Design of MUstT Trials and Leveraging MIDD

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Topical Drug Development: Evolution of Science and Regulatory Policy II

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Presented a regression methodology for comprehensive analysis of topical PK data using crisaborole as an example (2019 Presentation).

More complete details of the analysis and results are now published (Purohit et.al., 2020)

Model Informed Drug Development (MIDD) Methodology described:

- Quantified the relationship of ointment dose with systemic exposure parameters.
- Allowed estimation of the impact of disease on systemic exposures relative to healthy volunteers.
- Allowed estimation and assessment of significance of other demographic covariates on the systemic exposures.
- Synthesized all the data: Accounting for differences in dose, treated BSA, age and body size.
- Allows prediction of systemic exposures at any ointment dose at a relevant application rate to relevant %treated BSA.
Non-Linear Regression Models – Ointment Dose Vs PK Parameter

- Linear slope-intercept models with weight included as a covariate in the form of an allometric power function\(((Wt/70)^{-0.75})\) can be used to describe the relationship between PK parameters \(\frac{AUC_{ss}}{C_{avg,ss}}\) or \(C_{max,ss}\) and ointment dose.

\[
AUC_{ss,i} \text{ or } C_{max,ss,i} = \text{Intercept} + \left( \text{Slope} \times \left( \frac{Wt_i}{70} \right)^{ex_1} \right) \times \text{Ointment Dose}_i
\]

- Intercept is fixed to 0
- \(ex_1\) can be fixed to -0.75 based on allometric principles or estimated.
- Allometric power function allows scaling of clearance across the age range as a function of weight.
- Effect of other covariates such as disease status/severity, race, gender etc. on “Slope” parameter can be tested.
Interpretation of “Slope”\(^1\)

From PK first principles

- For \(\text{AUC}_{\text{ss}}\):
  \[
  \frac{\text{AUC}}{\text{Dose}} = \frac{F}{\text{CL}}; \quad \text{AUC} = \frac{F}{\text{CL}} \times \text{Dose}
  \]
  Hence, \(\text{Slope} = \frac{F}{\text{CL}}\)

- For \(\text{C}_{\text{max,ss}}\), for a drug undergoing first order absorption and following monoexponential elimination:
  \[
  \text{Concentration} (t) = \frac{F \times k_a}{V_d (k_a - k_e)} \times \left( \frac{e^{-k_e t}}{1 - e^{-k_e \tau}} - \frac{e^{-k_a t}}{1 - e^{-k_a \tau}} \right) \times \text{Dose}
  \]
  Hence for \(\text{C}_{\text{max,ss}}\), \(\text{SLOPE} = \frac{F \times k_a}{V_d (k_a - k_e)} \times \left( \frac{e^{-k_e T_{\text{max}}}}{1 - e^{-k_e \tau}} - \frac{e^{-k_a T_{\text{max}}}}{1 - e^{-k_a \tau}} \right)\)

\(^1\)Purohit et.al., The Journal of Clinical Pharmacology 2019, 59(6) 811–820
• Tend to summarize the data with intent to provide some context.
  • Made up Example: The pharmacokinetics of Drug A were investigated in 43 subjects with A disease and a mean ± SD body surface area involvement of 50 ± 30% (range C to D). In this study, subjects applied approximately X mg/cm² of Drug A twice daily for 14 days. The mean ± SD Cmax and AUC for Drug A on Day 14 were XXX ± YYY ng/mL and WWW ± ZZZ ng*h/mL, respectively.

• Everything in the above presentation is factual but with limited interpretation or context.

• Additionally, using the summary as above are we truly estimating exposures at the upper range of doses? Probably not!

• Presenting PK concentrations or parameters without context is like telling a story without an ending.

• MUst study results constitute a very rich dataset which if analyzed and interpreted appropriately can provide a lot more than a descriptive summary of PK concentrations/parameters.
Most MUst studies will describe objective as – “Estimation or Characterization of PK characteristics of ………”

However, the intent of MUst is to utilize to systemic exposure data in conjunction with toxicology to estimate safety margins.

- Similar intent applicable for drugs with human data from other routes of administration.

MUst study also serves to confirm that exposures maintain adequate margins to systemic exposures associated with potential of AE’s or producing systemic pharmacology.

Hence, the key word here is PRECISION.

- MUst study should be able to precisely estimate the safety margin to preclinical toxicology or established clinical exposure threshold.

- Precision is a study design element dependent on sample size.
A simple example: Topical drug applied as a fixed dose with a known maximum dose and known exposure threshold for calculation of safety margin.

- May also be applicable to topical agents where systemic concentrations don’t correlate with dose.

- Utilizing PK data from a pilot PK study*:
  - Assuming the log transformed PK parameters follow a t-distribution with same geometric mean and SD as previously observed data power can be calculated for a range of sample sizes.
  - Power >80-90% to show that estimated geometric mean would not exceed established threshold can help decide the sample size.
  - For topical agents with large margins to thresholds and typical variability a large number of subjects may not be required.
    - A minimum number of subjects in consultation with regulators can be targeted.

