# M13 and PKWP Q&A from the perspective of generic DPI development

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# Mandatory disclaimer:

- This presentation represents the author’s personal opinion and does not necessarily represent the policy or recommendations of Zakłady Farmaceutyczne Polpharma S.A.

# M13 and PKWP Q&A from the perspective of generic DPI development

To be discussed

- PKWP Q&A: inhaled products & charcoal study waiver
  - Eligibility for waiver case studies
    - Decision tree for charcoal waiver
    - Model substances for charcoal waiver justification
    - Validation of charcoal blockade
- ICH M13 (A and following)
  - Outliers and exclusion of data
    - 1st point Cmax
    - Low exposure
    - Justified outliers? Flagged extreme values? Proven by route-couse analysis / Clinical documentation findings? Sensitivity analysis?
  - Non-replicate vs. partial replicate vs. fully replicate studies
    - Reliability of point estimate vs. calculated power

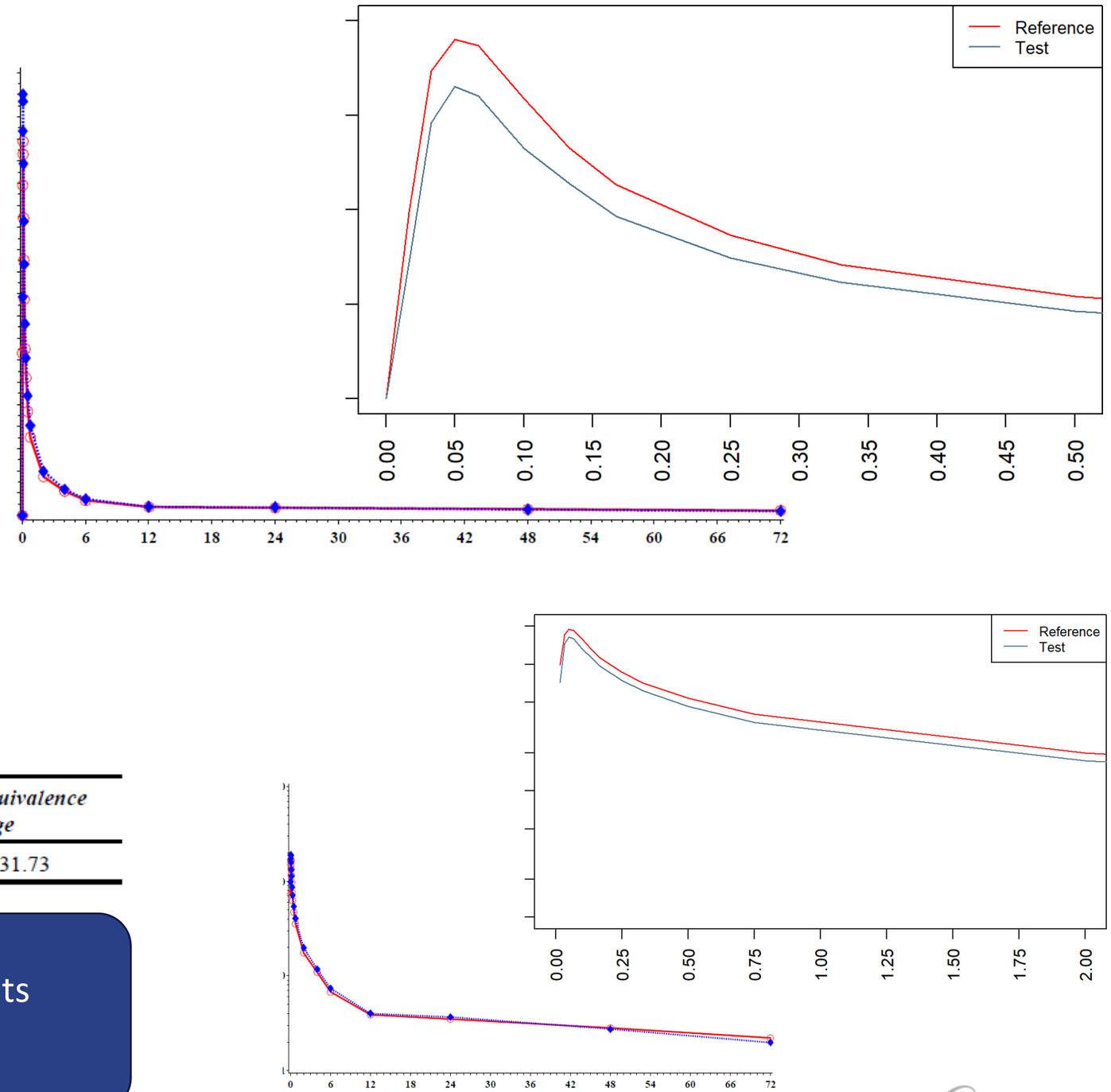
# Charcoal or not charcoal? #1

## Substance #1 BE results:

| *Parameter* | *Contrast* | *Ratio (%)* | *90% Confidence Interval* | *Intra-Sbj CV(%)* |
|---|---|---|---|---|
| **$AUC_t$** *(hr*pg/mL)* | **A vs B** | 94.76 | 89.09 - 100.79 | 20 |
| **$AUC_{inf}$** *(hr*pg/mL)* | **A vs B** | 108.33 | 97.62 - 120.22 | 31 |
| **$C_{max}$** *(pg/mL)* | **A vs B** | 90.04 | 81.04 - 100.05 | 35 |
| **$AUC_{0\text{-}30min}$** *(hr*pg/mL)* | **A vs B** | 86.72 | 79.89 - 94.14 | 27 |

| *Parameter* | *Intra-Subject-within-Reference CV (%) B1 vs. B2* | *Wider Bioequivalence Range* |
|---|---|---|
| **$C_{max}$** | 37.49 | 75.91 - 131.73 |

Imaging having received such study results
Success or not yet?



