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Systemic Tofacitinib Concentrations in Adult Patients With Atopic Dermatitis Treated With 2% Tofacitinib Ointment and Application to Pediatric Study Planning

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Abstract

Atopic dermatitis is a chronic eczematous, pruritic, inflammatory skin condition affecting children and adults. Tofacitinib is a Janus kinase inhibitor. The efficacy, safety, and pharmacokinetics of 2% tofacitinib ointment twice daily have been evaluated in a 4-week phase 2a multisite randomized, double-blind, vehicle-controlled, parallel-group study (NCT02001181) in adult patients with mild to moderate atopic dermatitis and 2% to 20% body surface area (BSA) involvement. Tofacitinib ointment demonstrated significantly greater efficacy versus vehicle for all efficacy end points and had an acceptable safety profile. Predose and postdose pharmacokinetic samples were collected in week 2 and week 4. The objective of this analysis was to assess if predicted mean tofacitinib concentrations with topical application at higher treated BSA across age groups would exceed relevant concentration thresholds based on oral doses of tofacitinib. In this analysis, the pharmacokinetic concentrations were characterized using a linear mixed-effects model. The model was used to predict concentrations for adults with higher (>20%) treatable BSA. Adult concentrations were used to extrapolate concentrations to a pediatric population (2 to 17 years) using allometric principles. The predicted systemic concentrations for 2% tofacitinib ointment in both adult and pediatric populations at treated BSA ≤50% for a mild to moderate atopic dermatitis population did not exceed those reported for the 10th percentile of observed oral tofacitinib 5-mg twice-daily doses in patients with moderate to severe plaque psoriasis. The methodology described will enable analysis and prediction of systemic concentrations for topical agents.

Keywords

atopic dermatitis, pharmacokinetics, systemic concentration, tofacitinib, topical

Atopic dermatitis is an inflammatory skin condition affecting up to 20% of children and adults.[1] The disease is characterized by the appearance of eczematous skin lesions associated with unrelenting pruritus.[2] Onset of atopic dermatitis generally occurs in early childhood and is associated with a high socioeconomic burden and an impact on quality of life, particularly on the mental health and sleep quality of patients.[3–5] The pathogenesis and etiology of atopic dermatitis are similar in adults and children[6,7] and, although not clearly known, is thought to involve a complex interaction between genetic, environmental, and immunologic factors. In particular, the T-helper cell 2 cytokines (interleukin [IL]-4, IL-5, IL-13, and IL-31) have been implicated in the pathogenesis of atopic dermatitis.[6,8] Treatment usually involves the use of topical creams or ointments including emollients, corticosteroids, calcineurin inhibitors, and phosphodiesterase 4 inhibitors.[9] Additional treatments for atopic dermatitis include refined coal tar, topical and oral antibiotics, phototherapy, and systemic immunosuppressants.[10–12]

Tofacitinib is a Janus kinase (JAK) inhibitor. A phase 2a trial evaluated the efficacy, safety, and pharmacokinetics of 2% tofacitinib ointment in adult patients with mild to moderate atopic dermatitis with 2%-20% body surface area (BSA) involvement.[13] This trial demonstrated the efficacy of tofacitinib as a topical ointment to treat mild to moderate atopic dermatitis,[13] which may be because of the direct inhibition of cytokines such as IL-4 through attenuation of JAK-signal transducer and activator of transcription signaling in keratinocytes, as shown in studies of tofacitinib for rheumatoid arthritis and psoriasis.[14,15] The most common treatment-emergent adverse event reported in the phase 2a trial of tofacitinib in mild to moderate atopic dermatitis was nasopharyngitis (n = 2).[13]

Topical treatment of atopic dermatitis ensures targeted local treatment of affected areas while minimizing

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systemic exposures. Atopic dermatitis is a disease with high incidence in children[6,7]; therefore, development of new treatments typically progresses sequentially in clinical studies from adults to pediatric populations. Considering that atopic dermatitis can affect large BSA (90% or more) in both adults and children, topical therapies should ensure that systemic exposures remain low relative to concentrations likely to cause systemic pharmacological effects or cause systemic adverse effects and hence maintain a favorable benefit:risk profile of treatment.

The knowledge of expected systemic concentrations is critical in designing future adult and pediatric studies; however, the extrapolation of concentrations from adults to pediatrics is complicated by the differences in clearance, varying dose because of differences in absolute and treated BSA and variations in patient-administered ointment application rates. Studies predicting systemic concentrations of topical therapies have been performed in the context of primary hyperhidrosis[16] and in plaque psoriasis.[17] The latter study evaluated scenarios in which BSA ranged from 5% to 75%, with simulations showing calcipotriene concentrations following topical therapy would be unquantifiable in pediatric patients with psoriasis.[17] However, to the best of our knowledge, data collection and the methods used to extrapolate observed systemic concentrations for topically applied drugs within adults and from adults to pediatric populations, using data collected from placebo-controlled efficacy trials with limited pharmacokinetic collection, have not been extensively discussed in the literature.

