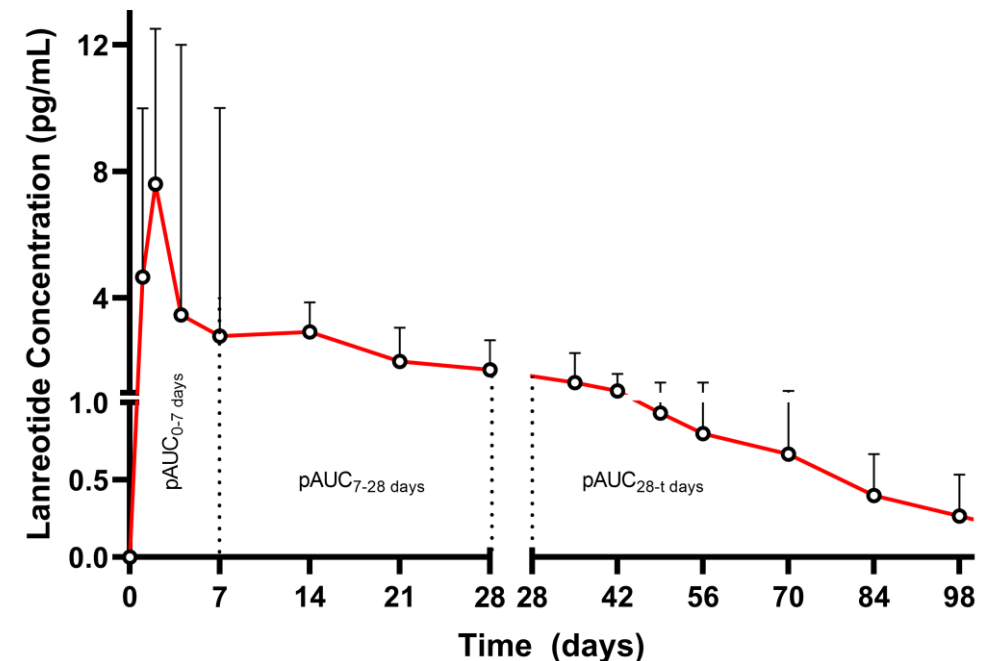
e. if you go for direct switching, how you will handle the potential carry over

- If you must power the study only for total AUC (total ~CV 35%, intraCV ~20%)
- If you must power the study for pAUC_{0-28d} (total CV >45%, intraCV ~30%)

* Excluding dropouts

Case study: Lanreotide LAI

- Extended-release injectable depot, administered **once per month** subcutaneously
- Used for the treatment of acromegaly and neuroendocrine tumors (GEP-NETs)
- EMA's and FDA's PSGs are offering the option of a biowaiver approach based on a physicochemical sameness exercise
- If biowaiver cannot be justified, EMA is recommending a **single dose parallel** pk study in healthy volunteers with primary PK parameters being AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , C_T , **AUC_{0-7d} , AUC_{7-28d} and AUC_{28d-t}** (to compensate for the waiver of the multiple dose study)
- No pAUCs are recommended by FDA



Case study: Lanreotide LAI

- The release profile of lanreotide is characterized by an initial burst release on the first day of administration that determines the C_{max}, followed by a sustained release
- Blood concentration levels above a threshold safeguards efficacy
- Clinically relevant individual release phases are difficult to distinguish within the dosing interval

Intersubject variability	
AUC _t	29.4%
AUC _{0-7d}	52,71
AUC _{7-28d}	64,11
AUC _{28d-t}	108,9

Astruc et al, J.Clin.Pharmacol. 2005

Lanreotide LAI: pK study design considerations

Parallel study design

	95%	90%
30%	76	156
50%	194	400
60%	266	550
110%	684	1416

Inter-subject variability



*duration of clinical part ~4months/subject

Crossover study design

	95%	90%
20%	19	37
40%	66	134
70%	173	357

Intra-subject variability



*duration of clinical part
~12months/subject

*is it safe to administer twice in healthy?
*are those numbers feasible for patients?