# Charcoal or not charcoal?

## Partial AUC0-30min as a surrogate to clinical efficacy

- GL text

297 ***2.1.8.3 Early Exposure***

298 For orally administered IR drug products, BE can generally be demonstrated by measurement of
299 rate and extent of absorption, i.e., $C_{max}$ and $AUC_{(0-t)}$. However, in some situations, $C_{max}$ and
300 $AUC_{(0-t)}$ may be insufficient to adequately assess the BE between two products, e.g., when the
301 early onset of action is clinically relevant. In these cases, an additional PK parameter, such as area
302 under the concentration vs. time curve between two specific time points (pAUC), may be applied.
303 This pAUC is typically evaluated from the time of drug administration until a predetermined time-
304 point that is related to a clinically relevant pharmacodynamic measure. Samples should be spaced
305 such that the pAUC can be estimated accurately.

Partial AUC 0-30mins is more variable than AUC72/t, highly influenced by the variable Cmax, if Cmax estimation is biased – AUC0-30min is also biased when we have 1st point Cmax

Substance-specific?

# Charcoal or not charcoal?

## PKWP Q&A on use of active charcoal and truncated AUCs

*Use of active charcoal and truncated AUCs*

For some inhaled medicinal products, the contribution of intestinal absorption to systemic exposure is negligible (5%) and a single dose PK study without charcoal can be used for both efficacy and safety comparisons. Reasons for the negligible contribution include poor intestinal absorption (e.g., chromoglycate, nedocromil), or an extensive first-pass metabolism (e.g., beclomethasone, fluticasone, mometasone, ciclesonide). For drugs with significant oral bioavailability (e.g., budesonide, formoterol, salmeterol), a PK study with active charcoal is necessary to assess efficacy, and a study without charcoal is used to assess safety. The charcoal blockade needs to be validated to demonstrate that oral contribution to total bioavailability is negligible. In case the absorption of the drug in the lung is very quick (e.g., $t_{max} \leq 5$ min) and absorption occurs before the contribution of gastrointestinal absorption is significant (e.g., salbutamol/albuterol, salmeterol), $AUC_{0-30}$ 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.

To be noted, most respiratory medicinal products are now being approved in the EU based on PK studies (e.g., nasal sprays of mometasone in suspension; pMDI in suspension of salbutamol, salmeterol, fluticasone and salmeterol/fluticasone; and DPI of salmeterol/fluticasone).

23 February 2017
EMA/CHMP/267194/2016

Update of the GL on Clinical requirements to OIP products is pending, draft may be released any time soon?

How am I understanding this?

Other potential metrics?
Another Pandora's box opened: $T_{max}$ comparison ☺

# Charcoal or not charcoal?

## Current OIP Guideline:

23 February 2017
EMA/CHMP/267194/2016

### 6.1.1 Pharmacokinetic studies

A pharmacokinetic study designed to assess pulmonary deposition, has to be able to exclude absorption of the active moiety from the gastrointestinal tract (for example by using charcoal blockade). A pharmacokinetic study may be used for determination of pulmonary deposition but may also investigate systemic safety. In the investigation of systemic safety total systemic exposure has to be measured in the intended patient population and therefore the study must include the measurement of that amount of the active moiety absorbed through the lung and the gastrointestinal tract.

However it may be possible for substances with negligible gastrointestinal absorption that the pharmacokinetic study designed to assess pulmonary deposition may be sufficient in the assessment of therapeutic equivalence.

In accordance with the standard accepted methods of assessment of bioequivalence the maximum concentration ($C_{max}$), the area under the curve (AUC) and the time to $C_{max}$ ($T_{max}$) should be compared. Equivalent pulmonary deposition and equivalent systemic safety of two inhaled products may be concluded if the 90 % confidence interval for each parameter lies within the acceptance range of 0.8 to 1.25. However, in some circumstances, for example, for active substances with a narrow therapeutic window, the 90% CI may require tighter limits when assessing systemic safety. Conversely, for products with high variability it may be acceptable if certain conditions are satisfied to widen the acceptance range for $C_{max}$ to 0.75 to 1.33 (see CHMP/EWP/QWP/1401/98 Rev.1 for further details).

If pharmacokinetic studies are carried out in children for the assessment of systemic safety the active substance should be measured in plasma.

Update of the GL on Clinical requirements to OPI products is pending, draft may be released any time soon?

