# pAUCs CASE STUDY AND BEYOND…

# MELATONIN SR

**Vit Perlik**
**Marina Fertek**

**BioBridges 2025, September 25-26, Prague, CZ**

# MELATONIN SR: Nice to meet you…☺

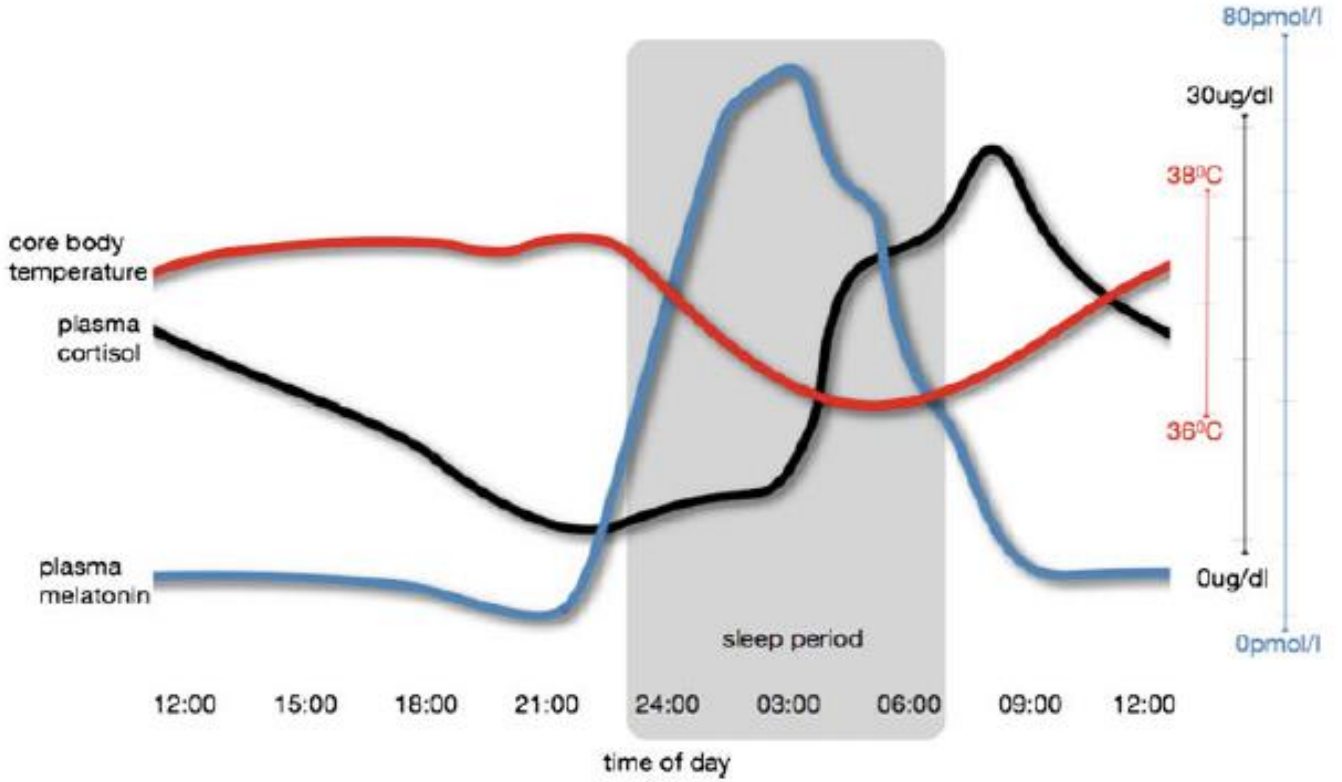
- **Circadin 2 mg** prolonged-release tablets (Reference)

- **Therapeutic indication**: as monotherapy for the short-term treatment of primary insomnia… in patients who are aged 55 or over
- **Posology:** 2 mg **once daily**, 1-2 hours before bedtime and **after food**
- **Pharmacokinetic properties:**
  - Absorption is complete
  - Bioavailability is 15% with significant first pass effect
  - $T_{max}$ 3 hours in a fed state versus $T_{max}$ 0.75 h fasting state
  - **Terminal half life is 3.5-4 hours** (melatonin IR $T_{1/2}$ ~ 45 minutes)

| $T_{1/2}$ (multiple) | % eliminated / absorbed |
|---|---|
| 1 | 50 |
| 2 | 75 |
| 3 | 87.5 |
| 4 | 93.8 |
| 5 | 96.9 |
| 6 | 98.4 |
| 7 | 99.2 |
| 8 | 99.6 |

Circadin 2 mg Prolonged-release Tablets, SmPC

# MELATONIN SR: Nice to meet you…☺



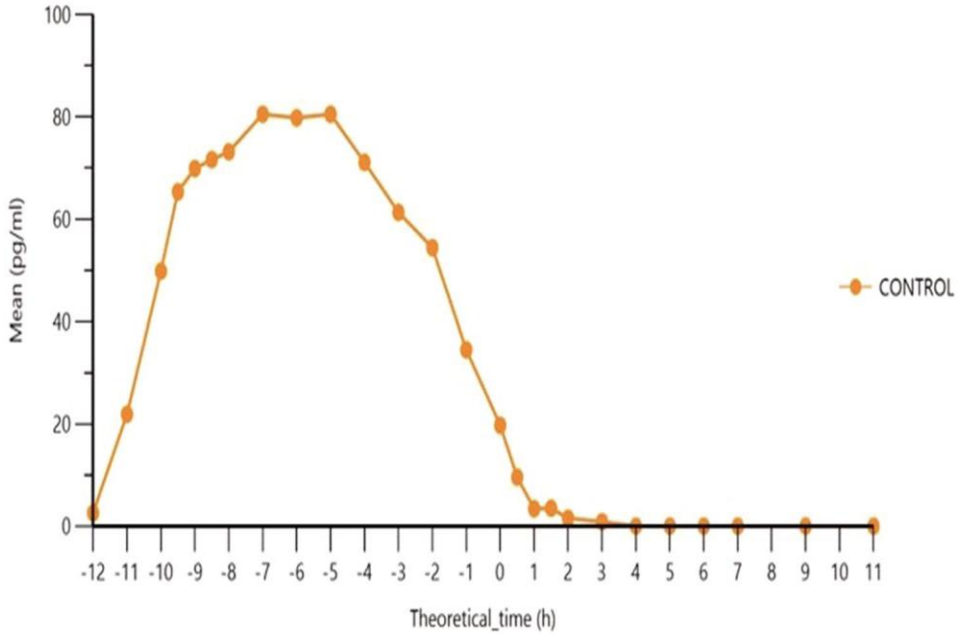




**Figure 3 The normal synchronous relationships between sleep and daytime activity and cortisol, melatonin and body temperature.**

Hickie et al, 2013
Martinez et al, 2022

- Melatonin is a **naturally occurring hormone**
- **Baseline adjustment needed**
  - Martinez et al., study drug administration approx at 10 a.m.