Here, we describe the analysis used to predict systemic concentrations in adults and children with higher treated BSA, based on the pharmacokinetic data obtained for tofacitinib ointment following topical application over 2% to 17% treated BSA in a phase 2a trial in adults with mild to moderate atopic dermatitis.

Methods

Study Design

The study described here was performed in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol and documentation were reviewed by the institutional review board and/or ethics committees of each study center. All patients provided written informed consent.

This was a phase 2a multisite randomized, double-blind, vehicle-controlled, parallel-group study (A3921214; NCT02001181) in patients with mild (Physician's Global Assessment [PGA] score = 2) or moderate (PGA score = 3) atopic dermatitis.[13] Patients were randomized 1:1 to 2% (20 mg/g) tofacitinib ointment (n = 35) or matching vehicle ointment (n = 34) for 4 weeks. Tofacitinib or vehicle was applied twice daily to treatment-eligible affected areas (the head [including face but excluding hair-bearing scalp], neck, trunk [excluding groin and genitals], or limbs [including palms and soles]) at a target application rate of 3 mg/cm^2. With the aid of a pictorial guide, patients were instructed how much ointment to apply per 1% BSA (using the "handprint method," the area represented by the palmar [ie, outstretched] surface of the patient's hand with all 5 digits adducted together is approximately 1% of the patient's BSA, regardless of age) to achieve the target application rate. Patients were instructed not to bathe or shower for ≥4 hours after study drug application.

Pharmacokinetic Sampling

Pharmacokinetic samples were collected at all investigator sites. Patients were instructed not to apply the study drug at home for the visits at which pharmacokinetic samples were collected. Dosing was done by the site personnel for the morning or evening dose. Predose blood samples for pharmacokinetic analysis were collected at all study sites on day 1, week 2, and week 4. Following collection of the predose pharmacokinetic plasma sample and the in-clinic dosing in the week 2 and week 4 visits, 1 postdose pharmacokinetic sample was collected within the time range of 0.5 to 3 hours. For pharmacokinetic sample collection, a phlebotomy site remote from study drug application sites was selected if possible. The phlebotomy site was properly and thoroughly cleansed to avoid contamination of the pharmacokinetic blood sample with any residual study drug ointment on the skin. The collected sodium heparinized human plasma was analyzed using a validated liquid chromatography-mass spectrometry assay employing PF-04994438-10 as an internal standard. The assay had a lower limit of quantification of 0.01 ng/mL with demonstrated linearity up to the upper limit of quantification of 5 ng/mL.

Study Drug Dispensing, Application Instructions and Usage, and Data Collection

Study drug was dispensed to patients on day 1 and in week 2. At each dispensing visit, patients received a sufficient quantity of study drug to last until their next scheduled visit. For each patient, the number of study drug containers to be dispensed on day 1 and in week 2 were calculated based on the day 1 BSA affected with treatment-eligible atopic dermatitis (treatable BSA). Patients were instructed that study drug should be applied to the treatable BSA determined on day 1 throughout the treatment period, regardless of clearing or improvement of atopic dermatitis. Any new treatment-eligible locations occurring following day 1

should also be treated with the study drug. Study drug tubes were weighed before dispensing and after return. At scheduled study visits following day 1, all study drug containers were returned to each site for accountability and weighing. The recorded weights were used to estimate usage for each patient as described below.

For each patient at each dosing interval of interest (day 1 to week 2, week 2 to week 4), ointment applied per dose (mg) was calculated as:

$$\begin{aligned} &\textit{Amount of ointment applied per dose } (mg) \\ &= \frac{\textit{Amount of ointment dispensed } (mg) - \textit{Amount of ointment returned } (mg)}{\textit{Number of actual doses}} \end{aligned} \quad (1)$$

It is important to note that the amount of ointment applied per dose (equation 1) represents the average amount of ointment applied per dose over the dispensing interval (eg, day 1 to week 2). In addition, the ointment application rate per dose is related to the amount of ointment applied per dose and to the treated BSA (equation 2).

$$\begin{aligned} &\textit{Ointment application rate } \left(\frac{mg}{cm^2}\right) \\ &= \frac{\textit{Amount of ointment applied per dose } (mg)}{\textit{Treated BSA } (cm^2)} \end{aligned} \quad (2)$$

Linear Mixed-Effects Model Development and Predicting Adult Systemic Concentrations