Fully replicate study design

	95%	90%
20	10	19
40	18	27
70	30	40

Intra-subject variability



*duration of clinical part
~28months/subject

*is it safe to administer 4 times in healthy?
*are those numbers feasible for patients?

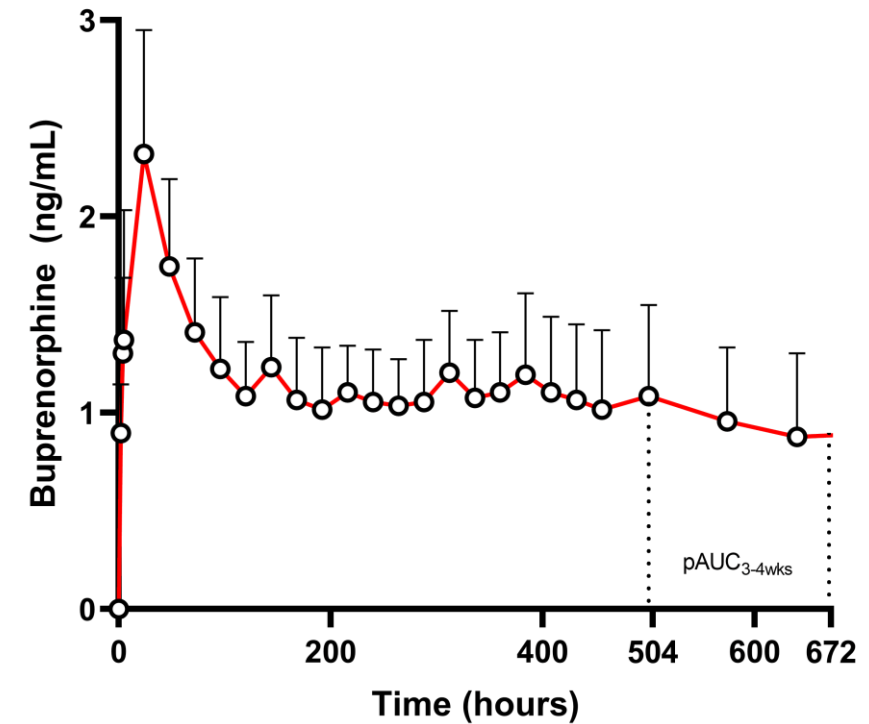
- If you must power the study for total AUC (total CV ~30%, intraCV ~20%)
- If you must power the study for AUC_{28d-t} (total CV ~110%, intraCV ~70%)

**Which
alternative
is the most
viable?**

* Excluding dropouts

Case study: Buprenorphine LAI

- Extended-release injectable suspension, administered once per month
- Used for the treatment of opioid addiction
- There is no PSG in EU
- FDA's PSG recommends, a **single dose parallel** pk study in Patients with Opioid Use Disorder, with primary endpoints being C_{max} , AUC_{0-t} and **pAUC_{3-4 weeks}**,
 - - C_{max} , to confirm a comparable pK profile during the initial absorption phase and
 - - pAUC from 3 to 4 weeks (pAUC_{3-4 weeks}) as a surrogate measure of the average plasma concentration over the final week



Case study: Buprenorphine LAI

Applying EMAs general recommendations the cut-off points should be either

- at the half of the dosing interval (ie **pAUC_{0-14d}** and **pAUC_{14-28d}**)
- or
- based on the PK profile of the product (buprenorphine shows a clean-cut initial burst completed at day 3 ie **pAUC_{0-3d}** and **pAUC_{3-28d}**)

	Intersubject variability
AUC _t	34,4%
pAUC _{0-3d}	59.51%
pAUC _{0-14d}	37.14 %

Data from Albayaty et al, 2017

Buprenorphine LAI: pk study design consideration

Parallel study design

Inter-subject variability		95%	90%
35%		102	208
40%		130	266
50%		194	400
60%		266	550

*duration of clinical part ~3 months/subject

Crossover study design

Intra-subject variability		95%	90%
25%		28	56
35%		52	105
40%		66	134

*duration of clinical part ~8 months/subject

Fully replicate study design

Intra-subject variability		95%	90%
25		14	28
35		19	32
40		18	27

*duration of clinical part ~18months/subject

*is it ethical to wash out patients so many times?

