Analysis and Interpretation of Systemic Exposures from Topical Agents: Learnings from Crisaborole Ointment

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Topical Drug Development: Evolution of Science and Regulatory Policy

Pfizer
CLINICAL PHARMACOLOGY
Global Product Development

July, 29th 2019

Background

- Atopic dermatitis (AD) is a highly prevalent, chronic inflammatory skin disease characterized by eczematous lesions and intense pruritus[1,2]
  - Most patients have mild-to-moderate AD that can be managed with topical therapies[3-5]
- Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD patients aged 2 years and older[6]

1.Bieber T. *N Engl J Med*. 2008;358:1483-1494.
2.Bieber T. *Ann Dermatol*. 2010;22:125-137.
3. Silverberg JI et al. *Dermatitis*. 2014;25:107-114.
4. Silverberg JI. *Dermatol Clin*. 2017;35:283-289.
5. Silverberg JI et al. *Pediatr Allergy Immunol.* 2013;24:476-486.
6. Eucrisa (crisaborole) ointment, 2%, for topical use [package insert]. New York, NY: Pfizer Labs; 2017.

MUsT for Crisaborole Ointment[1]

- A multicenter, open-label maximal use, systemic exposure study with a PK Phase and a non-PK Safety Phase in children and adolescents with mild to moderate AD.
  - Cohort 1 comprised subjects aged 12–17 years, inclusive, with ≥25% Treatable BSA;
  - Cohort 2 comprised subjects aged 6–11 years, inclusive, with ≥35% Treatable BSA;
  - Cohort 3 comprised subjects aged 2–5 years, inclusive, with ≥35% Treatable BSA.
- Patients applied 3 mg/cm^2 of Crisaborole Topical Ointment, 2% BID for 28 days except on Days 1 and 8 when only a single morning dose was applied.
- Blood samples for determination of plasma concentrations of crisaborole and its two identified oxidative metabolites (inactive), AN7602 and AN8323, were collected:
  - Screening, Baseline, and predose on Days 2, 7, 8, and 9.
  - On days 1 and 8 Post dose samples at 3, 12 and 24 hours.
- Noncompartmental methods were used to determine PK parameters for crisaborole, AN7602, and AN8323, including Cmax, time to maximum measured plasma concentration (Tmax), $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-}T}$.
- Predose samples on Days 7, 8, and 9 were used to assess whether steady state had been reached.
- The Cmax and AUC values of crisaborole were compared among the three age cohorts using an ANOVA model.
- Safety parameters included AEs, clinical laboratory tests, and vital signs were monitored.

[1]Zane et.al., Pediatric Dermatology Vol. 33 No. 4 380–387, 2016

Crisaborole Ointment MUsT Results[1]

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- Crisaborole was rapidly absorbed with median Tmax of 3 hours.
- Systemic exposure to crisaborole increased with increasing treated BSA.
- Crisaborole showed marginal accumulation over 8 days.
- Steady state for crisaborole was achieved over duration of dosing.
- No significant differences were observed in PK parameters between the cohorts (ANOVA: p value>0.05).

Summary of PK Parameters for Crisaborole and Metabolites.

Parameter	Crisaborole	AN7602	AN8323
Day 1			
T_{max}, hours, median (range) (n = 34)	3.00 (3–12)	3.00 (3–12)	12.0 (3–24)
C_{max}, ng/mL, mean ± SD (n = 34)	111 ± 113	37.8 ± 35.0	2,270 ± 2,640
AUC_{0-12}, ng·hour/mL, mean ± SD (n = 32)	759 ± 730	247 ± 224	16,800 ± 16,900
AUC_{0-T}, ng·hour/mL, mean ± SD (n = 34)	863 ± 759	288 ± 237	30,800 ± 30,500
AUC_{0-24}, ng·hour/mL, mean ± SD (n = 29)	833 ± 694	274 ± 207	32,500 ± 32,500
Day 8			
T_{max}, hours, median (range) (n = 33)	3.00 (3–24)	3.00 (0–12)	3.00 (0–24)
C_{max}, ng/mL, mean ± SD (n = 33)	127 ± 196	40.8 ± 48.6	6,150 ± 4,790
AUC_{0-12}, ng·hour/mL, mean ± SD (n = 32)	949 ± 1240	290 ± 313	63,400 ± 49,000
AUC_{0-T}, ng·hour/mL, mean ± SD (n = 33)	1320 ± 1310	398 ± 347	119,000 ± 87,600
AUC_{0-24}, ng·hour/mL, mean ± SD (n = 32)	1320 ± 1330	391 ± 351	116,000 ± 86,700