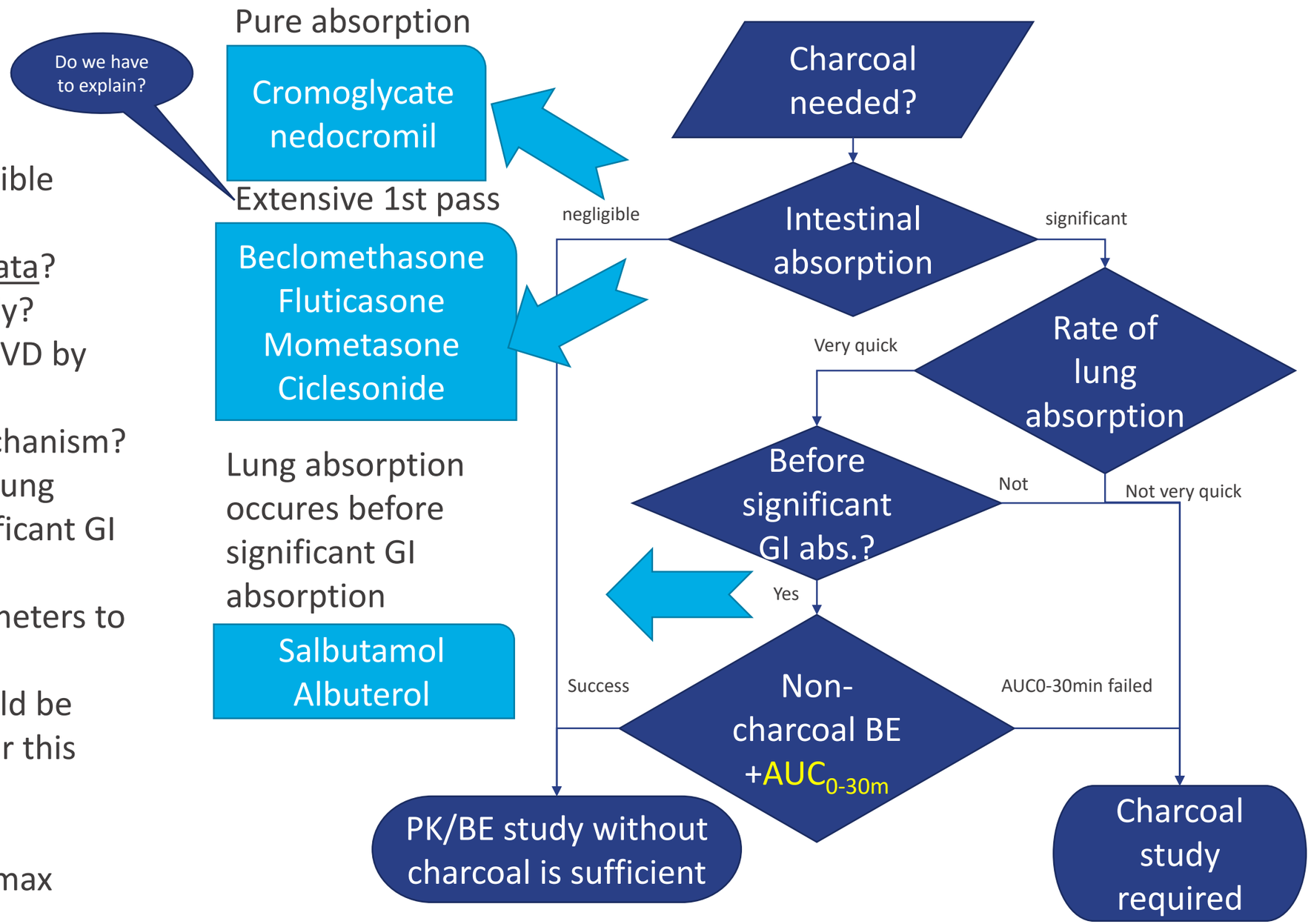
How am I understanding this?

Other potential metrics?
Another Pandora's box opened: $T_{max}$ comparison ☺

# Charcoal waiver

## Open questions

- Is this understanding correct?
- How should we prove a ‚negligible intestinal absorption' (5%)?
  - Absolute bioavailability data?
  - Originator's charcoal study?
    - 10% difference for HVD by chance
- Do we have to explain the mechanism?
- How to prove that ‚very quick lung absorption occurs before significant GI absorption'?
  - Will similarity of PK parameters to salbutamol be sufficient?
- Why AUC0-30min? Study should be powered to demonstrate BE for this parameter.
  - Variable parameter
  - Biased due to 1st point Cmax observations



# Charcoal waiver #1

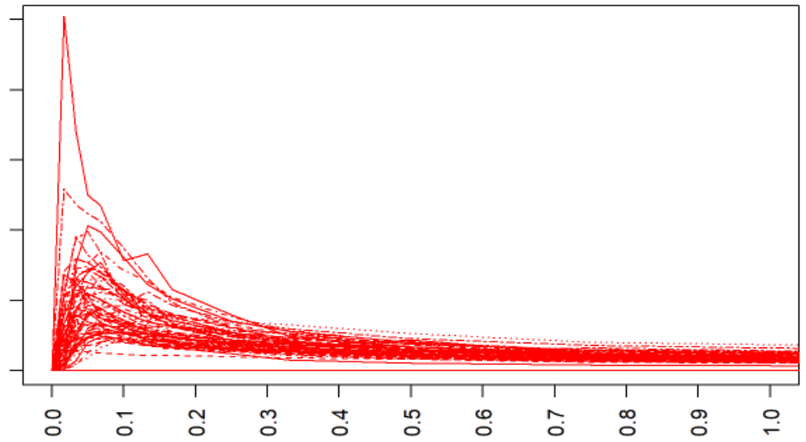
## Examples

### Substance 1

- Absolute oral bioavailability ~3% (oral vs. I.V. administration) reported for oral tablets formulation
- Originator estimated 5% oral bioavailability
- Originator [SmPC!] reports ~10% difference in bioavailability between DPI inhalation without charcoal and DPI inhalation with charcoal blockade
- Intra-subject CV for $AUC_{t/72h}$ is moderate (20-25%)
- Based on data on oral bioavailability – substance has a negligible absorption.
- Do we need to report AUC0-30 in non-charcoal bioequivalence study?
- Do we need to perform charcoal study?
- OK!

### Substance 2

- Absolute oral bioavailability is around 10%. Median $T_{max}$ after oral administration is 45 minutes
- Originator reports [SmPC] median $T_{max}$ at 5 minutes, but post-dose PK sampling started only at 5 minutes post-dose
- Intra-subject CV for $AUC_{t/72h}$ is moderate (20-25%)
- Substance has a very quick lung absorption with median $T_{max}$ about 2 minutes and a lot of 1st point $C_{max}$ at 1 minute sample.
- Charcoal waiver is still possible based on $AUC_{0-30}$.
- But study should be powered to demonstrate BE on this parameter and due to 1st point $C_{max}$ it may be biased, expect differences around 15%!
- Does it make sense?