Linear mixed-effects modeling was used to characterize the relationship between plasma concentrations and ointment dose. Tofacitinib plasma concentrations were the dependent variable and ointment dose (equation 1) — which contains 2% tofacitinib as the active ingredient — was chosen as the independent variable. Slope was treated as a random effect. The intercept was fixed to zero, which assumed that concentrations should be zero in the absence of treatment. A slope-by-visit interaction term was tested in the model. Model selection between the tested models was based on goodness of fit, the likelihood ratio test, and the Akaike information criterion. The final model was used to extrapolate concentrations to higher treated BSA up to 90% (18 000 cm^2, for an average male adult). The extrapolation to higher treated BSA used application rates of 1.5, 2, and 3 mg/cm^2 of ointment. The application rate was necessary to determine the ointment dose based on treated BSA as defined by equation 2. The target application rate of 3 mg/cm^2 was within the range of average application rates that are practical for topical dermatologic products (approximately 2 to 5 mg/cm^2, based on experience in Pfizer studies). Actual application rates can vary widely, as demonstrated in this study, in which application rates ranged from 0.5 to 13.4 mg/cm^2, with a mean of 2.5 mg/cm^2. Application rates when patients are instructed to apply a "thin layer" can be different from the target rate, which is represented by a mean application rate of 1 to 2 mg/cm^2.[18]

The modeling, parameter estimation, and predictions from final model were conducted using functions from the nlme package (version 3.1-128) in R (version 3.3.1).

Extrapolation of Concentrations to Pediatric Populations

The extrapolated adult concentrations obtained at various treated BSAs were used to predict concentrations in pediatric populations of 2 to 17 years of age using an allometric approach.[19] The pediatric clearance was estimated using equation 3.

$$CL_{ped} = CL_{adult} \times \left(\frac{Weight}{70}\right)^{0.75} \quad (3)$$

Concentrations in pediatric populations were then calculated using equation 4.

$$\begin{aligned} C_{avg,SS,ped} = C_{avg,SS,adult} \times \frac{Dose_{ped} \times F_{t,ped}}{Dose_{adult} \times F_{t,adult}} \\ \times \frac{CL_{adult} \times F_{o,ped}}{CL_{ped} \times F_{o,adult}} \end{aligned} \quad (4)$$

where $C_{avg,SS,ped}$ is the average steady-state concentration in the pediatric population (ng/mL), $C_{avg,SS,adult}$ is the average steady-state concentration in the adult population (ng/mL), CL_{ped} is pediatric clearance (L/h), CL_{adult} is adult clearance (L/h), $Dose_{adult}$ is the adult dose of tofacitinib drug applied as 2% tofacitinib ointment to BSA at a 3 mg/cm^2 application rate, $Dose_{ped}$ is the pediatric dose of tofacitinib drug applied as 2% tofacitinib ointment to BSA at a 3 mg/cm^2 application rate, $F_{t,ped}$ and $F_{o,ped}$ are topical and oral bioavailability, respectively, in pediatric subjects, and $F_{t,adult}$ and $F_{o,adult}$ are topical and oral bioavailability, respectively, in adult subjects. Oral and topical bioavailability were assumed to be identical in adults and pediatric subjects. The 50th

percentile data of height and weight for the pediatric population were obtained from the Centers for Disease Control and Prevention growth charts.[20,21] The median weight at each respective age was used to calculate the pediatric clearance in equation 3. The median height and weight for the respective ages were used to calculate the absolute BSA in square meters using the Mosteller formula.[22] The adult clearance estimate of 26.7 L/h,[23] observed in patients with moderate to severe chronic plaque psoriasis following oral tofacitinib doses, was used to estimate pediatric clearance.

Results

Efficacy, safety, and pharmacokinetic outcomes from the original Phase 2a study, including baseline demographics and disease characteristics, have been reported previously.[13]

Plasma Concentrations of Tofacitinib

A total of 136 plasma concentrations (predose and postdose) were obtained from 34 patients in week 2 and week 4. All samples collected in weeks 2 and 4 had measurable tofacitinib concentrations indicating that tofacitinib was absorbed following topical application. Of the observed concentrations, approximately 24% were ≥1 ng/mL. Most concentrations (~64%) were in the range of 0.1 to <1 ng/mL, and approximately 11% were between the range of 0.01 (lower limit of quantification) to <0.1 ng/mL. Visual examination of predose and postdose concentrations indicated no trend of higher concentrations following dosing. This observation is consistent with previously reported data showing flat profiles following dosing with tofacitinib ointment in plaque psoriasis.[24] The pre- and postdose pharmacokinetic collection had a median (range) time after last dose of 11.6 hours (8.4 to 23.6 hours) and 0.6 hours (0 to 1.8 hours), respectively. Visual examination of the plot of concentration versus treated BSA (Figure 1) for weeks 2 and 4 showed a trend of increasing concentrations with increasing treated BSA and consequently ointment dose.