AUC_{0-12}, area under the plasma concentration-versus-time curve from time 0 to 12 hours after dosing; AUC_{0-24}, area under the plasma concentration-versus-time curve from time 0 to 24 hours after dosing; AUC_{0-T}, area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration; C_{max}, observed maximum plasma concentration after dosing; SD, standard deviation; T_{max}, time to reach C_{max}.

Summary of Crisaborole Data by Cohort.			
Parameters	Cohort 1 (12 -17 years, N=12)	Cohort 2 (6 -11 years, N=12)	Cohort 3 (2 - 5 years, N=10)
Day 8 AUC_{0-12} [Mean (range)]	599 (52.7 – 2960)	1490 (309 – 7360)	702 (272 -1120)
Day 8 Cmax [Mean (range)]	81.4 (20.6 – 179)	205 (27.8 – 1170)	83.3 (27.9 – 122)
%Treated BSA [Mean(range)]	35.8 (27 – 61)	54.9 (35 – 92)	47 (35 – 91)
Pfizer, Inc. Data on file.			

[1]Zane et.al., Pediatric Dermatology Vol. 33 No. 4 380–387, 2016

MUsT Results Interpretation

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- Characterized the systemic exposures for Crisaborole ointment across the age groups.
  - Systemic exposures appear similar across age groups.

- Characterized systemic exposures at the upper range of ointment doses across the age range.
  - The mean %treated BSA ranged from 35.8 to 54.9 across the cohorts with mean of 48.7 across all cohorts.
  - The average %treated BSA for patients with mild-moderate AD in pivotal phase 3 trials (AD-301 and AD-302) was 18.3%.

- Characterized systemic exposures to generate conservative estimates for safety margins.
- What else?
  - Comprehensive analysis of all the PK data for crisaborole including the MUsT data can answer several additional questions

Other PK Data for Crisaborole

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Crisaborole Studies in Healthy Volunteers and Atopic Dermatitis Subjects Included in the Analyses				
Anacor Study ID*	**Population**	**Design**	**Number of Subjects and Age Range (years)**	**Study Objective**
AN2728-PSR-104	Healthy Volunteers	Single-center, randomized, double-blind, vehicle-controlled, multiple cohort, ascending dose	16 Males 19–31 years	Ascending dose PK study in healthy volunteers.
AN2728-TQT-108	Healthy Volunteers	Single-center, randomized, parallel cohort with nested crossover QT/QTc interval study.	98 Males, 82 Females 18-45 years Crisaborole: Supratherapeutic dosing, 60 subjects; therapeutic dosing, 60 subjects Moxifloxacin control, 60 subjects	Thorough QT Study
AN2728-PK-101	Healthy Volunteers	Open-label, 3 period, fixed-sequence DDI study	15 Males, 9 Females 21-55 years	Drug interaction study with warfarin
AN2728-AD-203	AD Patients	Multicenter, open-label, nonrandomized, safety/ tolerability, PK study	4 Males, 19 Females 12–17 years	Safety and tolerability study in adolescent AD patients
AN2728-AD-102	AD Patients	Multicenter, open-label, MUSE study to assess safety and PK in 2 years – 17 years old AD subjects	15 Males, 19 Females 2.1–17.7 years	MUsT study in 2 – 17 year AD patients.

AD = atopic dermatitis; BID = twice a day; BSA = body surface area; DDI = drug-drug interaction; MUSE = maximal use systemic exposure; PK = pharmacokinetics; QD = once daily.

*All studies evaluated crisaborole PK at steady state.

Note - Data from MUsT trial conducted in adult patients with psoriasis was also included in the analysis. However, the safety and efficacy of crisaborole has not been established in clinical trials and crisaborole is not indicated for the treatment of psoriasis.

