Design of MUsT Trials and Leveraging MIDD

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Topical Drug Development: Evolution of Science and Regulatory Policy II

Pfizer
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Global Product Development

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Recap from Analysis and Interpretation of Topical PK Data July 29th 2019

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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 ($AUC_{ss}/C_{avg,ss}$ or $C_{max,ss}$) and ointment dose.

$$AUC_{ss_{,i}} \; or \; Cmax_{ss_{,i}} = Intercept + \left(Slope \times (\frac{Wt_i}{70})^{ex_1}\right) \times Ointment\ Dose_i$$

- 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 AUC_{ss}:

$$\frac{\mathrm{AUC}}{\mathrm{Dose}} = \frac{\mathrm{F}}{\mathrm{CL}}\ ;\ \mathrm{AUC} = \frac{\mathrm{F}}{\mathrm{CL}} \times \mathrm{Dose}$$

Hence, $\boldsymbol{Slope = \frac{F}{CL}}$

- For $C_{max,ss}$, for a drug undergoing first order absorption and following monoexponential elimination:

$$Concentration\ (t) = \frac{F \times k_a}{V_d(k_a - k_e)} \times \left(\frac{e^{-k_e \times t}}{1 - e^{-k_e \times \tau}} - \frac{e^{-k_a \times t}}{1 - e^{-k_a \times \tau}}\right) \times Dose$$

Hence for $Cmax_{ss}$, $\boldsymbol{SLOPE = \frac{F \times k_a}{V_d(k_a - k_e)} \times \left(\frac{e^{-k_e \times Tmax}}{1 - e^{-k_e \times \tau}} - \frac{e^{-k_a \times Tmax}}{1 - e^{-k_a \times \tau}}\right)}$

[1]Purohit et.al., The Journal of Clinical Pharmacology 2019, 59(6) 811–820

Typical MUsT Data Presentation

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- 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/cm^2 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.

MUsT Study – Estimation or Confirmatory or Both

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- 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.

Estimating Sample Size of a MUsT Study - 1

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- 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

Estimating Sample Size of a MUsT Study - 2

- 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/cm^2)
- 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.

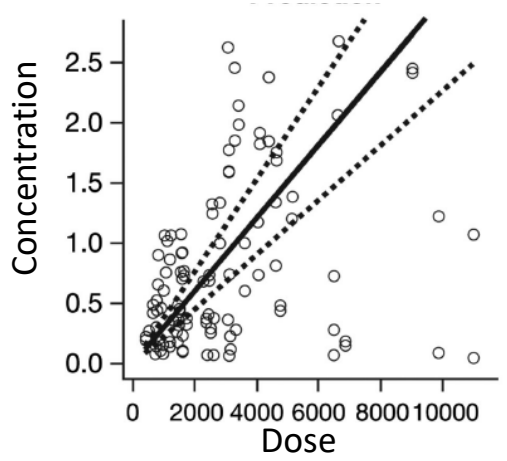
A Hypothetical MUsT Design – Prior Information

- 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:

$$Concn_{ij} = \alpha_o + (\beta_o+\beta_i)\times(Wt_i/70)^{-0.75}\times Ointment\ Dose_{ij}+\varepsilon_{ij}$$

Where,
$Concn_{ij}$ is the j^{th} observed concentration for patient i,
$Ointment\ Dose_{ij}$ is the j^{th} recorded ointment dose for patient i,
α_o is the average intercept fixed at 0 based on the expectation of no drug levels without treatment,
β_o is the average slope for patients, and β_i is the deviation from the average slope for patient *i*,
ε_{ij} is the random residual error of the jth measurement from patient *i*
Wt_i is weight in kilograms
An allometric power model of the form $(Wt/70)^{-0.75}$ can be included as a multiplicative term to scale clearance for pediatric subjects.