Ointment Usage and Application Rates

For the 34 patients randomized to vehicle, 29 patients had ointment usage data. Five patients had missing ointment usage data because of unreturned ointment tubes at scheduled visits. The pooled median (range) ointment dose for vehicle between day 1 and week 2 and week 2 to week 4 was 1941 mg (224 to 18 420 mg) for a median (range) treated BSA of 1154 cm^2 (338 to 3379 cm^2), which corresponded to a median (range) application rate of 2.0 mg/cm^2 (0.4 to 8.2 mg/cm^2). Because vehicle usage data are not relevant to the discussion on pharmacokinetic concentrations of tofacitinib, they are not discussed in further detail here. Of the 34 patients with pharmacokinetic samples who were randomized to tofacitinib ointment, 31 patients had tofacitinib ointment usage data, whereas 3 patients were missing these data because of unreturned ointment tubes. The pooled median (range) tofacitinib ointment dose per application between day 1 and week 2 and week 2 to week 4 was 2284 mg (388 to 10 981 mg) for a median (range) treated BSA of 978 cm^2 (317 to 3385 cm^2), which corresponded to a median (range) application rate for tofacitinib ointment of 1.7 mg/cm^2 (0.4 to 13.4 mg/cm^2). The median application rate was identical (1.7 mg/cm^2) between day 1 and week 2 and week 2 to week 4, with minor differences in range for week 2 and week 4 (Figure 2A) based on the ointment usage data collected. There was no trend between visits to suggest changes (increase or decrease) in application rates over the 4 weeks of treatment; patients were instructed to apply study drug to the treatable BSA determined on day 1 regardless of clearance or improvement of atopic dermatitis. Examination of the relationship between treated baseline BSA and application rate from day 1 to week 4 (Figure 2B) suggests a trend for higher application rate with lower treated BSA.

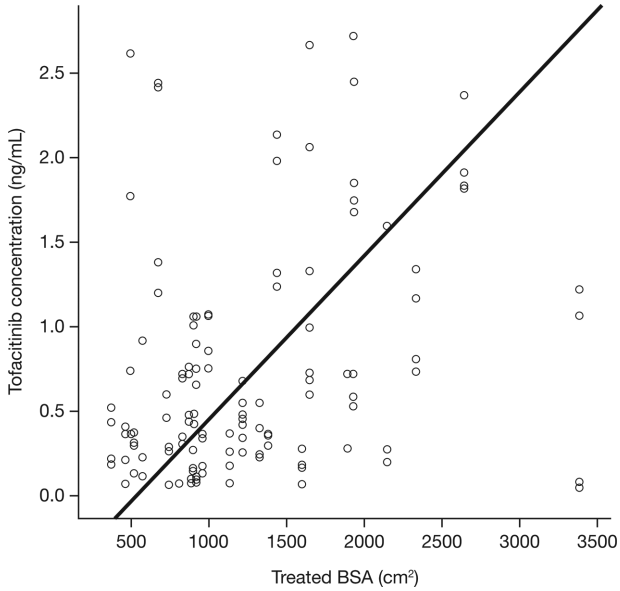

Figure 1. Relationship between the observed systemic tofacitinib concentration (predose and postdose) in week 2 and week 4 and treated BSA in adults with mild to moderate atopic dermatitis. The solid line represents the naive-pooled linear regression fit of the data. BSA, body surface area.

Relationship Between Systemic Concentrations and Ointment Dose

The observed concentrations in the pre- and postdose pharmacokinetic samples collected in week 2 and week 4 were used as the dependent variables. The ointment dose (*Oint Dose*) derived using equation 1,

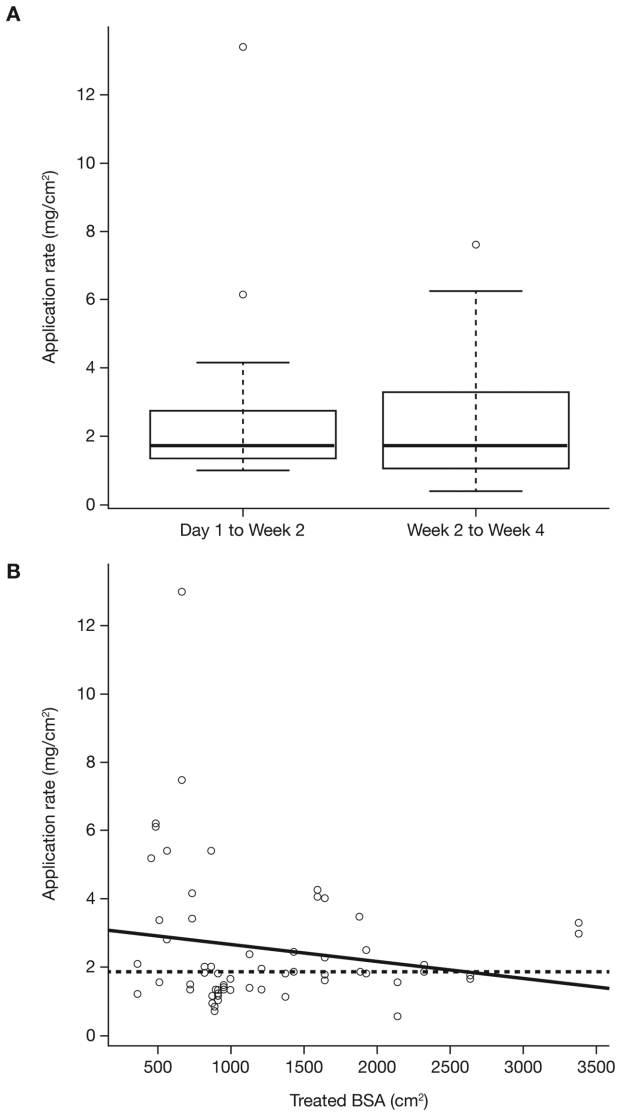

Figure 2. (A) Box-and-whisker plot of application rate of 2% tofacitinib ointment from day 1 to week 2 and from week 2 to week 4. (B) Relationship between tofacitinib application rate and treated baseline BSA from day 1 to week 2 and from week 2 to week 4. The solid line represents the naive-pooled linear regression fit of the data; the dashed line represents the median application rate (mg/cm^2). BSA, body surface area.