* Ideally MUsT study should never be the first PK study – Nathalie Wagner
A more frequent example: Topical drug applied as a % of BSA with a maximum %Treated BSA of up to 90% and known exposure threshold for calculation of safety margin.

Complexities:
- Variable, %treated BSA and dose
- What represents maximum dose?
  - 90% treated BSA OR the mean treated BSA from the study OR ....
- What are we estimating precision of?

Most dermatological indications likely fall under this category.

Ideally some kind of pilot PK study or data from a Phase 2 study if available can be used to calculate sample size with a target precision to achieve MUsT objectives.
Principles of Estimating Sample Size of a MUsT Study with Variable Dose

- Exposure threshold – Could be based on NOAEL or clinical data.
- Maximum dose or Maximum %treated BSA
  - Need to fix the maximum application rate (mg/cm²)
- Precision criteria – as an example, mean exposure at 60% treated BSA does not exceed the exposure threshold
- Analysis approach – A more quantitative analysis of the relationship between dose and systemic exposure parameter.
  - Regression models as described for crisaborole (Purohit et.al., 2020) or tofacitinib (Purohit et.al., 2019) can be considered.
  - Utilizing summary statistic based approach can also be considered (Slide 7) but this approach has limitations.
Drug X was evaluated in a Phase 2 study in patients of mild to moderate severity.

Steady state average concentration data (Cavg = AUC/Dosing Interval) was collected along with average daily dose.

The Cavg and ointment dose were analyzed using a linear mixed effect model and used to project exposures to higher %treated BSA.

Model predicted that mean Cavg could be greater than C pg/ml at ~70% treated BSA.

Exposure Threshold: Cavg<C pg/ml, was identified as a threshold concentration to ensure that systemic concentrations after topical application do not approach levels that can produce systemic pharmacology.

Linear mixed effect model:

$$
\text{Concn}_{ij} = \alpha_o + (\beta_o + \beta_i) \times \left(\frac{\text{Wt}_i}{70}\right)^{-0.75} \times \text{Ointment Dose}_{ij} + \varepsilon_{ij}
$$

Where,

- $\text{Concn}_{ij}$ is the jth observed concentration for patient i,
- $\text{Ointment Dose}_{ij}$ is the jth recorded ointment dose for patient i,
- $\alpha_o$ is the average intercept fixed at 0 based on the expectation of no drug levels without treatment,
- $\beta_o$ is the average slope for patients, and $\beta_i$ is the deviation from the average slope for patient i,
- $\varepsilon_{ij}$ is the random residual error of the jth measurement from patient i.

An allometric power model of the form $(\text{Wt}/70)^{-0.75}$ can be included as a multiplicative term to scale clearance for pediatric subjects.
A Hypothetical MUst Design – Design Elements

• Objective:
  • Estimate systemic exposures of Drug X at steady state following treatment with Drug X ointment 0.2% and confirm systemic exposures at %treated BSA of <70% are <C pg/ml.
  
• Patient population – mild to moderate patients.
• Age range - > 2 years
• %Treated BSA at baseline - >30%
• Dose regimen – 0.2% ointment BID at application rate of 3 mg/cm²
• Treatment duration – 14 days
• Cohorts:
  • Cohort 1: ≥ 18 years
  • Cohort 2: ≥ 12 years – 17 years
  • Cohort 3: ≥ 6 years – 11 years
  • Cohort 4: ≥ 2 years – 5 years
• PK assessments - Day 14 at steady state
• Primary endpoint – Cavg
  • For Drug X ointment PK profile is essentially flat where Cmax = Cavg = Cmin
• Key objective is to estimate at %treated BSA <70% the systemic exposures are <C pg/ml.

• The practical limitation is that you cannot recruit enough number of subjects at a given %treated BSA to attain the precision of the estimate needed to make the decision.

• Application of MIDD approaches can efficiently overcome this issue.

• The linear mixed effects models can be used to
  • Determine sample size for the MUsT study using simulations
  • Analyze the MUsT study results, to provide estimates of systemic exposures at %treated BSA of interest.
1. Key Assumption: The linear mixed effect model as the truth

2. Generate a demographic dataset of subjects:
   1. Age range >2 years with associated age appropriate weights and BSA
   2. Assign %treated BSA in the target range of the MUsT trial (e.g., 25% to 90%)
      1. Careful here – make sure you account for the true distribution of %treated BSA’s.
   3. Use the linear mixed effects model to predict exposures for all subjects in demographic dataset for the relevant ointment dose.

3. Draw a random sample of required number of subjects per cohort (4 or 6 or 8 etc.)

4. Analyze the random sample of subjects using a linear regression model.

5. Use the fitted regression model to predict exposures at relevant %Treated BSA e.g., 60% or 70%

6. Repeat steps 4,5 and 6 large number of time (e.g. 5000 times) to approximate a large number of MUsT trials and summarize.

A Hypothetical MUsT Design – Simulation Strategy or Steps

Don’t assume a uniform distribution when in reality the population is log normally distributed.