- If you must power the study for total AUC (total CV ~35%, intraCV ~25%)
- If you must power the study for $pAUC_{0-3d}$ (total CV ~60%, intraCV ~40%)

Study population, patients....

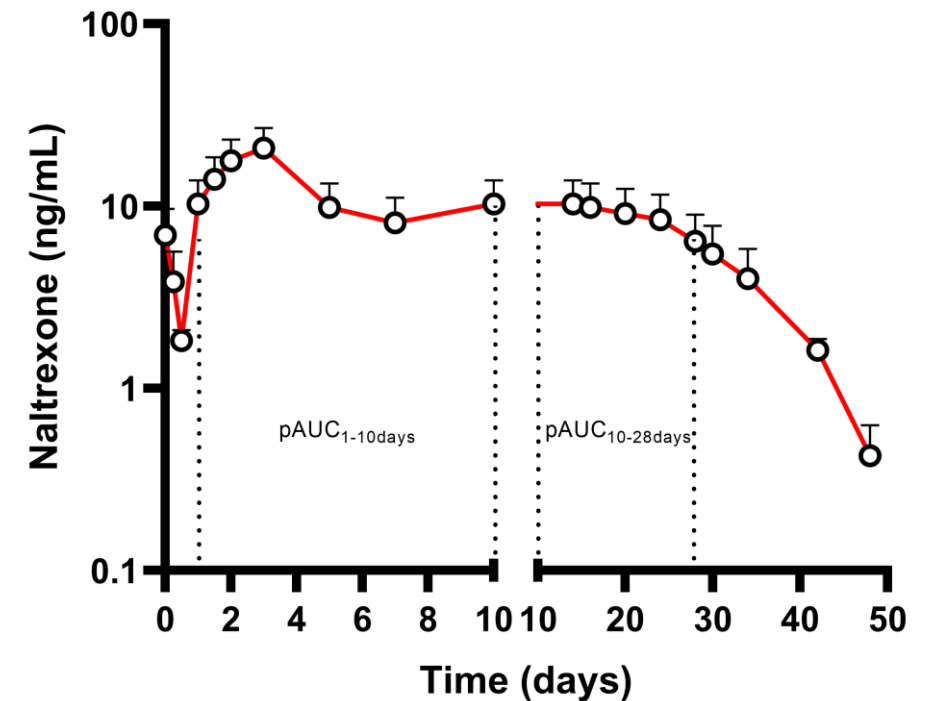
- with moderate or severe opioid use disorder
- already treated with a transmucosal buprenorphine-containing product
- a washout period may employed before administration
- confined at the clinical unit during the washout period and until their opioid use disorder and withdrawal symptoms are appropriately managed
- **Where those patients are being treated?**

Which alternative is the most viable?

* Excluding dropouts

Case study: Naltrexone LAI

- ❑ Extended-release injectable suspension, administered once per month intramuscularly
- ❑ Used for the treatment of alcohol dependence and prevention of relapse following opioid detoxification
- ❑ The product is not marketed in EU
- ❑ FDA's PSG recommends **a single dose parallel** pk study in healthy volunteers, with primary endpoints being C_{max} , AUC_{0-inf} , **$pAUC_{1-10\text{ days}}$** and **$pAUC_{10-28\text{ days}}$**



Data from Albayaty et al, 2017

Case study: Naltrexone LAI

- ❑ A clear pK/pD relationship is not defined
- ❑ After IM injection, naltrexone plasma concentration peaks at 2 h, and then again 2–3 days later. From day 14, concentration slowly declines, retaining measurable levels for greater than 28 days.