which is a product of the treated BSA and application rate (equation 2), was used as the independent variable. The final model formula is provided below in equation 5.

$$Concn_{ij} = \alpha_0 + (\beta_0 + \beta_i) \cdot Oint\ Dose_{ij} + \varepsilon_{ij} \qquad (5)$$

where $Concn_{ij}$ is the jth observed concentration for patient i, $Oint\ Dose_{ij}$ is the jth recorded ointment dose for patient i, α_0 is the average intercept that was fixed at 0 based on the expectation of no drug levels without treatment, β_0 is the average slope for patients, and β_i is the deviation from the average slope for patient i. The random effect β_i is assumed to be independent for different i and normally distributed with a mean of 0 and variance of Ω. ϵ_{ij} is the random residual error of the jth measurement from patient i and is assumed to be independent and identically normally distributed with a mean of 0 and variance of σ^2.

The tested models are shown in Table 1. Based on the likelihood ratio test, Akaike information criterion, and goodness-of-fit plots (Figure 3), model 4 was selected as the final model (equation 5). The impact of visit (week 2 or week 4) was tested as a categorical variable and was not identified as a significant covariate (Table 1 [model 3]). Based on the estimate of the slope, every milligram increase in ointment dose, which equated 0.02 mg of tofacitinib (2% ointment strength), was likely to increase the mean concentration by 0.0003 ng/mL.

Extrapolation of Systemic Concentrations for Higher Treated BSA in Adults

The model described by equation 5 (model 4) was used to extrapolate to higher treated BSAs, assuming that a linear relationship was maintained between ointment dose and systemic tofacitinib concentrations and that the application rate was fixed. Expected systemic concentrations were extrapolated up to 90% treated BSA, which is the maximum practical treatable BSA with a topical ointment and excludes the scalp, groin, and genitals. The mean predicted systemic concentrations with 95% confidence intervals are provided in Table 2 for various application rates. For application rates of 3 mg/cm^2 and treated BSA of 70% or higher, the mean concentrations could exceed an average concentration (C_{avg}) of 12.4 ng/mL. C_{avg} of 12.4 ng/mL represents the 10th percentile of the observed concentrations of oral tofacitinib 5 mg twice daily in phase 3 clinical trials of patients with moderate to severe plaque psoriasis.[13] At typical application rates of 1.5 or 2 mg/cm^2 observed in the current study, the mean tofacitinib concentrations were unlikely to exceed 12.4 ng/mL, even at high treated BSA (eg, 70% to 90%). At application rates of 1.5 and 2 mg/cm^2, the mean predicted concentrations (representing the C_{avg} because of the flat pharmacokinetic profile) at 90% treated BSA would maintain margins of 1.6-fold and 1.2-fold, respectively, to 12.4 ng/mL.

Extrapolation of Adult Concentrations to Pediatric Populations

Pediatric concentrations were calculated from predicted adult concentrations for 50%-treated BSA corresponding to the respective pediatric age using equations 3 and 4. As the height and weight of an average child increases with age, the absolute maximum treatable BSA also increases (Table 3). Hence, the ointment dose based on square centimeters of treated BSA for an average

Table 1. Model Selection and Parameter Estimates for Final Model

Model Number[a]	Fixed-Effects Model	Random Effects	Akaike Information Criterion	Likelihood Ratio Test	*P*
1	Concentration ~ 1	~1|ID	185.8	—	—
2	Concentration ~ ointment dose	~Ointment dose|ID	138.8	1 vs 2	<.0001
3	Concentration ~ ointment dose + visit	~Ointment dose|ID	140.4	2 vs 3	.5696
4 (Final)	Concentration ~ ointment dose (intercept = 0)	~Ointment dose -1|ID	140.7	2 vs 4	.0484

Final Model Parameter Estimates

Parameter	Estimate	Lower 95%CI	Upper 95%CI
α_0 (ng/mL), mean intercept	0 (Fixed)	—	—
β_0 (ng/mL/mg), slope	0.0003	0.0002	0.0004
Ω_{22} (ng/mL/mg), slope, SD	0.0002	0.0001	0.0003
σ (ng/mL), residual error	0.3232	0.2784	0.3752

CI, confidence interval; ID, patient identifier; SD, standard deviation.

[a]Model 1: intercept-only model; model 2: regression model with ointment dose as the independent variable and concentration as the dependent variable; model 3: regression model with ointment dose and visit as the independent variables and concentration as the dependent variable; model 4: as per model 2 with intercept fixed to 0.