Same substance – different set of literature data

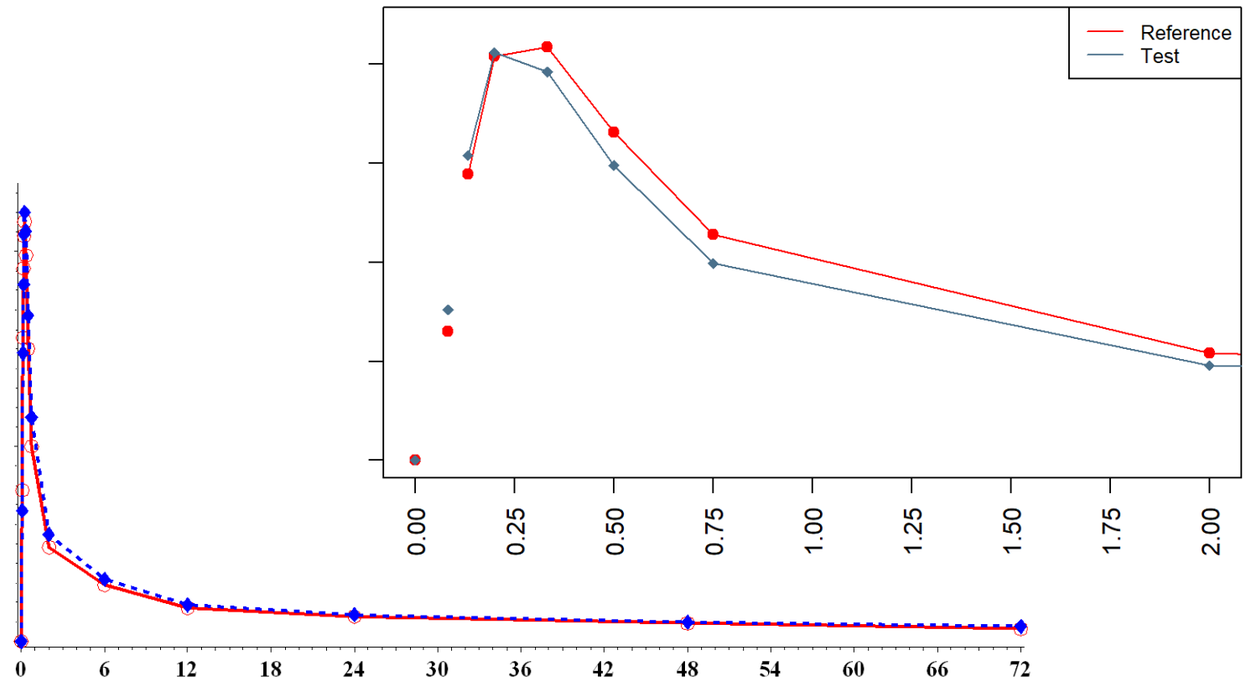
If we convince assessor that true absolute bioavailability is 3% (less than 5%) – no problem!

If not – suddenly problematic BE outcome for AUC0-30min becomes a problem

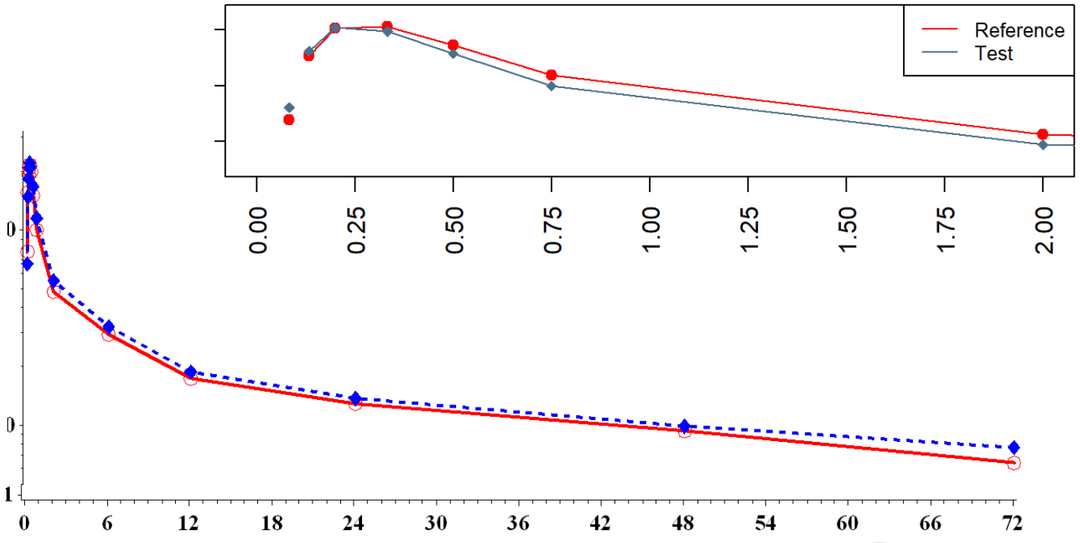
# Charcoal or not charcoal #2

BE results:

| Parameter | Contrast | Ratio (%) | 90% Confidence Interval | Intra-Sbj CV(%) |
|---|---|---|---|---|
| $AUC_{72}$ (hr*pg/mL) | A vs B | 90.81 | 87.83 - 93.90 | 13 |
| $C_{max}$ (pg/mL) | A vs B | 97.76 | 94.58 - 101.05 | 13 |
| $AUC_{0\text{-}30min}$ (hr*pg/mL) | A vs B | 97.96 | 94.78 - 101.25 | 13 |




| Parameter | Intra-Subject-within-Reference CV (%) B1 vs. B2 | Wider Bioequivalence Range |
|---|---|---|
| $C_{max}$ | 15.17 | N/A |




Successful in non-charcoal study!
Do we need to perform charcoal one?

# Charcoal waiver #2

## Examples

### Substance 3

- Absolute oral bioavailability is about 25%. Oral absorption is definitely non-negligible.

- $T_{max}$ after oral intake 1.8-3 h
- $T_{max}$ after inhalation 13 min (0.22h)
- Can we assume that pulmonary absorption occurs before the contribution of GI absorption takes place?