May sound complicated but it really is not
A Hypothetical MUsT Design – A Note on Interpretation of Simulation Outputs.

- Simulation results always provide a mean prediction with uncertainty (confidence interval) around the mean estimate.
  - Criteria for interpretation of simulation results can use:
    - Mean prediction which ignores the uncertainty of the estimate
    - OR
    - Upper Confidence Interval (since we don’t want to exceed a certain threshold) which is a very conservative approach and consistent with the MUsT philosophy
- When dealing with MUsT studies with a very wide age range, you may want to rely on age group with the highest predicted concentrations for adequate sample size.
  - Base expectation is that exposures in children will not be higher than adults by clinically significant levels.
  - However marginally high exposures can have an impact on sample size if concentrations are close to the thresholds.
A Hypothetical MUsT Design – Simulation Summary (Applying Conservative Criteria of Upper CI of Mean Prediction)

- The simulation amounts to a virtual conduct of a MUsT multiple times over.
- The power to demonstrate that exposures don’t exceed exposure threshold can be calculated.
- Based on the %treated BSA, slightly higher sample size may be needed for pediatric cohorts because of the relationship of weight, associated BSA and scaled clearance.
- If predicted exposures have a good margin to the exposure threshold adequate power can be achieved with relatively small sample size.
  - In the current example at 70% treated BSA, concentrations exceed the exposure threshold.
- Irrespective of power, a minimum number of patients in each age cohort may need to be evaluated.
- With the current example, sample size of 10 – 12 per cohort (i.e. total 40 – 48 subjects) will provide adequate power to demonstrate that at 50% - 55% treated BSA, systemic exposures don’t exceed exposure threshold across all age groups.
A Hypothetical MUsT Design – Simulation Summary (Applying less Conservative Criteria of Mean Prediction)

- Applying a less conservative criteria by ignoring the uncertainty around the mean prediction:
  - At 50% treated BSA, adequate power can be achieved at all age groups with a relatively small number of subjects.
  - At 60% treated BSA you may have adequate power to demonstrate that mean exposures don’t exceed the threshold in certain age groups. However in reality the study is underpowered.
  - At 70% treated BSA, you have a small chance of showing that mean exposures don’t exceed threshold which is not real.

- Hence, choice of criteria is very important when evaluating simulation results and choice of less stringent criteria that ignore the uncertainty can result in flawed study design.
Summary and Conclusions

• MUsT study is one of the most important studies which underwrites the pharmacokinetic characteristics, the systemic safety expectations and safety profile of a topical product.

• Application of MIDD approaches to design, analyze and interpret the MUsT study can enable achievement of study objectives efficiently and with adequate precision.

• Described application of linear mixed effect models and simulation methodology to support sample size for MUsT studies can improve study efficiency and interpretation.

• Use of MIDD based predictions of systemic exposures at relevant %treated BSA are more informative than the summary statistics traditionally provided for topical products.
Future Possibilities of Leveraging MIDD

- A key feature of MIDD approaches is the ability to predict with precision when data is collected from well designed studies.
- Make the label more informative by using model based predictions of exposures at relevant treated BSA’s and eliminate guesswork.
- Tabulated systemic exposures predicted from an adequately qualified model can provide a quick reference for assessing benefit risk to physicians and prescribers.
  - If systemic exposures are different in children that can be highlighted and summarized using similar tabulation.
- Appropriately account for outliers both spurious and real to further inform the central tendencies of the data and define real differences in the population.

<table>
<thead>
<tr>
<th>%treated BSA</th>
<th>AUC or Cavg</th>
<th>Margins to safety exposure thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>40%</td>
<td>XX</td>
<td>YY</td>
</tr>
</tbody>
</table>

*Maximum recommended application rate = ZZ mg/cm²
Backup
Impact of Age on Systemic Exposure: Expectations From First Principles

- From first principles at similar %Treated BSA pediatric subjects will receive a lower dose relative to adults.
- Pediatric subjects will also have a lower clearance relative adults.
- However, similar systemic exposures at a given %treated BSA can be explained by the lower dose in pediatric subjects which offsets the lower clearance.
- From first principles the above is applicable when the bioavailability (F) is constant across age groups.
- The crisaborole dataset provides evidence that F is approximately the same for subjects >2 years (Purohit et.al., 2020).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BSA (cm²)*</th>
<th>%Treated BSA</th>
<th>Application Rate (mg/cm²)</th>
<th>Ointment dose (mg)</th>
<th>Relative Dose</th>
<th>Relative Clearance**</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5516</td>
<td>90</td>
<td>3</td>
<td>14900</td>
<td>0.30***</td>
<td>0.29</td>
</tr>
<tr>
<td>18</td>
<td>18120</td>
<td>90</td>
<td>3</td>
<td>48900</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

• BSA calculated using 50th percentile height and weight from CDC growth charts

**Calculated using allometric function:

\[ CL_{ped} = CL_{adult} \times \left(\frac{Weight}{70}\right)^{0.75} \]

***Ratio of pediatric dose to adult dose.

Data represents theoretical expectations.