Demographics of PK Data for Crisaborole

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	Statistic	Total
Baseline Body Weight (Kg)	N Mean (SD) Median (min, max)	244 69.6 (21.6) 69.8 (11.8, 163.4)
Age (year)	N Mean (SD) Median (min, max)	244 30.4(14.0) 31.0(2.1, 70.0)
Ointment Dose (mg)	N Median (min, max)	244 16550 (4800, 47100)
Gender	N	244
Male	N (%)	139 (57)
Female	N (%)	105 (43)
Subject Status	N	244
Healthy	N (%)	154 (63)
Atopic Dermatitis	N (%)	57 (23)
Mild	N (%)	25 (44)
Moderate	N (%)	32 (56)
Psoriasis	N (%)	33 (14)
Moderate (PGA = 2 or 3)	N (%)	22 (67)
Severe (PGA = 4 or 5)	N (%)	11 (33)
Race	N	244
White	N (%)	184 (75)
Black	N (%)	30 (12)
Asian	N (%)	4 (1.6)
Other	N (%)	26 (11)

max = maximum; min = minimum; N = number of subjects; SD = standard deviation.

Note - Data from MUsT trial conducted in adult patients with psoriasis was also included in the analysis. However, the safety and efficacy of crisaborole has not been established in clinical trials and crisaborole is not indicated for the treatment of psoriasis.

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

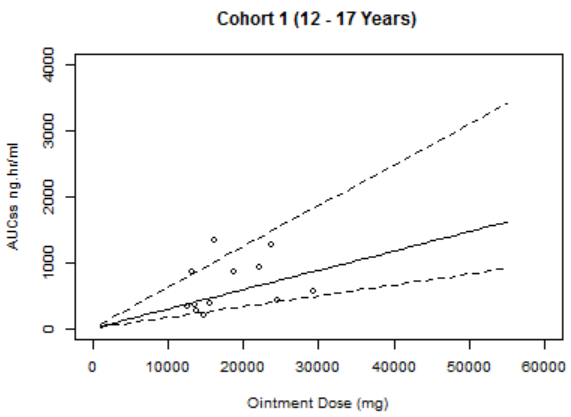
- For $C_{max,ss}$, for a drug undergoing first order absorption and following monoexponential elimination:

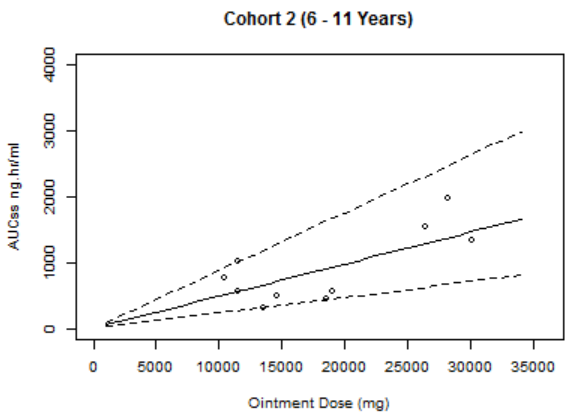
$$Concentration\ (t) = \frac{F \times k_a}{V_d(k_a - k_e)} \times \left(\frac{e^{-k_e \times t}}{1 - e^{-k_e \times \tau}} - \frac{e^{-k_a \times t}}{1 - e^{-k_a \times \tau}}\right) \times Dose$$

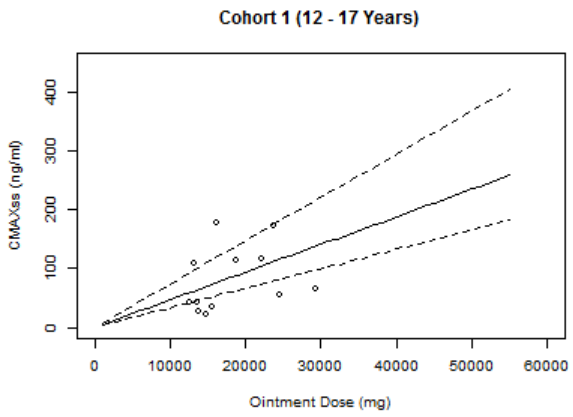
Hence for $Cmax_{ss}$, $\boldsymbol{SLOPE = \frac{F \times k_a}{V_d(k_a - k_e)} \times \left(\frac{e^{-k_e \times Tmax}}{1 - e^{-k_e \times \tau}} - \frac{e^{-k_a \times Tmax}}{1 - e^{-k_a \times \tau}}\right)}$