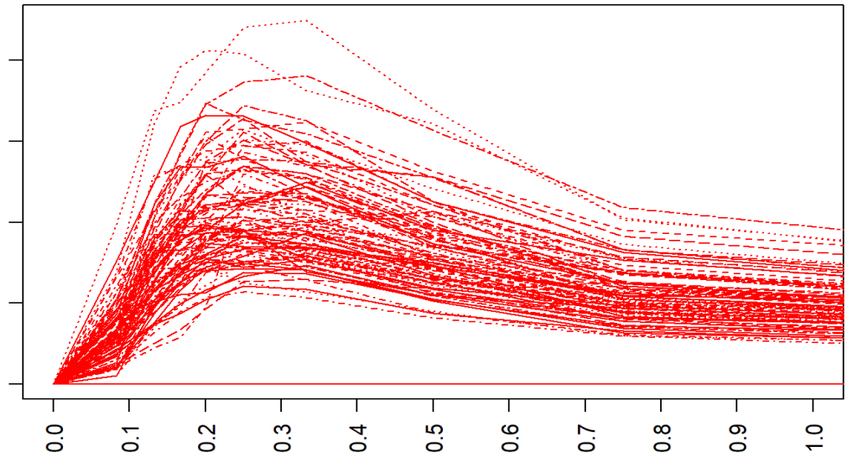
Salbutamol

### Substance 4

- Absolute oral bioavailability is about 25%. Oral absorption is definitely non-negligible.

- $T_{max}$ after oral intake 1.75-2.5 h
- $T_{max}$ after inhalation 12 min (0.2h)
- Can we assume that pulmonary absorption occurs before the contribution of GI absorption takes place?

Mystery drug #2




Good news?
Low ISCV
Maybe a less unpredictable study?
Still may fail by chance
Waiting for the results!

# Bonus questions for charcoal study

Validation of charcoal blockage procedure / study

Charcoal studies history
Methodology largely developed by Astra
Most commonly used charcoal granules brand: Carbomix (availability?)

- Impossible question in deficiency letter?
- In order to validate the procedure you must present study data with and without charcoal to demonstrate that charcoal blockade works for substance in question – perform at least 2 studies??
- Literature validation? Astra's publications since 1990s
- Choice of charcoal product?
- Charcoal administration timepoints vs. PK timepoints?
- Mouth rinse/swish after charcoal administration?
- Dose, Number and Timepoints for charcoal administration? = no single approach


necessary to assess efficacy, and a study without charcoal is used to assess safety. The charcoal blockade needs to be validated to demonstrate that oral contribution to total bioavailability is negligible. In case the absorption of the drug in the lung is very quick (e.g.,

# Issues of very rapid absorption

## Influence of 1st point Cmax

| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
|---|---|---|---|---|---|---|---|
| 1 | ABAB | A | 3 | 0.02 | 699.0 | 74.41000 | 308.34 |
| 1 | ABAB | B | 2 | 0.02 | 274.0 | 35.87000 | 91.88 |
| 1 | ABAB | B | 4 | 0.02 | 1010.0 | 113.80000 | 375.90 |

| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
|---|---|---|---|---|---|---|---|
| 4 | BABA | A | 2 | 0.02 | 112.0 | 32.17 | 314.06 |
| 4 | BABA | A | 4 | 0.07 | 116.0 | 35.53 | 302.06 |
| 4 | BABA | B | 1 | 0.02 | 114.0 | 36.28 | 316.14 |
| 4 | BABA | B | 3 | 0.05 | 94.3 | 32.28 | 321.78 |

| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
|---|---|---|---|---|---|---|---|
| 30 | ABAB | A | 1 | 0.04 | 189 | 40.98 | 262.09 |
| 30 | ABAB | A | 3 | 0.03 | 203 | 42.37 | 300.57 |
| 30 | ABAB | B | 2 | 0.02 | 519 | 91.37 | 375.64 |
| 30 | ABAB | B | 4 | 0.03 | 133 | 37.34 | 310.24 |

1st point Cmax

Statistically detected outlier

- 6 observations with Cmax occurring at first post-dose sampling point out of 118 total observations (~5%) have been detected
- One of 1st point Cmax observations is also a red flag based on outlier detection analysis – lower than expected Reference absorption
- **Exclusion of 1st point $C_{max}$ observations significantly reduced within-Reference ISCV**
- **$C_{max}$ – BE conclusions not changed**
- **$AUC_{0-30min}$ passes BE criteria**

| Comparison | Cmax (90% CI), ISCV | $AUC_{0-30min}$ (90% CI), ISCV | $ISCV_{wR}$ $C_{max}$ |
|---|---|---|---|
| Original dataset | 90.04 (81.04 - 100.05), 35% | 86.72 (79.88-94.15), 27% | 37.49% |
| 1st point $C_{max}$ data removed | 90.77 (82.05 - 100.42), 32% | 87.18 (80.60 - 94.31), 25% | 28.01% |

Opening Pandora's box of 'data exclusion' wider

284 ***2.1.8.1 First Point $C_{max}$***

285 The sampling schedule should include frequent sampling around the anticipated $T_{max}$ to provide a
286 reliable estimate of $C_{max}$. In particular, the occurrence of $C_{max}$ at the first post-dose sampling time
287 point should be avoided by careful consideration of the known pharmacokinetic properties of the
288 drug and selection of a suitable early sampling schedule. Datasets where $C_{max}$ occurs at the first
289 post-dose sampling time may result in exclusion of the data from affected subjects from the
290 analysis.

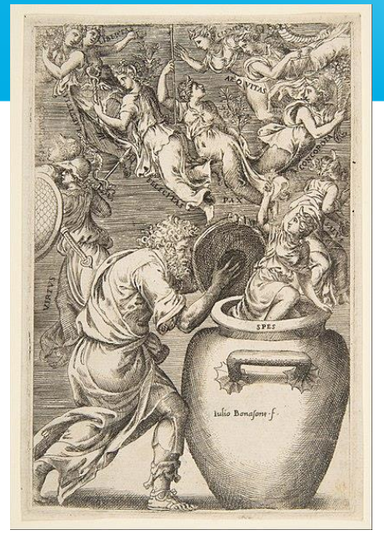
Add a specific wording to the Protocol to reserve the possibility of ‚sensitivity analysis' excluding 1st point Cmax? Don't wait for the defficiency letter?

17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

Step 5

# ICH M13A Draft: First Point $C_{max}$



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288 drug and selection of a suitable early sampling schedule. Datasets where $C_{max}$ occurs at the first
289 post-dose sampling time may result in exclusion of the data from affected subjects from the
290 analysis.