A Hypothetical MUsT Design – Design Elements

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- 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/cm^2
- 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

A Hypothetical MUsT Design – Sample Size Considerations

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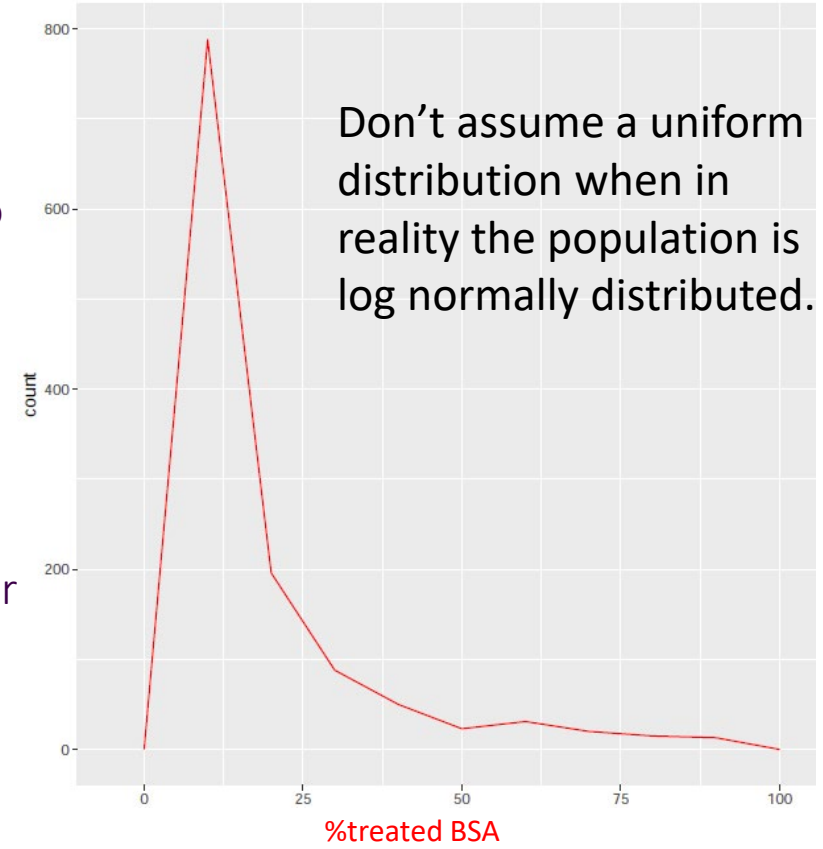
- Key objective is to estimate at %treated BSA <70% the systemic exposures are <C pg/ml.
- The practical limitation is that you cannot recruit enough number of subjects at a given %treated BSA to attain the precision of the estimate needed to make the decision.
- Application of MIDD approaches can efficiently 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.

A Hypothetical MUsT Design – Simulation Strategy or Steps

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.
4. Draw a random sample of required number of subjects per cohort (4 or 6 or 8 etc.)
5. Analyze the random sample of subjects using a linear regression model.
6. Use the fitted regression model to predict exposures at relevant %Treated BSA e.g., 60% or 70%
7. Repeat steps 4,5 and 6 large number of time (e.g. 5000 times) to approximate a large number of MUsT trials and summarize.



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

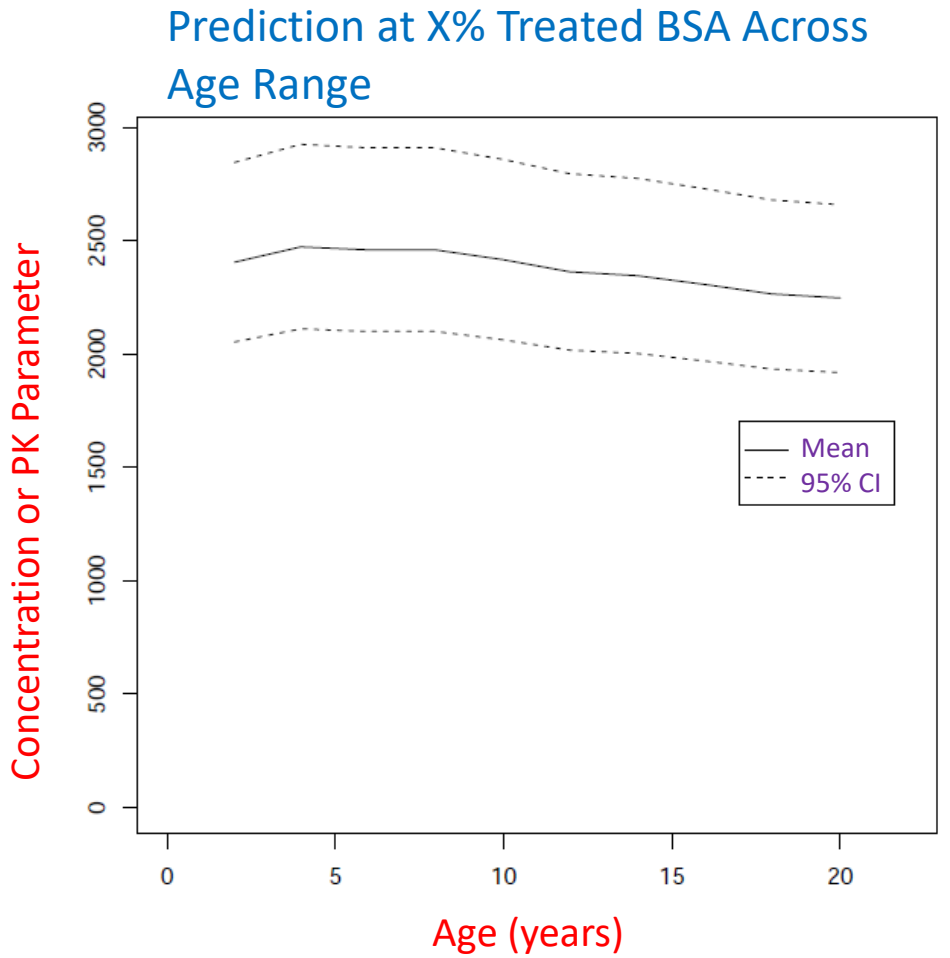
May sound complicated but it really is not