2-year-old child is lower than that for older children treated for the same percent BSA. Consequently, the mean systemic concentrations for younger children are not predicted to be higher than those observed in adults after accounting for the difference in clearance by allometric scaling, using an exponent of 0.75 (Table 3). Similar to adults, pediatric patients with high treated BSA (90%) with ointment application rates of 3 mg/cm^2 are predicted to exceed the C_{avg} of 12.4 ng/mL.

Discussion

In a proof-of-concept study, topical tofacitinib ointment was effective in the treatment of atopic dermatitis when used in a twice-daily regimen.[13] Although 2% tofacitinib ointment demonstrated significant efficacy for treatment of mild to moderate atopic dermatitis, it is necessary to understand expected systemic exposures, as this is a key determinant of a drug's safety profile. In this analysis, we described the collection, analysis, and interpretation of limited pharmacokinetic and dosing data to predict systemic concentrations for 2% tofacitinib ointment.

For topical agents, definitive systemic exposure data are usually obtained in maximal usage trial (MUsT) studies.[26] MUsT studies are typically conducted in patients at the upper range of the disease severity relevant to the disease (eg, treated BSA >20% to 30%) under the maximum recommended application rates. MUsT studies are done with final market image formulation at the highest recommended dose strength and frequency, longest proposed dosing duration, and maximum total BSA to be treated at one time with the topical formulation.[26] Hence, a MUsT study is frequently undertaken following the completion of proof-of-concept and dose-ranging studies once substantial evidence for efficacy has been established. However, an early assessment of likely systemic exposures is useful to predict if the desired product safety profile is viable. In addition, an assessment of likely systemic exposures could help in the future clinical trials with respect to inclusion/exclusion criteria and safety monitoring requirements and to accelerate development decision-making.

The pharmacokinetic data collected in the phase 2a trial of topical tofacitinib ointment for treatment of patients with mild to moderate atopic dermatitis were analyzed using linear mixed-effects models. The pharmacokinetic sampling times of 1 predose and postdose assessment in week 2 and week 4 were selected based on previous observations of flat pharmacokinetic profiles following topical administration of tofacitinib ointment in psoriasis patients.[24] Because a typical pharmacokinetic profile characterized by absorption followed by an elimination phase was not observed, a practical pharmacokinetic sampling scheme maximizing patient convenience was adopted. The flat pharmacokinetic profiles also suggest that the observed concentrations are representative of the C_{avg} (area under the curve/dosing interval) following topical application of tofacitinib ointment. The choice of a linear model was supported by visual examination of the plots of observed concentrations versus treated BSA or ointment dose (Figure 1). The linear mixed-effects model (equation 5) adequately described the observed concentration data