Who should perform an exploratory exclusion of the data from affected subjects (1st point Cmax)?

Should Sponsors/CROs use framework of 'sensitivity/supplementary statistical analysis' and test dataset excluding 1st point Cmax?

What if the PK sampling was adequate, but avoidance of 1st point Cmax cannot be practically warranted?

What is the threshold for 'early enough' sampling? 0.5, 1, 2, 3, 4 or 5 minutes?
For IR oral formulation? For inhaled product?

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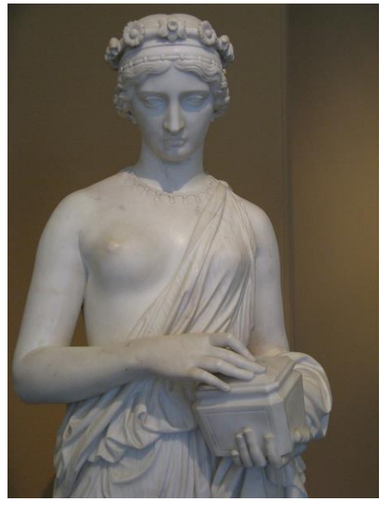
Committee for Medicinal Products for Human Use

Data exclusions

# Per protocol population = BE analysis population?

What is critical and what is not?



**2.2 Data Analysis for Non-Replicate Study Design**

***2.2.1 Considerations for the Bioequivalence Analysis Population***

It is imperative that all criteria for study subject inclusion into the BE analysis population be clearly defined in the study protocol. Any exclusions from the BE analysis population should be documented prior to bioanalytical analysis, e.g., subjects that are withdrawn from the study, have protocol violations, or experience GI disturbances potentially affecting absorption.

Under what circumstances are we open to data exclusions?
Clinically justified?

Thoroughly defined subject exclusion criteria:
dosing failure (remaining powder)? Cough?
Sign of weak airflow (no whirling sound)?

There is no way back! Decision should be made before the bioanalytical phase!

# Outlier detection tests

## Data exclusions

- M13A section 2.2.1.1

312 ***2.2.1.1 Removal of Data Due to Low Exposure***

313 BE studies are studies with a smaller number of subjects compared to other clinical trials. An
314 extreme value in the dataset can have a large impact on the outcome of the BE study. Although
315 statistical tests may identify extreme values in the PK variables, such data should not be removed
316 from the statistical analysis of BE studies solely on this basis. Data should only be removed from
317 the statistical analysis based on protocol violations which are contemporaneously documented. A
318 prospective plan should be included in the study protocol for removing data from the BE statistical
319 analysis.

Outlier detection is mentioned, not accepted as a sole reason of data exclusion. Set a lot of exclusion criteria and then re-include for sensitivity analysis or avoid excessive criteria and exclude in justified cases as sensitivity analysis?

So, we can perform an outlier detection analysis

What if a plausible explanation is possible for an outlier? First ever powder inhalation with reduced flow rate?

# Exceptional cases allowing data exclusion


## Data exclusions

- M13A section 2.2.1.1

320 An exception to the above can be made for a subject without measurable concentrations or only
321 very low concentrations following either comparator or test product administration. A subject is
322 considered to have very low concentrations if the AUC for that period is less than 5% of the
323 geometric mean AUC of the product in question, which should be calculated without inclusion of
324 data from the subject. These very low concentrations are considered the result of subject non-
325 compliance and should, as far as possible, be avoided by documenting mouth check of subjects
326 after administration of study medication to ensure the subjects have swallowed the drug product.
327 The exclusion of data for this reason will only be accepted in exceptional cases (in general with
328 no more than 1 subject in each study) and may bring the reliability of dose administration into
329 question.
332 Note that all subject data should be submitted and potential extreme values flagged with
333 appropriate documentation as part of the application.

In some inhaled products we cannot practically check if the dosing was complete. We can use repetitive inhalation from the same capsule if SmPC suggests this!

# Mandatory justification for data exclusion?


Data exclusions

- M13A sections 2.2.3.3 & 2.2.3.5

409 ***2.2.3.3 Carry-over***

414 If there are subjects for whom the pre-dose concentration is greater than 5% of the $C_{max}$ value for
415 the subject in that period, then the pivotal statistical analysis should be performed excluding the
416 data from that subject.

424 ***2.2.3.5 Multi-Group Design Studies***

441 Statistical methods and models should be fully pre-specified. Data-driven post hoc analysis is
442 highly discouraged but could be considered only in very rare cases where a very robust scientific
443 justification is provided.

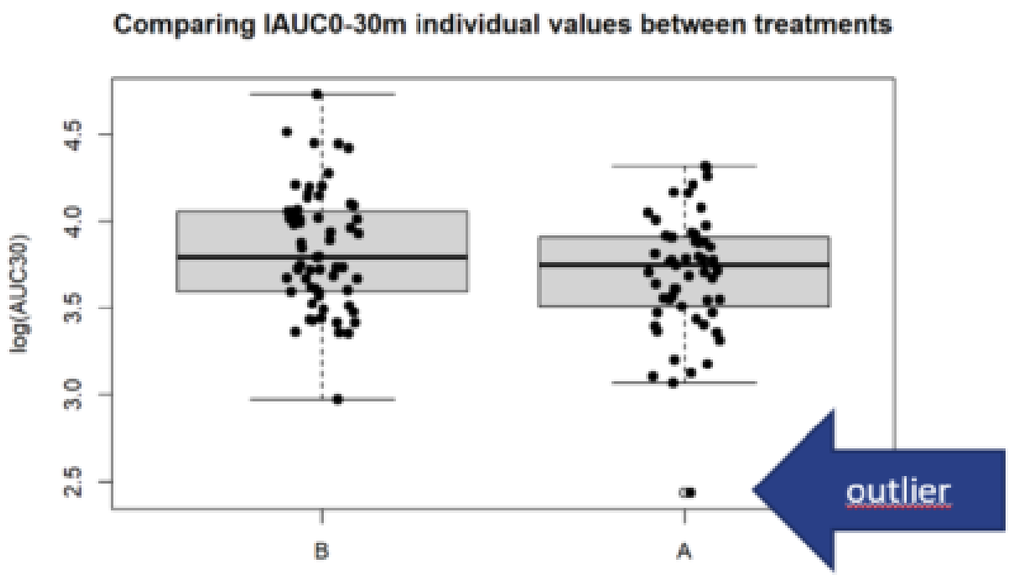
EMA BE GL, Section 4.1.10 (HVD)

acceptance criteria for $C_{max}$ can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for $C_{max}$ of the reference compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.