# Regulatory Considerations – MR Guideline

- **Single dose studies**
  - **FASTING and FED conditions**
- **Multiple dose studies – can be waived if there is no accumulation, but:**
  - Mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$
  - BE for an early $_{partial}AUC_{(0\ -\ cut\text{-}off\ t)}$ and a terminal $_{partial}AUC_{(cut\text{-}off\ t\ -\ tlast)}$, separated by a predefined **cut-off time point**, e.g. the **half of the dosage interval** are recommended, unless otherwise scientifically justified.
- In other words, **potential shift of PK profiles MUST be addressed** either
  - Via **pAUCs** or
  - Via **multiple dose study**
- **pAUCs in the game**

EMA/CPMP/EWP/280/96 Corr1

# Case Study

# MA in its beauty – ALL IN game…

- **Development program**
  - Pilot study to investigate release profile and baseline melatonin conditions
  - **SD Fasting** – pivotal, fully-replicated 4-period, N = 60 healthy volunteers, **sampling up to 23 h** after study drug administration **09:00 - 09:58 a.m.**
    - **Primary endpoints:** baseline corrected **$AUC_{(0-t)}$ and $C_{max}$, NO pAUCs defined**
    - **BE demonstrated**
  - **SD Fed** - pivotal, two-way crossover study, N = 38 healthy volunteers, **sampling up to 23 h** after study drug administration **09:00 - 10:18 a.m.**
    - **Primary endpoints:** baseline corrected **$AUC_{(0-t)}$ and $C_{max}$, NO pAUCs defined**
    - **BE demonstrated**

# MA in its beauty – life is a tick box…

- **CMS Comment 1st round**
- … in case a **low extent of accumulation is expected, a multiple dose study is not needed**. 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.
- In this case, partial AUCs were not included as primary PK parameters; thus, no cut-off was pre-specified by the applicant.
- The applicant is **asked to present 90% CIs for the test/reference ratio** for partial AUCs with an adequate cut-off so that the partial AUCs may represent the shape of the plasma concentration versus time curve. As this is a post-hoc analysis and in order **to avoid cherry-picking**, the applicant should first investigate the time point where the **AUCt can be divided into two equal parts and then present the 90% CIs for the partial AUCs based on that time point as cut-off for both fasted and fed study**.

# MA in its beauty – oops…

- Company response with the CRO data

| Dependent FASTING | Ratio_%Ref | CI_90_Lower | CI_90_Upper | EQ* |
|---|---|---|---|---|
| Ln(AUC(0-2.667h)) | 100.77 | 94.22 | 107.79 | YES |
| Ln(AUC(2.667-23h)) | 107.69 | 100.90 | 114.94 | YES |
| Ln(AUC(0-3h)) | 101.40 | 94.83 | 108.43 | YES |
| Ln(AUC(3-23h)) | 107.67 | 100.83 | 114.97 | YES |
| *Equivalence Test to Reference | | | | |

| Dependent FED | Ratio_%Ref | CI_90_Lower | CI_90_Upper | EQ* |
|---|---|---|---|---|
| Ln(AUC(0-3h)) | 100.65 | 92.30 | 109.76 | YES |
| Ln(AUC(3-23h)) | 117.52 | 108.29 | 127.54 | NO |
| *Equivalence Test to Reference | | | | |

- Clinical interpretation of non-BE FED terminal pAUC data
- Fasting vs Fed data interpretation - physiology

# MA in its beauty – life is a tick box…

- **CMS Comment 2nd round**
- If a multiple dose study is waived for a PR formulation, the MR guideline states that BE must be demonstrated for an early and a late pAUC separated by a pre-defined cut-off. **As no cut-off was pre-specified, and to avoid cherry-picking**, CMS proposed to use a cut-off dividing AUCt into two equal parts. The applicant presented the requested data. For the fasting study, the 90% confidence interval for the early pAUC and terminal pAUC was within the acceptance range of 80.00-125.00%.
- However, for the **fed study**, the 90% confidence interval for **the terminal pAUC was outside the upper limit** of 125.00%. Thus, **bioequivalence has not been shown** between the test and reference product.
- For a generic application, it is **not possible to justify that deviations from BE are not clinically relevant**.

# MA in its beauty – life is a tick box…

- **Company response with the CRO data**
  - …FED data suggesting **slightly different shape** of the PK profile in time interval from **3 to 23 hrs** after dosing, **more pAUCs presented**

| Parameter (h*pg/mL) | Geometric least squares means | | Ratio %Ref | 90% confidence limits (%) | | EQ* |
|---|---|---|---|---|---|---|
| | Test | Reference | | Lower | Upper | |
| $Ln(AUC_{(0\text{-}3h)})$ | 2012.2 | 1999.2 | 100.65 | 92.30 | 109.76 | YES |
| $Ln(AUC_{(0\text{-}6h)})$ | 3335.1 | 3167.5 | 105.29 | 97.66 | 113.52 | YES |
| $Ln(AUC_{(0\text{-}12h)})$ | 3965.3 | 3680.3 | 107.75 | 100.21 | 115.85 | YES |
| $Ln(AUC_{(3\text{-}23h)})$ | 2167.8 | 1844.6 | 117.52 | 108.29 | 127.54 | NO |
| *Equivalence Test to Reference | | | | | | |