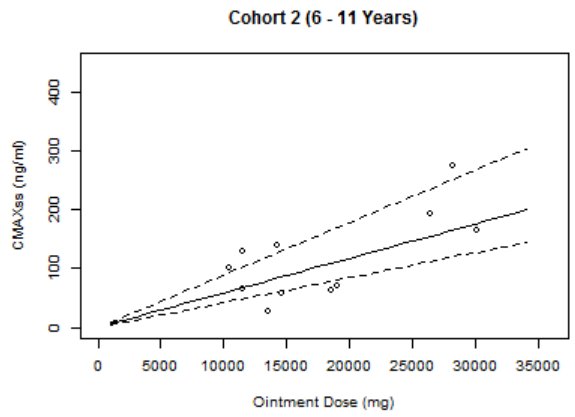
[1]Purohit et.al., The Journal of Clinical Pharmacology 2019, 59(6) 811–820

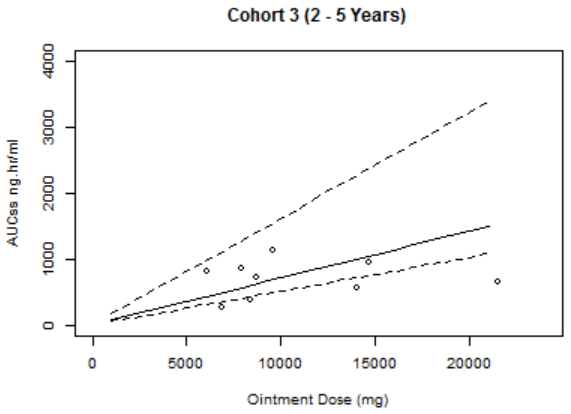
Predictive Performance of AUC_{ss} and $Cmax_{ss}$ Models for MUsT