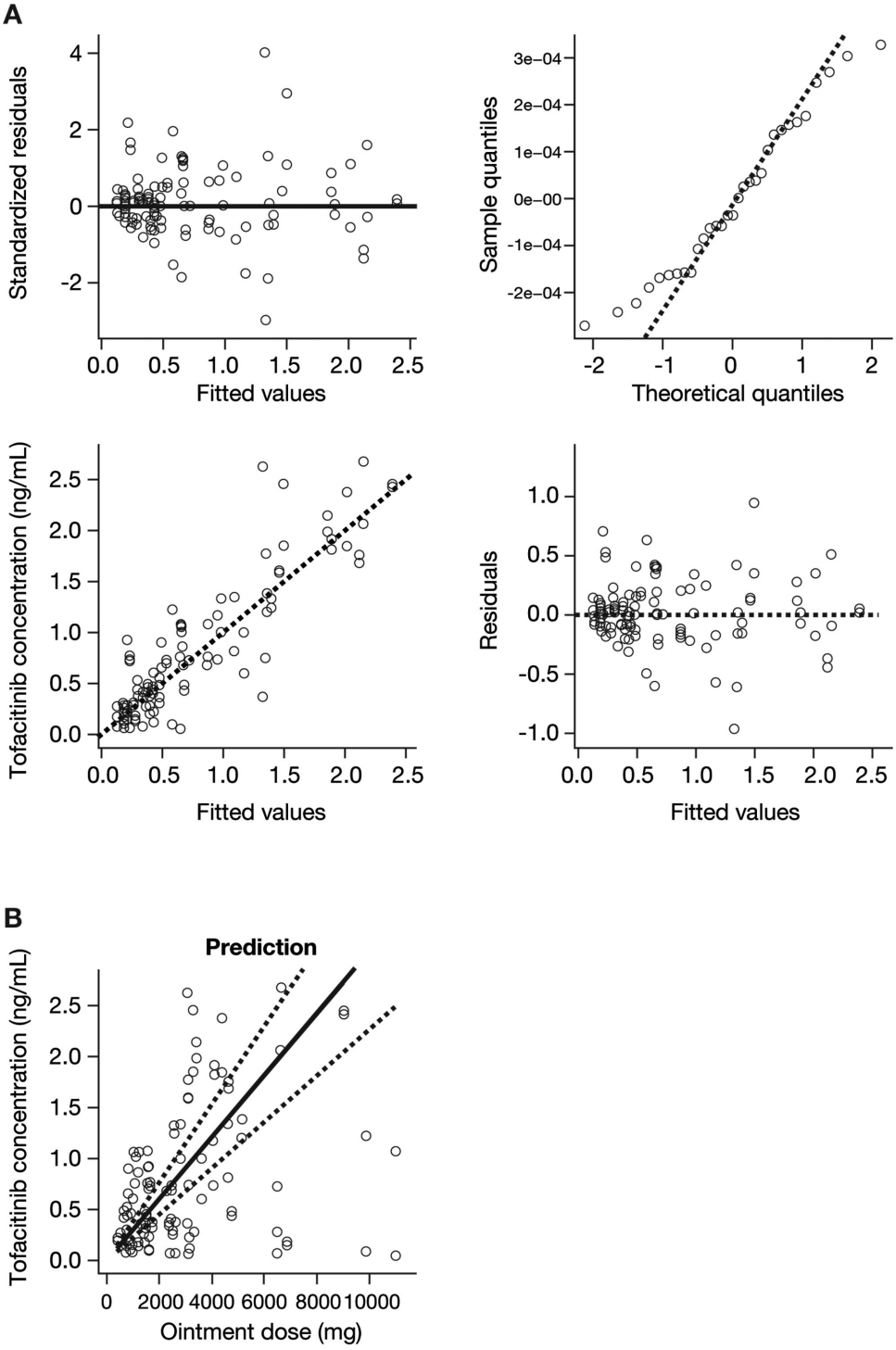

Figure 3. (A) Goodness-of-fit plots for the final linear mixed-effects model (model 4; equation 5). (B) Solid line represents the mean prediction from model 4; the dashed lines represent the 95% bootstrap confidence interval of the mean prediction.

(Figure 3). Although ointment dose and tofacitinib dose in milligrams are perfectly correlated, ointment dose was selected as the independent variable for ease of future communication with investigators, site personnel, health-care professionals, and patients. The choice of ointment dose is also the most clinically relevant, as it avoids the need to convert the tofacitinib dose back to ointment dose when providing usage instructions. The ointment dose used for this analysis represented the average ointment dose per application used during the period preceding the pharmacokinetic collection times. In addition, excess amounts of

Table 2. Predicted Concentrations at Higher Treated BSA in Adults (≥18 Years)

Treated BSA (%)	Treated BSA (cm^2)[a]	Predicted C_{avg} (ng/mL)[b] for Application Rate of 1.5 mg/cm^2	Predicted C_{avg} (ng/mL)[b] for Application Rate of 2 mg/cm^2	Predicted C_{avg} (ng/mL)[b] for Application Rate of 3 mg/cm^2
50	10 000	4.5 (3.4 to 5.7)	6.0 (4.5 to 7.6)	9.1 (6.8 to 11.5)
60	12 000	5.4 (4.1 to 6.9)	7.2 (5.4 to 9.2)	10.9 (8.1 to 13.7)
70	14 000	6.3 (4.7 to 8.0)	8.4 (6.3 to 10.7)	12.7 (9.5 to 16.0)
80	16 000	7.2 (5.4 to 9.2)	9.7 (7.2 to 12.2)	14.5 (10.8 to 18.3)
90	18 000	8.1 (6.1 to 10.3)	10.9 (8.1 to 13.7)	16.3 (12.2 to 20.6)

BSA, body surface area; C_{avg}, average systemic concentration.
[a]Based on treatment-eligible areas for an average adult male: head (including face but excluding scalp), neck, trunk (excluding groin and genitals), or limbs (including palms and soles).
[b]Mean (95% confidence interval).

ointment dispensed from the study drug tube but not used by the patient also contribute to the average dose and hence may result in an overestimate for the dose. A more accurate collection of ointment dose per application, although desirable, would be impractical in a phase 2 multisite study conducted over 4 weeks. These variables would be more tightly controlled and recorded in any subsequent MUsT study. The model described by equation 5 was used to extrapolate concentrations to higher treated BSA and associated ointment dose under the assumption of linearity. The assumption of linearity is supported by the dose-proportional, or linear, pharmacokinetics observed for tofacitinib at single oral doses of up to 100 mg.[27] Although the tofacitinib dose amounts in the ointment applied are several-fold higher than the oral doses (for 2%-treated BSA, corresponding to 24 mg of tofacitinib at an application rate of 3 mg/cm^2), the relatively low expected bioavailability after topical application allows assumption of linearity with increasing ointment dose. As the observed tofacitinib concentrations can be considered an estimate of C_{avg} because of the flat pharmacokinetic profile, the linear model described by equation 5 can be summarized in terms of the fundamental pharmacokinetic parameters in which slope represents the reciprocal of clearance.