- **PK literature IR and PR and clinical interpretation**

# MA in its beauty – life is a tick box…

- **RMS Assessment – 3rd round**
- … **a small difference…,** which **occurred only in the time interval** in which the quantitative share of melatonin from an external source (given as the test or reference product) **was decreasing as a result of elimination**…
- Proposal to CMS: **to determine the cut-off** points for the partial fields to be compared (based on the values obtained **from the intersection of the alpha and beta hybrid coefficients of the two compartment kinetic** equation)…, the values of determined for t cut off resulting from the intersection of the logarithmic coefficients of the kinetic equation **appropriate for the distribution phase (α ) and elimination phase (ß)**.
- The method used by the applicant to determine the **endogenous background** (subtraction of pre-dose concentration values from concentrations at appropriate time points after administration) **may itself be the cause of additional variability** (not taken into account in the analysis of variance)

# MA in its beauty – life is a tick box…

- **CMS Comment 3rd round**
- … **not possible to justify** that deviations from BE are **not clinically relevant**.
- … **not agreed** that the plasma concentration time curve can be strictly **divided to distribution phase and elimination phase** due to the prolonged release characteristics of the applied product. Further, this is to our knowledge **not a standard approach in setting cut-offs for partial AUCs** in EU generics applications.
- … **no product-specific guideline available** for melatonin prolonged-release products, … one potential approach in this procedure might be to **present data for $AUC_{0\text{-cut-off t}}$ and $AUC_{\text{cut-off t-tlast}}$ for various cut-off times (ranging from $t_{max}$ to 6 hours)**.
- If equivalence can be demonstrated for the majority of partial AUCs.., the **totality of data may be considered sufficient** …

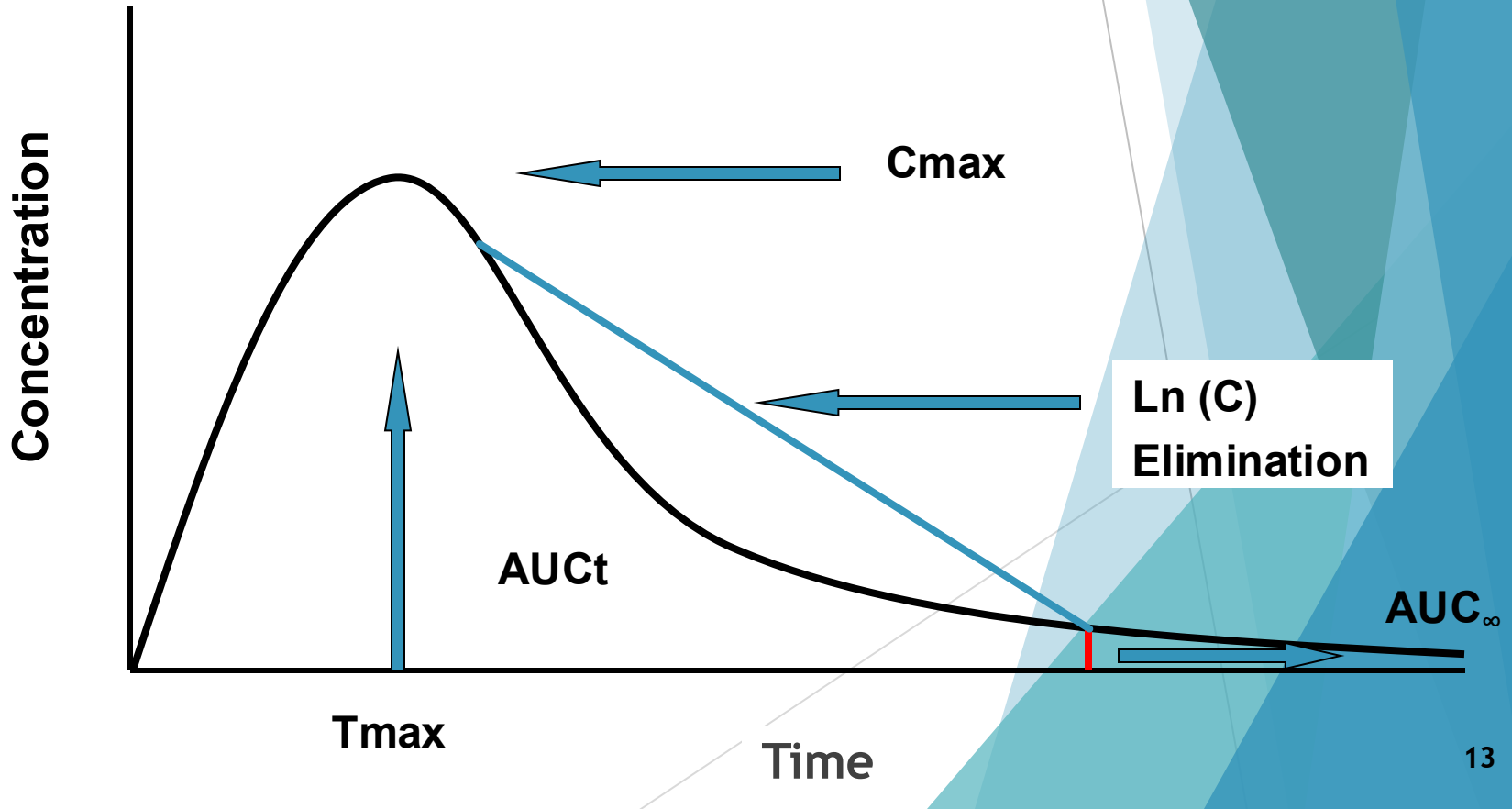
# Time to understand the data…

**3rd round**

**THANK YOU FOR CALLING US IN… ☺**

- **One** – talks about **elimination** and **baseline impact**
- **The other** – talks about **pAUCs - chop it more…**
- And