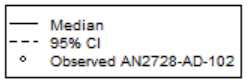


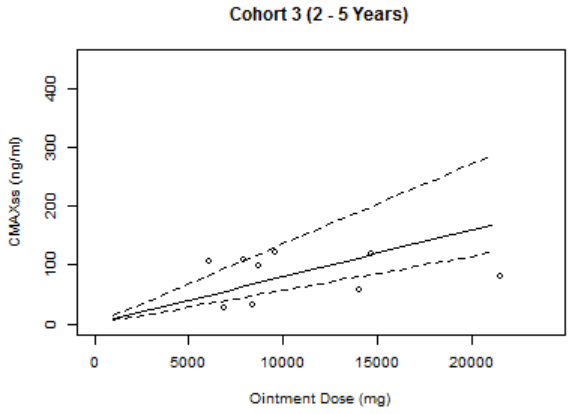


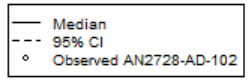








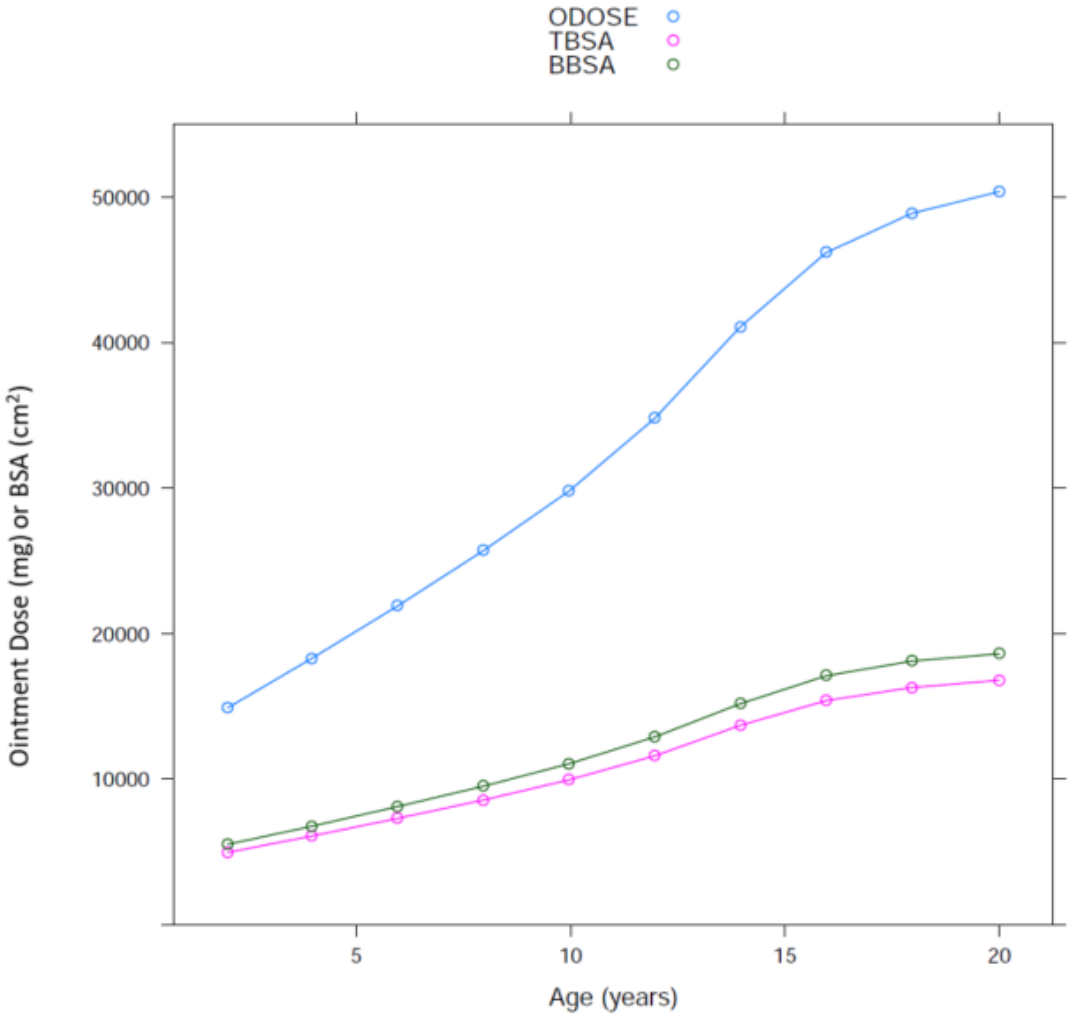




The ointment doses have been limited to the maximum treatable BSA for cohorts of subjects <11 years.

Pfizer, Inc. Data on file.

Note on Relationship of Ointment Dose, Treated BSA and Actual BSA Across Age



ODOSE = Ointment dose in mg, TBSA = Treated BSA in cm^2, BBSA = Actual BSA in cm^2.

Theoretical Relationship of Ointment Dose to Body Weight and Body Surface Area.

Ointment Dose (mg) [a]	Age (years)	Body Weight (Kg)	BSA (cm^2)	%Treated BSA	Treated BSA[b] (cm^2)	Ointment Dose (mg/cm^2)
14900	2	13	5516	90	4960	3.00
18300	4	16	6761	90	6090	3.00
21900	6	21	8113	90	7300	3.00
25700	8	26	9513	90	8560	3.00
29800	10	32	11054	90	9950	2.99
34800	12	40	12901	90	11600	3.00
41100	14	51	15188	90	13700	3.00
46200	16	61	17106	90	15400	3.00
48900	18	67	18120	90	16300	3.00
50400	20	71	18623	90	16800	3.00

a. Assumes application rate of 3 mg/cm^2.

b. The corresponding treated BSA was derived from absolute BSA calculated using the 50th percentile height and body weight obtained from CDC growth charts[1] at respective ages using the Mosteller formula.

Pfizer, Inc. Data on file.