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

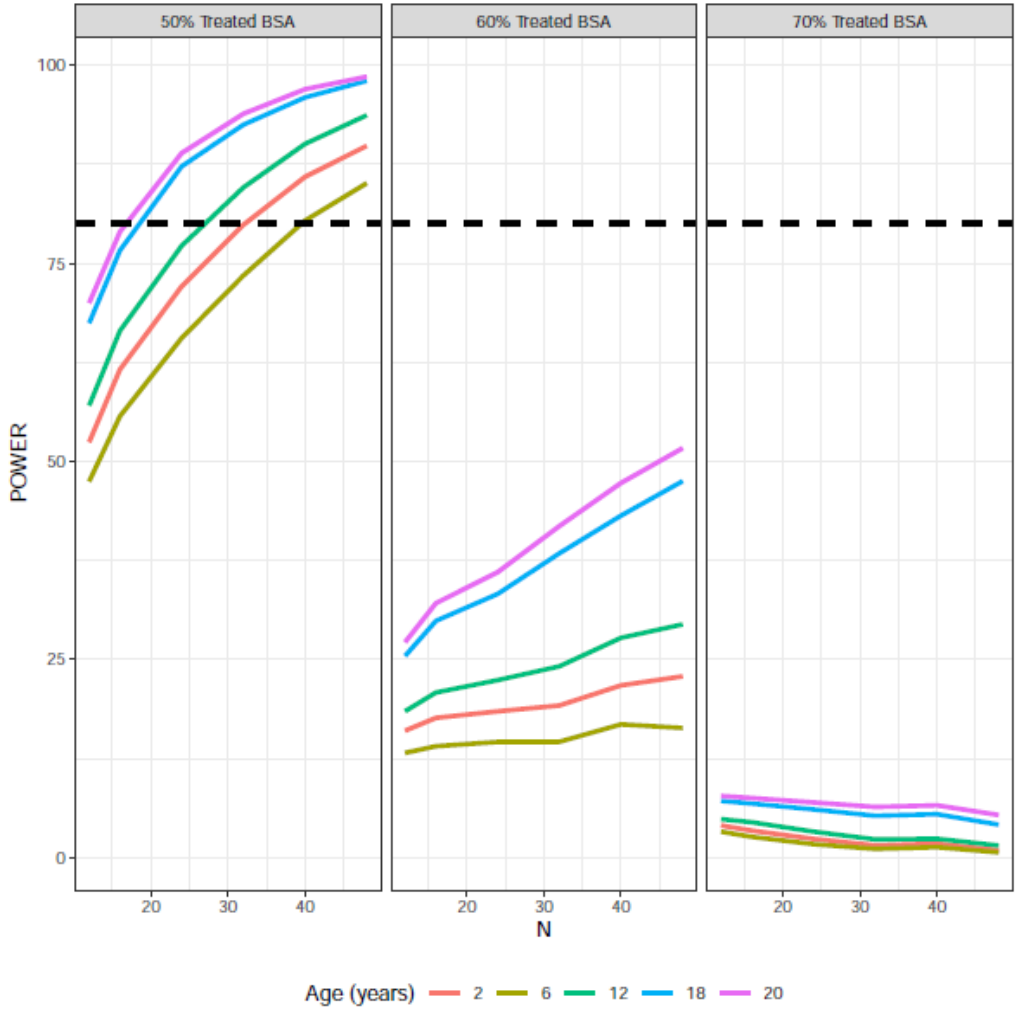
    OR

    - 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.