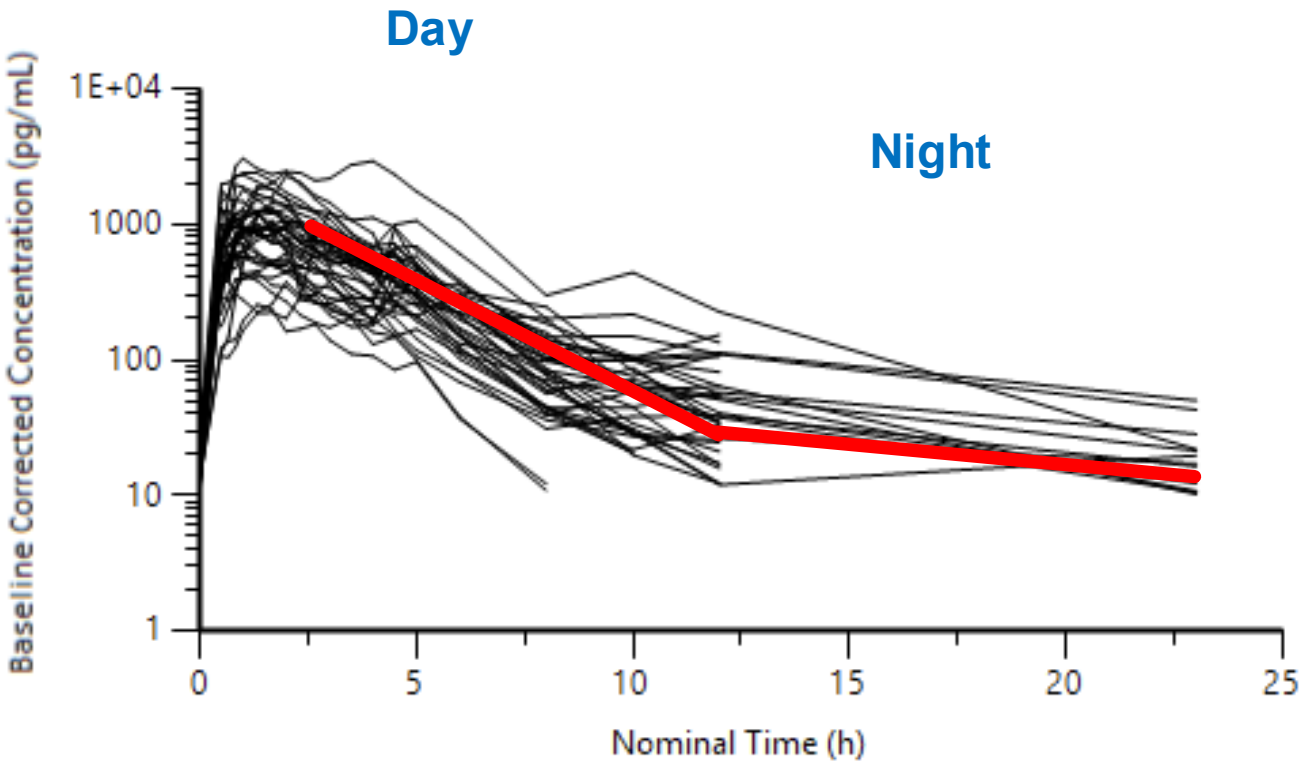
- You know you have one shot - **MISSION IMPOSSIBLE**



# Time to understand the data…

**3rd round**

- It looks like **two compartments** in elimination phase
- **NO** - melatonin **best fit one-compartment model (Bellapart 2016)**
- **“Second” compartment - effects of endogenous levels**
- **Even worse - pAUCs chop-it-more approach will not work** as concentrations do not end at the same time
- **Forgot to mention - one more consultant in the game…☺**



# Time to understand the data…

- Melatonin **baseline levels variability**
- **Single point(-s)** baseline correction employed