Intersubject variability	
AUC	7,7%
pAUC _{1-10d}	39,64%
pAUC _{10-28d}	45,22 %

Extraction from Dunbar et al, 2006

Naltrexone LAI: pk study design considerations

Parallel study design

Inter-subject
variability



	95%	90%
15%	22	42
40%	130	266
45%	160	332

*duration of clinical part ~2 months/subject

Crossover study design

Intra-subject
variability



	95%	90%
15%	12	22
30%	39	79

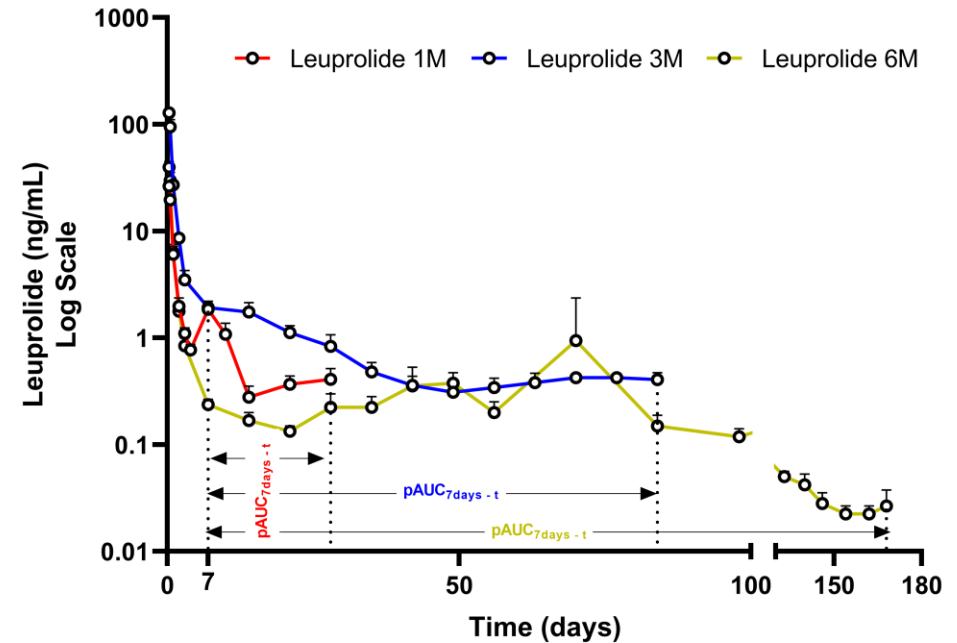
*duration of clinical part ~5months/subject

- If you must power the study for total AUC (total CV ~10%, intraCV ~10%)
- If you must power the study for $pAUC_{10-28d}$ (total CV ~45%, intraCV ~30%)

* Excluding dropouts

Case study: Leuprolide LAI

- Available as varying LAI formulations for IM and/or SC administration, such as ready-for-use implants, ampoules, or vials with powder and solvent for prolonged-release suspension (or solution) for injection, administered once per 1, 3/4, or 6 months
- Used for precocious puberty in children, endometriosis and advanced prostate cancer



Case study Leuprolide LAI

- The release of Leuprolide is multiphasic with an initial burst, a lag phase and a plateau phase.
- This multiphasic pK profile is linked to efficacy.
- Applying EMAs general recommendations the cut-off points for partial AUCs should be either at the half of the dosing interval or you have to choose based on the pk profile (**3 partial AUCs**)
- FDA recommends only one partial, **AUC_{7days-t}**

Intersubject variability	
AUC _t	20%
pAUC _{24h-t}	19,59%
pAUC _{48h-t}	19,07%
pAUC _{72h-t}	18,34%
pAUC _{5d-t}	60,88%
pAUC _{7d-t}	62%

Leuprolide LAI: pk study considerations

Parallel study design

Intra-subject variability



	95%	90%
20%	36	72
40%	130	266
60%	266	550

- a. duration of clinical part ~1 month per subject
- b. Recruitment rate <1 patients/site/month