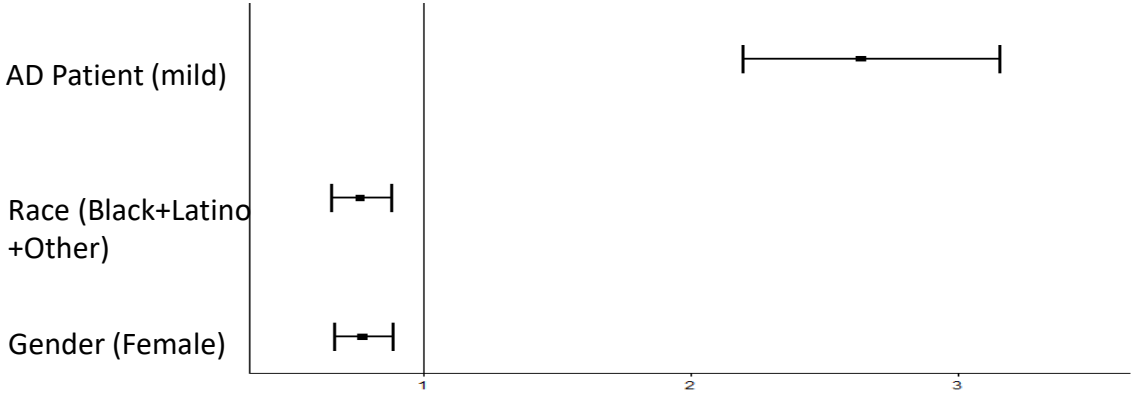
- At a given %Treated BSA, body size dictates ointment dose.
- At a given %Treated BSA a smaller pediatric subject will always have a lower ointment dose relative to an adult.

Results of Non-linear Regression Analysis

Effect of Covariates on Slope for AUC_{ss}

Reference of Body Weight=70 kg, Healthy, Male, White

Effect of Covariates on Slope for $Cmax_{ss}$



Reference of Body Weight=70 kg, Healthy, Male, White

Interpretation:

- For every milligram increase in ointment dose, subjects with AD will have ~2.5 fold higher unit increase in AUC_{ss} or $Cmax_{ss}$ compared to a healthy subject.
- Race and gender appear to have marginal impact on Slope.

The solid square represents median and the error bars represent the 95% CI obtained by a non-parametric bootstrap of the final model.

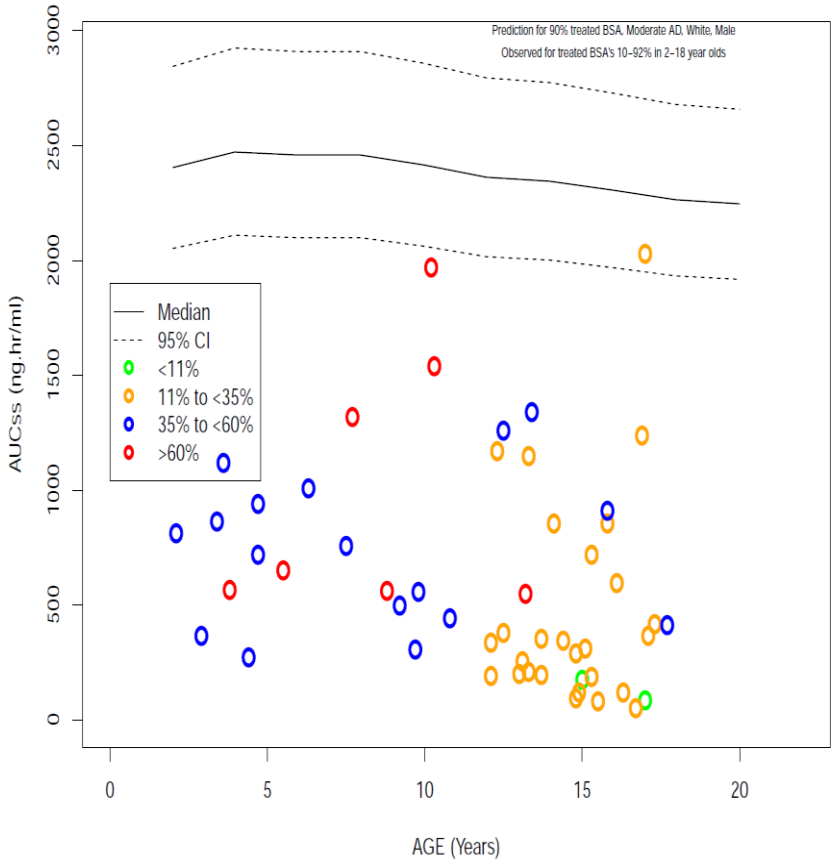
Pfizer, Inc. Data on file.