Selmaoui et al, 2003

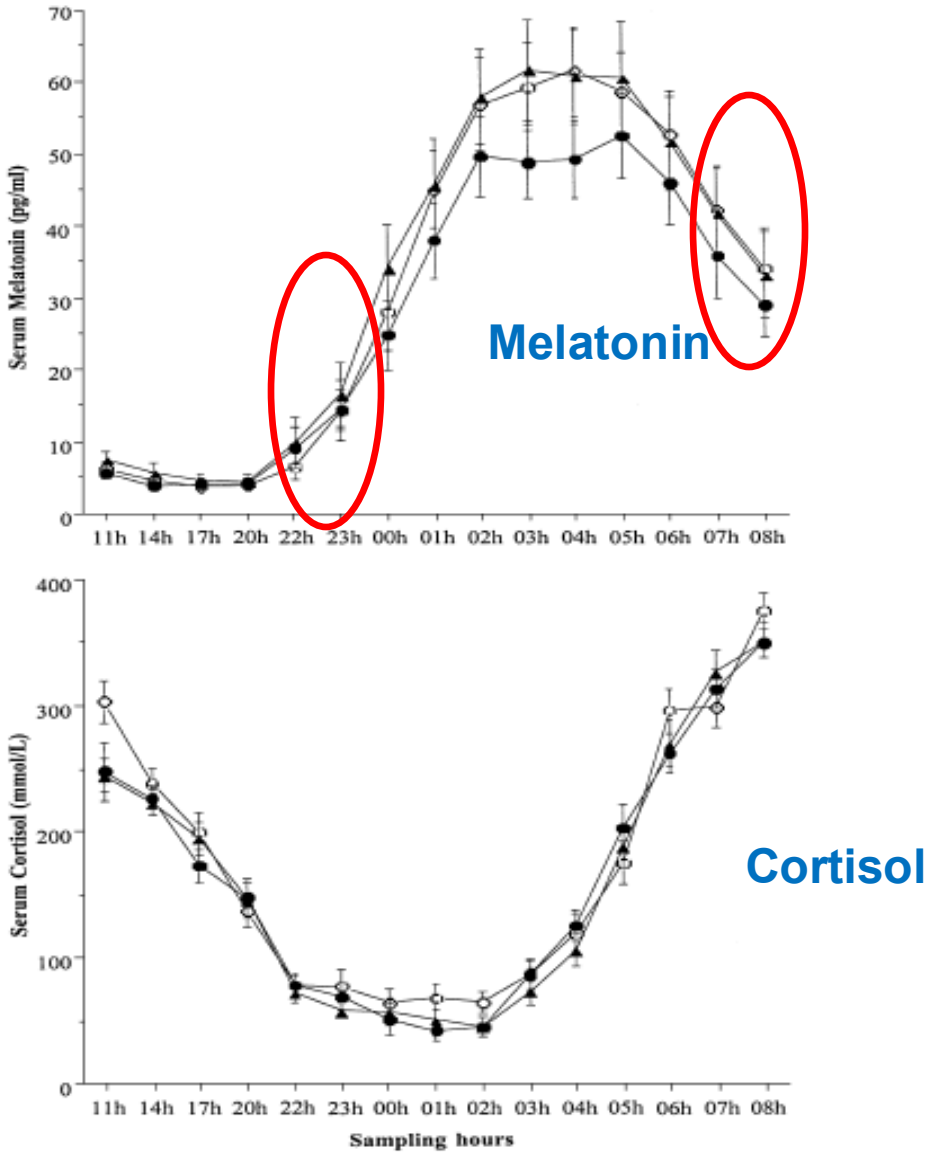


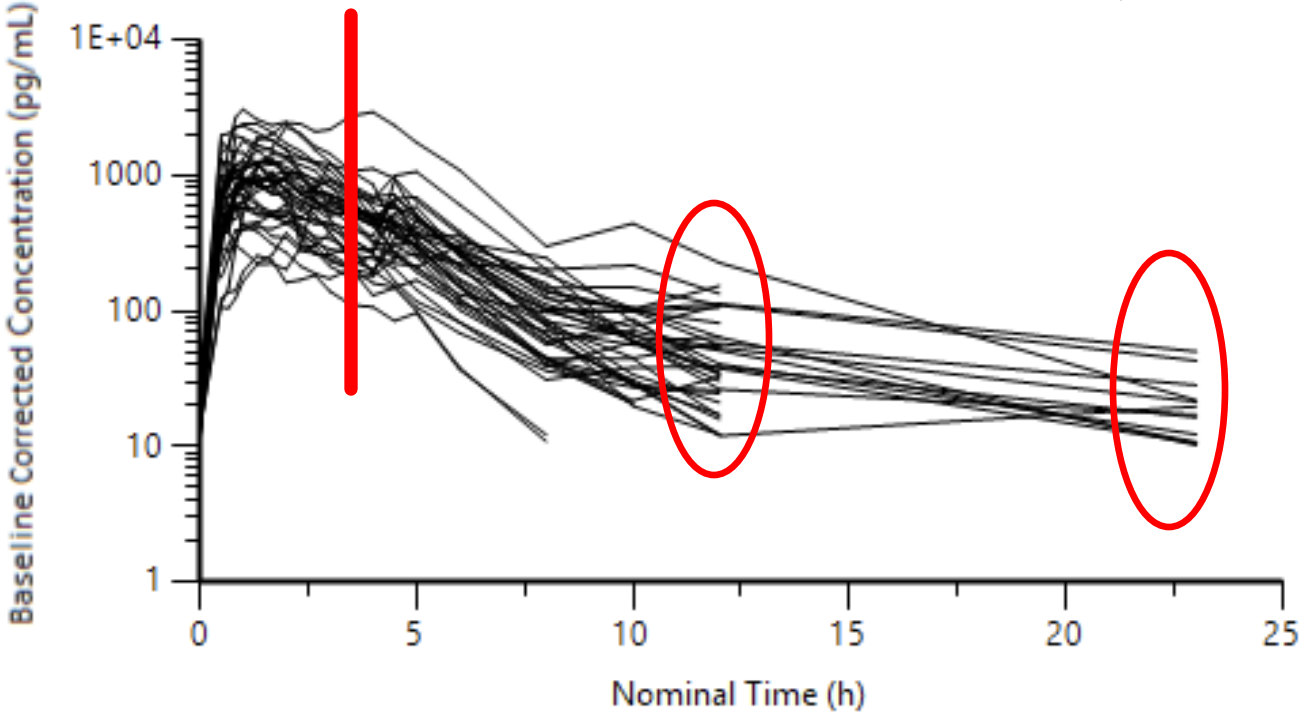

Fig. 1. Circadian rhythms of melatonin (top) and cortisol (bottom) in three different 24-h sessions spaced two weeks apart between the 1st and 2nd session then 4 weeks apart between the 2nd and 3rd session: S1(○), S2 (●) and S3 (▲). Each time point is the mean ± SEM of 31 subjects.

# Time to understand the data…

- Chop-it-more approach – **NO WAY**
- Terminal pAUC – **fails** already **at cut-off t 3h**
- Shift of PE between 12 – 24 h **approx. 10 %**
- pAUCs **beyond 3h** will always be **non-BE** (also requested by CMS)

**Cut-off t = 3h**

Selmaoui et al, 2003



# Company Response

## Let's use science to set the $t_{cut\text{-}off}$

- **Absorption in focus -** pAUC evolution over the time, starting at median $T_{max}$
- **All pAUCs BE**

| FED, pAUCs absortion, starting from median Tmax | | | |
|---|---|---|---|
| Dependent | Ratio_%Ref_ | CI_90_Lower | CI_90_Upper |
| Ln(AUC0_1.333) | 91,03 | 80,63 | 102,78 |
| Ln(AUC0_1.667) | 95,18 | 85,22 | 106,29 |
| Ln(AUC0_2) | 97,60 | 88,22 | 107,99 |
| Ln(AUC0_2.333) | 99,01 | 90,15 | 108,74 |
| Ln(AUC0_2.667) | 100,01 | 91,44 | 109,37 |
| Ln(AUC0_3) | 100,65 | 92,30 | 109,76 |
| Ln(AUC0_3.5) | 101,57 | 93,43 | 110,41 |
| Ln(AUC0_4) | 102,29 | 94,27 | 111,00 |
| Ln(AUC0_4.5) | 103,40 | 95,50 | 111,96 |
| Ln(AUC0_5) | 104,48 | 96,73 | 112,86 |
| Ln(AUC0_6) | 105,29 | 97,66 | 113,52 |
| Ln(AUC0_8) | 106,37 | 98,78 | 114,54 |
| Ln(AUC0_10) | 107,35 | 99,79 | 115,49 |
| Ln(AUC0_12) | 107,75 | 100,21 | 115,85 |