**Which
alternative
is the most
viable?**

Crossover study design

Inter-subject variability



	95%	90%
15%	12	22
30%	39	79
40%	66	134

- a. is it safe to administer 2 times in healthy?
- b. Where those patients are located
- c. is it acceptable to wash out cancer patients?
- d. if you go for direct switching, how you will handle the potential carry over
- e. Can you plan for 20+ blood samples per study period (40+ in total)

Fully replicate study design

Inter-subject variability



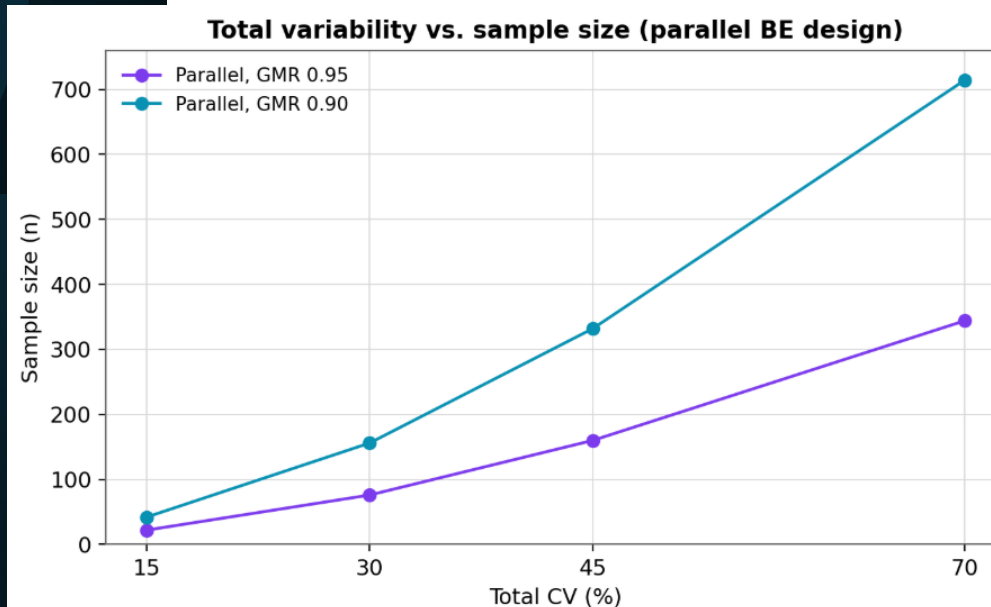
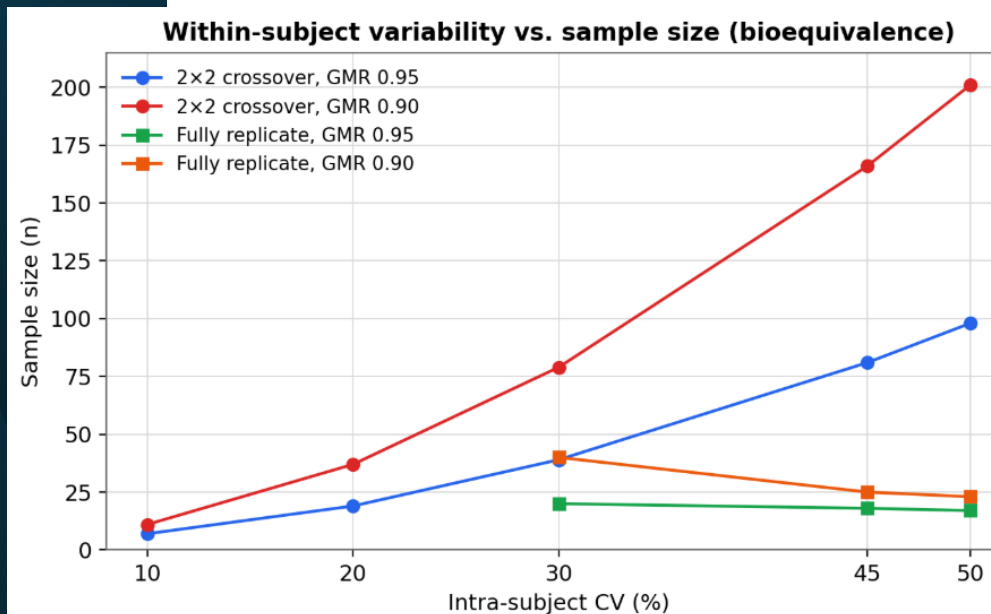
	95%	90%
15%	6	17
30%	20	28
40%	27	41