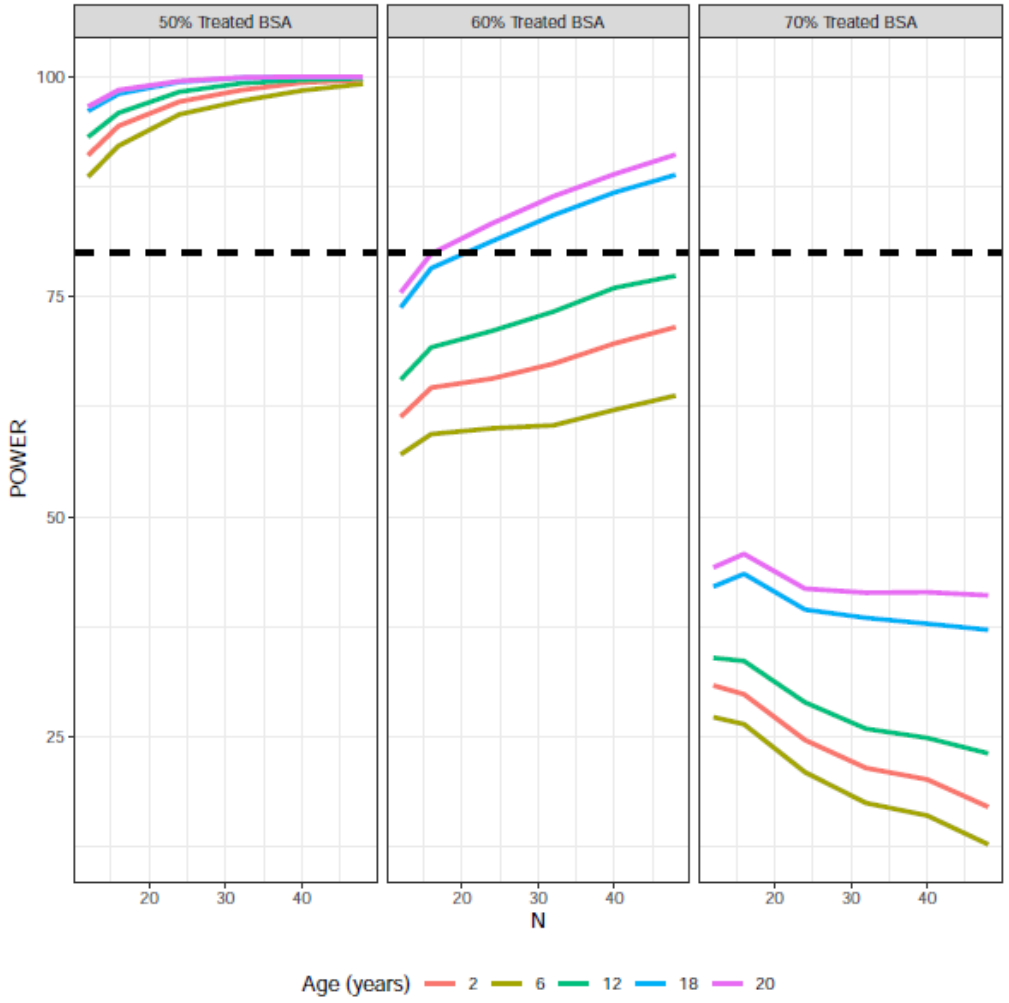
A Hypothetical MUsT Design – Simulation Summary (Applying Conservative Criteria of Upper CI of Mean Prediction)

- 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.

%treated BSA	AUC or Cavg	Margins to safety exposure thresholds
30%	X	Y
40%	XX	YY
↓	↓	↓
↓	↓	↓
*Maximum recommended application rate = ZZ mg/cm^2		

Backup

Impact of Age on Systemic Exposure: Expectations From First Principles

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- 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).

Age (years)	BSA (cm2)*	%Treated BSA	Application Rate (mg/cm^2)	Ointment dose (mg)	Relative Dose	Relative Clearance**
2	5516	90	3	14900	0.30***	0.29
18	18120	90	3	48900	1	1

- 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.