| FASTING, pAUCs absortion, starting from median Tmax | | | |
|---|---|---|---|
| Dependent | Ratio_%Ref_ | CI_90_Lower | CI_90_Upper |
| Ln(AUC0_0.833) | 93,38 | 85,77 | 101,67 |
| Ln(AUC0_1) | 95,16 | 87,77 | 103,18 |
| Ln(AUC0_1.333) | 96,97 | 89,91 | 104,59 |
| Ln(AUC0_1.667) | 98,15 | 91,30 | 105,52 |
| Ln(AUC0_2) | 99,09 | 92,38 | 106,29 |
| Ln(AUC0_2.333) | 99,99 | 93,35 | 107,09 |
| Ln(AUC0_2.667) | 100,79 | 94,23 | 107,81 |
| Ln(AUC0_3) | 101,42 | 94,84 | 108,45 |
| Ln(AUC0_3.5) | 102,19 | 95,58 | 109,27 |
| Ln(AUC0_4) | 102,87 | 96,22 | 109,97 |
| Ln(AUC0_4.5) | 103,46 | 96,83 | 110,56 |
| Ln(AUC0_5) | 103,86 | 97,26 | 110,91 |
| Ln(AUC0_6) | 104,13 | 97,59 | 111,11 |
| Ln(AUC0_8) | 104,20 | 97,73 | 111,11 |
| Ln(AUC0_10) | 104,22 | 97,80 | 111,06 |
| Ln(AUC0_12) | 104,21 | 97,82 | 111,03 |

# Company Response

- **Two methods for terminal pAUCs proposed**
  - One derived from **deconvolution of the PK profiles**, using literature IV data
  - Second based on the **flip-flop kinetics of melatonin** PR
    - Terminal half life is 3.5-4 hours vs melatonin IR $T_{1/2}$ ~ 45 minutes (SmPCs PR and IR)

| REFERENCE | | | |
|---|---|---|---|
| Variable | Mean 50% | Mean 90% | Mean 95% |
| %_Fraction_Input | 50,115 | 90,072 | 95,021 |
| Time (h) Median | 1,440 | 5,700 | 8,520 |

| FED (h) | Treatm | Min | Median | Max |
|---|---|---|---|---|
| HL_Lambda_z | R | 0,929 | 2,333 | 11,187 |

| FED, terminal pAUCs | | | |
|---|---|---|---|
| Dependent | Ratio_%Ref_ | CI_90_Lower | CI_90_Upper |
| Ln(AUC1.333_6) | 109,50 | 101,41 | 118,23 |
| Ln(AUC1.333_8) | 110,31 | 102,33 | 118,91 |
| Ln(AUC1.333_12) | 111,77 | 103,81 | 120,33 |
| Ln(AUC1.333_23) | 113,45 | 105,15 | 122,41 |

| FED, terminal pAUCs | | | |
|---|---|---|---|
| Dependent | Ratio_%Ref_ | CI_90_Lower | CI_90_Upper |
| Ln(AUC2.333_23) | 114,67 | 105,70 | 124,40 |

# MA in its beauty – life is a tick box…

- **CMS Evaluation – 4th round**
- …**no product-specific guideline** available for melatonin prolonged-release products
- … to use a **cut-off dividing** the dosage interval into **two equal parts**
  - **BE was not demonstrated** for the late partial AUC for the fed study
- … present data for AUC0-cut-off t and AUCcut-off t-tlast for various cut-off times (ranging from tmax to 6 hours)
  - **Instead of presenting data** for AUC0-cut-off t and AUCcut-off t-tlast for various cut-off times (ranging from tmax to 6 hours), **the applicant only presented**…
  - For the fed study, partial AUCs were presented with **cut-offs of 1.33h, 2h and 2.33h**.
- Thus, it cannot be outruled that the applicant only chose cut-off times that showed bioequivalence for pAUCs (i.e. **cherry picking**).
- **Bioequivalence cannot be concluded** between the test and reference product.

# Company Response

**Baseline conditions - push**

- **Tlast at 12h** (21 out of 38 subjects), reference product
- **20 out of 60 subjects** (one third) enrolled in **fully replicated fasting study** did not have the last measured concentration at the same time
- …for **unbiased comparisons** the applicant is presenting **additionally terminal pAUCs form 3 - 8 hours up to 3 - 12h** time (23 vs 12 h and/or earlier)
- **Terminal pAUC 3-23h entirely unreliable** for the purpose of treatment comparison
  - **pAUCs**, pre-set timepoints using **measured concentrations** or **addition of portions of $AUC_{inf}$ to the predefined pAUC** after the last measured concentration

**FED study**

| Dependent | Ratio_%Ref_ | CI_90_Lower | CI_90_Upper |
|---|---|---|---|
| Ln(AUC3_8) | 112,73 | 103,59 | 122,68 |
| Ln(AUC3_10) | 114,28 | 105,36 | 123,95 |
| Ln(AUC3_12) | 114,91 | 106,17 | 124,37 |

# MA in its beauty – life is a tick box…

- **CMS Evaluation - Request for Referral**
- This could however rather be interpreted as a **larger uncertainty** in the description **of the last part of the concentration-time curve**, probably explained by an **insufficient study design**. **No blood samples were taken between 12 and 23 hours** and endogenous melatonin levels were taken not accounting for fluctuations in the endogenous baseline due to circadian rhythms.
- **The applicant believes that, as AUC0-12h covers majority of AUC0-t, that showing pAUC of AUC0-3 and AUC3-12 may be sufficient.** However, there is no possibility in the MR Guideline to disregard a certain part of AUC, and it is not agreed that this can be done post-hoc, since this is a generic application.
- **MWP is asked to comment on their position** in the referral procedure, and this procedure highlights **the need for a product specific BE-guidance** defining the requirements and cut-offs for partial AUCs.