In some inhaled products we cannot practically check if the dosing was complete. We can use repetitive inhalation from the same capsule if SmPC suggests this!

# Outlier detection / exclusion of observations

## Influence of extreme outlier




| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
|---|---|---|---|---|---|---|---|
| 18 | ABAB | A | 1 | 0.05 | 58.1 | 11.38 | 182.32 |
| 18 | ABAB | A | 3 | 0.03 | 221.0 | 43.70 | 459.82 |
| 18 | ABAB | B | 2 | 0.05 | 217.0 | 49.09 | 410.48 |
| 18 | ABAB | B | 4 | 0.03 | 219.0 | 46.66 | 446.57 |

- An example of low exposure (above 5% rule!) statistically detected as an **outlier observation**
- Even in a fully replicate design such observation can have a critical **influence on BE assessment** of secondary (underpowered) endpoint;
- **No documented evidence of subject non-compliance** detected, but occurrence of low exposure and 1st period of the study **may indicate insufficient inhalation maneuver** due to first experience of powder inhalation;

| Comparison | Cmax (90% CI), ISCV(%) | $AUC_{0\text{-}30min}$ (90% CI), ISCV(%) | $ISCV_{wR}$ $C_{max}$ (%) |
|---|---|---|---|
| Original dataset | 90.04 (81.04 - 100.05), 35 | 86.72 (79.88-94.15), 27 | 37.49 |
| S18p1 data removed | 92.23 (83.52 - 101.86), 32.7 | 88.88 (82.64-95.6), 23.7 | 37.49 |

# Exclude or not to exclude?

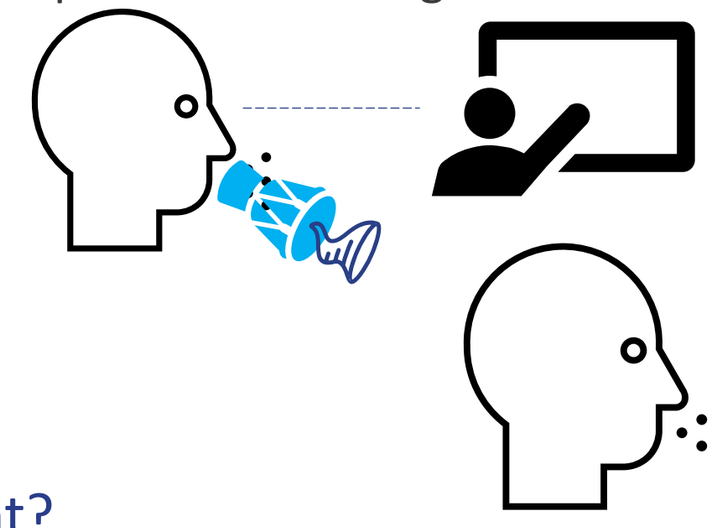
Extensive protocol violation criteria may lead to removal of good data! What is critical?

## Critical

- Good CRO (execution of Clinical part of the study)
- Good bioanalytical facility (validation and analysis of samples)
- Dosing procedure
- Dosing compliance verification (powder remains in the capsule)

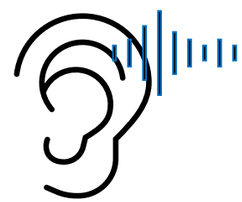
## Important

- Training of study subjects
- Use of placebo capsules for training?



## Not so important?

- Cough immediately post-dose
- Whirling sound
- FPD similarity
- Identical in-vitro deposition profiles



# Justification of outlier using extended dataset?

## Intent-to-treat population reanalysis

| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
|---|---|---|---|---|---|---|---|
| 1 | ABAB | A | 1 | 0.07 | 55.2 | 20.24688 | NA |
| 1 | ABAB | A | 3 | 0.02 | 699.0 | 74.41000 | 308.34 |
| 1 | ABAB | B | 2 | 0.02 | 274.0 | 35.87000 | 91.88 |
| 1 | ABAB | B | 4 | 0.02 | 1010.0 | 113.80000 | 375.90 |
| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
| 18 | ABAB | A | 1 | 0.05 | 58.1 | 11.38 | 182.32 |
| 18 | ABAB | A | 3 | 0.03 | 221.0 | 43.70 | 459.82 |
| 18 | ABAB | B | 2 | 0.05 | 217.0 | 49.09 | 410.48 |
| 18 | ABAB | B | 4 | 0.03 | 219.0 | 46.66 | 446.57 |

Remove an obvious dosing failure

| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
|---|---|---|---|---|---|---|---|
| 1 | ABAB | A | 3 | 0.02 | 699.0 | 74.41000 | 308.34 |
| 1 | ABAB | B | 2 | 0.02 | 274.0 | 35.87000 | 91.88 |
| 1 | ABAB | B | 4 | 0.02 | 1010.0 | 113.80000 | 375.90 |
| SUBJECT | SEQ | TRTMENT | PERIOD | TMAX | CMAX | AUC30 | AUCt |
| 18 | ABAB | A | 1 | 0.05 | 58.1 | 11.38 | 182.32 |
| 18 | ABAB | A | 3 | 0.03 | 221.0 | 43.70 | 459.82 |
| 18 | ABAB | B | 2 | 0.05 | 217.0 | 49.09 | 410.48 |
| 18 | ABAB | B | 4 | 0.03 | 219.0 | 46.66 | 446.57 |