- a. is it safe to administer 4 times in healthy?
- b. Where those patients are located
- c. is it acceptable to wash out cancer patients?
- d. if you go for direct switching, how you will handle the potential carry over
- e. Can you plan for 20+ samples per period (80+ in total)

- If you must power the study for total AUC (total CV ~20%, intraCV ~15%)
- If you must power the study for pAUC_{7days-t} (total CV ~60%, intraCV ~40%)

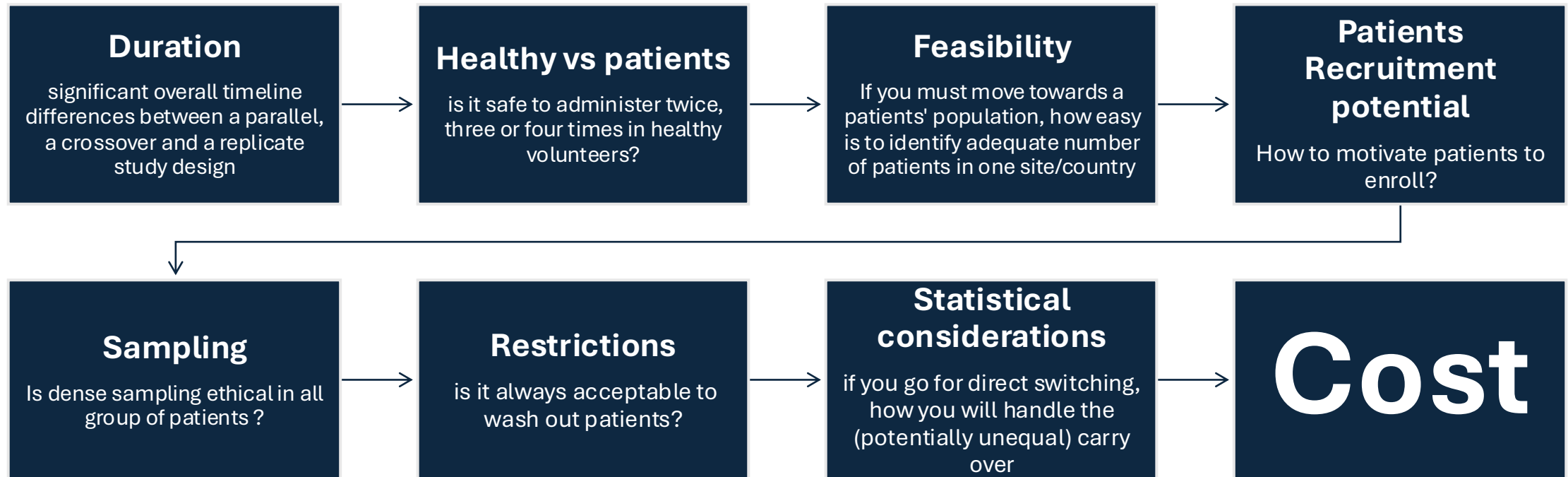
* Excluding dropouts

The Two Faces of Variability: Size and Design



Study design		No of subjects
Parallel study, total CV =45%	GMR 0.95	160
	GMR 0.90	332
2x2 crossover, within subjects CV=31%	GMR 0.95	41
	GMR 0.90	84
Fully replicate Within subjects CV=31%	GMR 0.95	19
	GMR 0.90	38

High Variability? Forget Simple.



Thank you

Tsakiridou G, Angelerou MFG, Efentakis P, Margaritis A, Papanastasiou AM, Kalantzi L.

Partial AUCs in Long-Acting Injectables: Rationale, Challenges, Variability, Usefulness, and Clinical Relevance

Pharmaceutics **2025**, 17(1), 21