# MWP position

- **Single dose BE study is sufficient** with as primary endpoints **$C_{max}$, $AUC_t$, $AUC_{inf}$, and early partial $AUC_{(0 - cut\text{-}off\ t)}$, and a terminal partial $AUC_{(cut\text{-}off\ t - tlast)}$**
- The **cut-off for the partialAUCs was not predefined** in the protocol
- **… No half of the dosing interval…** because **absorption and elimination** of melatonin prolonged-release tablets is **almost completed within 12 hours**, which is half of the dosing interval
- The purpose of the partialAUCs is to **compare the shape of the plasma profile…** the cut-off should **consider the pharmacokinetics of melatonin… rather than the pharmacodynamic** effects
- The **3h cut-off** resulted in approximately **comparable early- and late partialAUC** values, indicating that this cut-off would be appropriate. The **2h and 2.33h cut-off points** could also have been considered acceptable, if they had been **predefined in the protocol…**
- **… no cut-off was predefined** in the protocol, and this **concerns a post-hoc analysis** with selected cut-off points
- **clinical justification cannot be taken** into account for any failure to demonstrate bioequivalence

# Referral question

- The Applicant is requested to provide a **justification and supportive evidence** that the bioequivalence for generic product melatonin PR submitted under Article 10(1) has been shown **taking into account deviation from the acceptance range observed in fed BE study for one partial AUC value (AUC3-23h 108.29-127.54%).**

# Referral Response

**Sorry, we screwed it up – however the data talks**

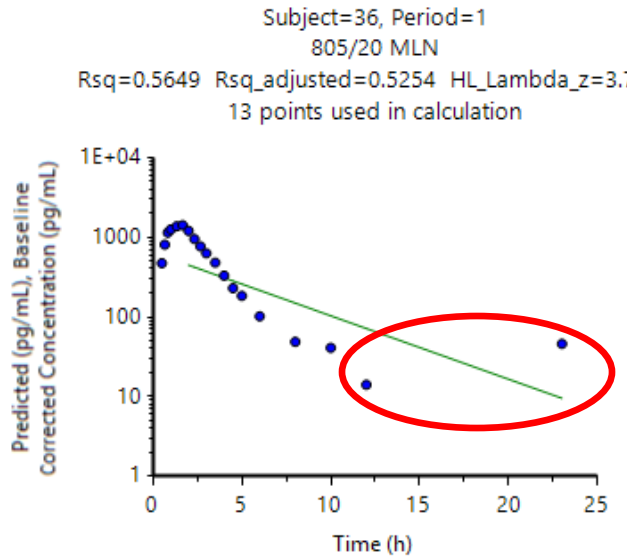
- **Summary of compound properties** – natural melatonin production – variable
- **Summary of clinical development program**
  - Melatonin **does not accumulate, no steady state is possible**, $T_{1/2}$ not reaching the steady state with once daily administration
  - **Product intended to be used on as-needed basis** and exert its **effect only during the nighttime**
  - More **IR like program and PK metrics employed**

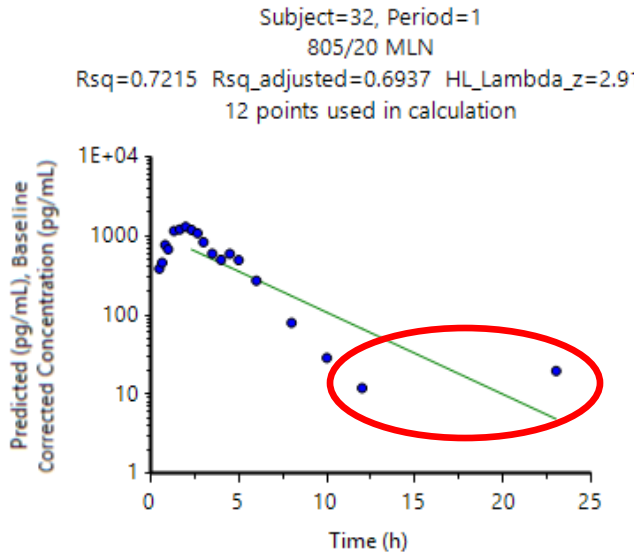
# Referral Response

- **Based on the literature - different cut-off time points used in the past**
- **Summary of previous applicant proposals for t cut-off**
  - **Half of the dosing - not appropriate** - 12 hours almost 4 half-lives are covered i.e. almost 93.8%
  - **Median $T_{max}$,** 1.333 h drug **absorption equals the rate of drug elimination**
  - **More data presented up to 2.333 h** with **BE demonstrated** for FED study
  - In addition, we have preformed, what you asked for i.e. t 3 h cut-off, with terminal pAUC failing to demonstrate BE

# Referral Response

- Endogenous production kicks in 12 h and further (night time)
- Even if you baseline correct, not enough, due to endogenous production variability




- Addition of sampling points would make it worst
- PK literature confirms the sampling till 8-12 h

# Referral Response

- **Endogenous levels variability confirmed**
  - FED study based on the **differences in the sequence**
  - Fasting study based on the **differences between periods**

| FED study Sequence | Ratio_%Ref_ | CI_90_Lower | CI_90_Upper |
|---|---|---|---|
| RT | 94,50 | 74,31 | 120,17 |
| TR | 107,27 | 82,17 | 140,03 |

| FASTING study Period | Ratio_%Ref_ | CI_90_Lower | CI_90_Upper |
|---|---|---|---|
| 2 | 85,33 | 75,59 | 96,33 |
| 3 | 95,50 | 84,94 | 107,38 |
| 4 | 84,19 | 74,83 | 94,73 |

- **Baseline melatonin values influenced the late phase of melatonin curve beyond 12h**
- Concentrations **beyond 12h do not enable meaningful interpretation** about the overall product bioequivalence