Detected by statistical methods

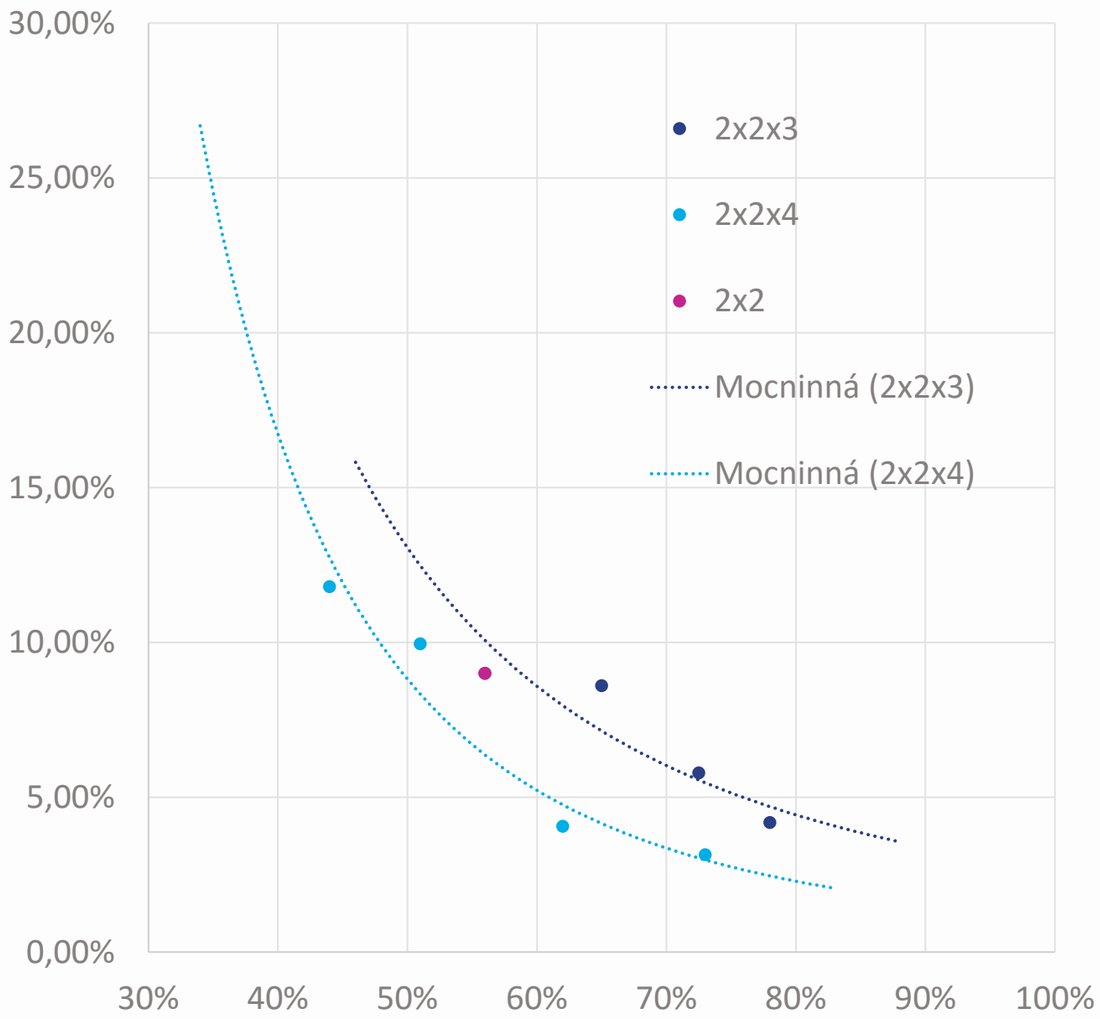
Period effect due to the learning curve?

- What if we reinclude the data excluded based on protocol-defined criteria before the bioanalysis?
- Dosing violations: cough, remaining powder
- That's a Safety/Intent-to-Treat population
- What data exclusion criteria were justified?

| Comparison | Cmax (90% CI), ISCV (%) | $AUC_{0\text{-}30min}$ (90% CI), ISCV (%) | $ISCV_{wR}$ $C_{max}$ |
|---|---|---|---|
| Original dataset | 90.04 (81.04 - 100.05), 35 | 86.72 (79.88-94.15), 27 | 37.49% |
| Full ITT/safety dataset | 86.94 (76.98 - 98.18), 41.4 | 85.37 (78.32 93.04), 28.7 | 37.49% |
| ITT – 1 obvious dosing failure | 90.43 (81.47 - 100.36) 34.9 | 86.99 (80.20 - 94.36) 26.9 | 37.49% |

# ICH M13B considerations: Higher order cross-over designs

## Fully vs. Partial vs. Non-replicate cross-over studies:




For further investigation:
Is there a true added value of a fully replicate cross-over studies allowing for a better characterization of the Point Estimate for a highly variable PK parameters? Regardless of the source of variability.

Ideally:

- Use your big fully-replicate study, ideally – slightly overpowered, because drop-out assumptions were conservative.
- Take BE outcome as a benchmark
- Create smaller datasets using original data and un BE tests and measure maximum deviation from the benchmark results
- What sample size and design of pilot study gives a more precise estimation of T/R ratios?
- Does it make sense to perform multiple small 12-subject 2x2 pilots (T1vs.R,  T2vs.R) for DPI/HVD??

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84 ***2.1.2 Study Design***

85 A randomised, single-dose, two-period, two-sequence crossover study design is recommended
86 when comparing two formulations, as single-dose studies provide the most sensitive conditions to
87 detect differences in the rate and extent of absorption. Treatment periods should be separated by a

- Would a fully-replicate study be accepted for a non-HVD product?
- Waiting for M13B which should provide some specific recommendations for use of replicate designs for highly-variable drugs (HVD)
- Only replicate can give use within-Test or within-Reference variability data
- Pilot studies? 6-period fully replicate if practical?
- Reduction of study sample size (COVID, limitations of the Clinical facility)
- Period drop-out ≠ study drop-out
- Potentially better point estimates, less sensitivity to outlying individual observations

- Thank you !