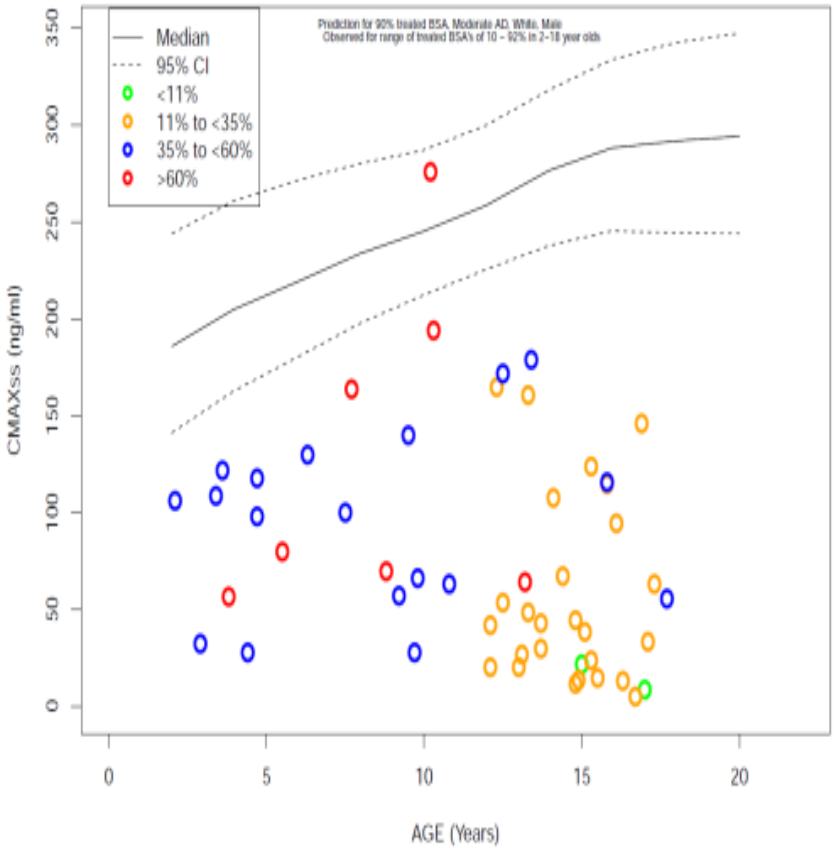
Impact of Age on Systemic Exposures

- Observed, data indicates that the range of systemic exposures remains similar across age groups for a given narrow range of treated BSA.

- Predictions from model indicate at a given treated BSA systemic exposures are similar across age range.
  - Pediatric subjects do not have higher systemic exposures relative to adults at similar %treated BSA

Model Predictions at Maximal Treated BSA of 90%





**Observed, data provided for context only and does not represent a predictive check.*

Pfizer, Inc. Data on file.

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.

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.

Systemic Exposures for Topical Agents Could be Higher in Pediatric Patients Vs Adults Under Following Conditions

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- Greater disease severity
- Greater skin barrier impairment
- Higher affected body surface area
- Alterations of systemic clearance (lower) depending on nature of disease

Conclusions

- The relationship between AUC_{ss} or $C_{max,ss}$ was adequately described by a Slope model with appropriate covariates.
- Disease status had a clinically significant impact on SLOPE for AUC_{ss} and $C_{max,ss}$ with a 2-3 fold higher SLOPE relative to healthy volunteers.
- The impact of race, gender and disease severity are not considered clinically significant.
- At similar % treated BSA, exposures across age groups are expected to be in a similar range.
  - The exposures in children at maximum possible dose are unlikely to exceed the exposures at the maximum possible dose in adults.

Cross Study Analysis of Systemic Exposures of Topical Agents.

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- Quantifies the relationship of ointment dose with systemic exposure parameters.
- Allows estimation of the impact of disease on systemic exposures relative to healthy volunteers.
- Allows estimation and assessment of significance of other demographic covariates on the systemic exposures.
- Synthesizes all the data:
  - Accounts for differences in dose, treated BSA, age and body size.