# Referral Response

- **Absorption** (the main determinant of the bioequivalence) and **elimination** of melatonin from the formulation was **near complete within 12 h**
- **Minimal interference** of the endogenous melatonin up to 12 h
- **PK parameters up to 12 h** post-dose **reliable to conclude T/R bioequivalence**
- **$AUC_t/AUC_{inf}$** for Reference and Test product of **96%**
- **BE $AUC_{inf}$ - no carryover** of melatonin during the daytime

| Dependent | Ratio_%Ref | CI_90_Lower | CI_90_Upper |
|---|---|---|---|
| Ln(Cmax) | 103,91 | 94,98 | 113,69 |
| Ln(AUClast) | 107,76 | 100,22 | 115,86 |
| Ln(AUCINF) | 108,58 | 100,69 | 117,08 |
| Ln(AUC0_2h) | 97,60 | 88,22 | 107,99 |
| Ln(AUC0_2_333h) | 99,01 | 90,15 | 108,74 |
| Ln(AUC0_3h) | 100,65 | 92,30 | 109,76 |
| Ln(AUC2_12h) | 112,97 | 104,54 | 122,08 |
| Ln(AUC2_333_12h) | 113,58 | 104,99 | 122,89 |
| Ln(AUC3_12h) | 114,91 | 106,17 | 124,37 |
| Ln(AUC2_AUCt) | 113,04 | 104,61 | 122,15 |
| Ln(AUC2_333_AUCt) | 113,67 | 105,07 | 122,97 |
| Ln(AUC3_AUCt) | 115,03 | 106,29 | 124,48 |

- **ALL pAUCs bioequivalent**

# Referral outcome

CMS assessment

The applicant argues that the **concentration profiles between 12-23 hours are not relevant due to:**

- Drug product **not being designed to be dosed under steady state conditions**
- **Absorption and elimination** of melatonin prolonged-release tablets is **almost completed within 12 hours**
- **Variable endogenous melatonin levels affecting the study results**

When using **partial AUCs of AUC0-3 and AUC3-12**, the results are just **within the acceptance interval** (90% CI being 92.30-109.76 and 106.17-124.37 respectively).

# Referral outcome

- It is a clear **weakness that no cut-off was pre-specified** in the performed study. Also, the late **partial AUC should generally have the last sampling point as limit**. Nevertheless, it can be agreed that the **exogenous melatonin concentrations after 12 hours are negligible** and that it would be **sufficient to sample up to 12 hours** for melatonin PR products. Further, the partial AUCs, **AUC0-3 and AUC3-12** are considered adequate as primary PK parameters based on current internal discussions for melatonin PR products. As **bioequivalence has been shown** for these PK parameters, it **can now be agreed that there are no concerns regarding bioequivalence** for the applied product.

- **Agreement reached…☺**

# Food for thought…PAR

- **Systematic failure**
  - Where is the **absorption paradigm i.e. AUC, $C_{max}$ and $t_{max}$** are influenced by **absorption rate**, surrogate of **efficacy and safety**
  - **Cutt-off t** related to a clinically **relevant pharmacodynamic measure** (ICH M13A)
- **Clinical development program**
- **SD Fasting** study, two-way crossover study, N = 100 healthy volunteers, **sampling 24h**
  - $AUC_{0-t}$, $AUC_{0-\infty}$, $AUC_{0-12}$ and $C_{max}$
  - **BE demonstrated**
- **Two SD Fed** full replicate studies performed, **sampling 24h**
  - 1. study: **N = 50**, $AUC_{0-t}$, $AUC_{0-\infty}$, $AUC_{0-12}$, $AUC_{12-24}$, and $C_{max}$
  - **BE NOT demonstrated**
  - 2. study: **N = 48**, $AUC_{0-t}$, $AUC_{0-\infty}$, $AUC_{0-3.5}$, $AUC_{3.5-t}$, and $C_{max}$
  - **BE demonstrated**

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

**Public Assessment Report**
**Scientific discussion**

**Melatonin Zentiva**
(melatonin)

**SE/H/2376/01/DC**

**This module reflects the scientific discussion for the approval of Melatonin Zentiva. The procedure was finalised on 2024-02-07. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

# Food for thought…FDA

- **Life can be so simple…**
  - **Sleeping pill example, Zolpidem ER**
- **Clinical development program**
- **SD Fasting** study
  - $AUC_{0-1.5}$, $AUC_{1.5-t}$, $AUC_{0-\infty}$ and $C_{max}$
  - Cut-off 1.5 hours - **BA for sleep onset and sleep maintenance - efficacy**
  - Btw **fasting Tmax 1.5 hours…**☺
  - $AUC_{0-\infty}$ - lack of **residual effects - safety**
- **SD Fed** study
  - $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$

*Contains Nonbinding Recommendations*

**Guidance on Zolpidem**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Zolpidem

**Form/Route:** Extended Release Tablets/Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 12.5 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Patients should be advised not to drive if they are experiencing drowsiness and/or dizziness at the end of the study.

---

2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 12.5 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: See comment above.

---

**Analytes to measure:** Zolpidem in plasma

**Bioequivalence based on:** Zolpidem

The 90% confidence intervals of the following PK parameters must meet the acceptable limits of [80.00-125.00]:

1. Fasting Study: Log-transformed $AUC_{0-1.5}$, $AUC_{1.5-t}$, $AUC_{0-\infty}$ and Cmax,

where $AUC_{0-1.5}$ is the area under the plasma-concentration vs. time curve from 0 to 1.5 hours, $AUC_{1.5-t}$, is area under the curve from 1.5 hours to the last measurable time point; $AUC_{0-\infty}$, is area under the curve from 0 to infinity, and Cmax, the maximum plasma concentration. The partial AUCs, $AUC_{0-1.5}$ and $AUC_{1.5-t}$, have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the sleep onset and sleep maintenance phases, respectively. These two partial AUCs replace the usual $AUC_{0-t}$, and together with the other bioequivalence parameters, $AUC_{0-\infty}$ and Cmax, will ensure that the pharmacokinetic profiles of test and reference products are sufficiently

*Finalized Oct 2011*

# Conclusion

- **To sponsors**
  - **Do your homework** and know your compound
  - **Do not try to outsmart** the regulators, you lose your face
  - **Go for SA** and present the case – development life is a bargain
  - **Do not play poker with ALL IN**, unless you have strong cards!!!
- **To regulators**
  - **One does not fit all**
  - **Life is not a tick-the-box** form
  - **Do your homework** and know the compound
  - **Post-hoc analyses** are not always cherry picking
  - **PSBEGs are the way to GO…☺**

## In memoriam to Pieter Guelen


- **Acknowledgments**
  - **Marina Fertek**
  - Ales Bartunek
  - Nora Sotolova


# Thank You For Your Attention!

vitperlik@gmail.com