The main objective of extrapolating systemic concentrations was to assess if the predicted mean concentrations at higher treated BSA would exceed relevant concentration thresholds based on experience from oral dosing, which is associated with increased risk for adverse drug reactions. The median (95% confidence interval) C_{avg} values for oral tofacitinib 5 and 10 mg twice daily were 17.0 ng/mL (10.2 to 25.6 ng/mL) and 33.9 ng/mL (21.3 to 52.7 ng/mL), respectively. The C_{avg} of 12.4 ng/mL, representing the 10th percentile of the C_{avg} for oral tofacitinib 5 mg twice daily in patients with moderate to severe psoriasis, was identified as a threshold concentration to ensure that systemic concentrations after topical application do not approach oral concentrations.[13] Based on an exposure-response analysis of oral tofacitinib psoriasis data, the

Table 3. Predicted Concentrations in Children Based on Allometric Scaling

Age (Years)	Maximum Treatable BSA (cm^2)[a]	Ointment Dose (mg)[b]	Tofacitinib Ointment Average[c] Systemic Concentration (C_{avg}, ng/mL)[d]
At 50%-treated BSA			
2	2772	8317	9.0 (6.7 to 11.4)
4	3408	10 224	9.2 (6.9 to 11.6)
6	4085	12 256	9.2 (6.9 to 11.6)
8	4787	14 360	9.2 (6.9 to 11.6)
10	5562	16 686	9.0 (6.8 to 11.4)
12	6494	19 482	8.8 (6.6 to 11.2)
17	8876	26 628	8.5 (6.4 to 10.8)
Adults (≥18)[e]	10 000	30 000	9.1 (6.8 to 11.5)
At 90%-treated BSA			
2	4990	14 971	16.2 (12.1 to 20.5)
4	6135	18 404	16.6 (12.4 to 21.0)
6	7353	22 060	16.6 (12.4 to 21.0)
8	8616	25 849	16.5 (12.4 to 21.0)
10	10 011	30 034	16.3 (12.2 to 20.6)
12	11 689	35 068	15.9 (11.9 to 20.1)
17	15 977	47 930	15.3 (11.5 to 19.4)
Adults (≥18)[e]	18 000	54 000	16.3 (12.2 to 20.6)

BSA, body surface area; C_{avg}, average systemic concentration.
[a]Based on treatment-eligible areas: head (including face but excluding scalp), neck, trunk (excluding groin and genitals), or limbs (including palms and soles).
[b]Amount of ointment per dose assuming an application rate of 3 mg/cm^2.
[c]Mean (95% confidence interval) at median height and weight.
[d]Calculated by allometric scaling from adult concentrations at equivalent treated BSA (%) using equation 4.
[e]An estimate of adult BSA of 20 000 cm^2 was used.[25]

C_{avg} of 12.4 ng/mL was not associated with increased incidence rates of serious infections and herpes zoster infections when compared with patients treated with placebo.[13] Based on the predicted mean concentrations in adult and pediatric patients with treated BSA >70%, concentrations could exceed 12.4 ng/mL for ointment application rates >2 mg/cm^2. In atopic dermatitis studies of topical calcineurin inhibitors, the average treated BSAs for patients with mild to moderate and moderate to severe disease are ~25% and ~45%, respectively, with a maximum BSA >90%.[28–30] Hence, for most patients with average affected BSA

requiring treatment for atopic dermatitis and average application rates of 1.5 to 2 mg/cm^2, the mean systemic concentrations will not exceed the C_{avg} of 12.4 ng/mL. However, for patients with >70%-treated BSA, additional safety monitoring requirements may have to be considered in the setting of a clinical trial.

The predicted adult concentrations were also used to extrapolate to pediatric populations using allometric scaling. It is important to recognize that children have a smaller absolute BSA because of their smaller size. This limits the maximum dose of ointment that may be required, even when 90% BSA needs to be treated. The pediatric clearance was scaled using adult oral clearance from patients with psoriasis, as this is the most relevant patient population affected by a cutaneous immune-mediated inflammatory condition in the absence of clearance data in adult patients with atopic dermatitis. Equation 4, which was used to calculate pediatric concentrations, assumes equivalent bioavailability following topical dosing between adults and pediatric populations. To the best of our knowledge, comparative bioavailability data for topically applied agents between adults and pediatric populations do not exist. However, the pathophysiology of adult and pediatric atopic dermatitis is similar,[6,7] and the mature epidermis of a full-term infant is a functional barrier to limit absorption of topically applied agents[31] and is expected to perform similarly to the adult epidermis, especially by 2 years of age. Although the existence of disease is likely to alter the barrier properties of the epidermis, it is expected to be affected to the same extent as in adults, depending on disease severity. The predicted pediatric concentrations suggest that systemic concentrations for children ≥2 years of age are not expected to exceed adult concentrations when a similar percentage BSA is treated. Systemic concentrations in children treated up to 90% BSA could exceed 12.4 ng/mL at an application rate of 3 mg/cm^2. Hence, if a subsequent study was to be carried out in children, it may need to be conducted with additional safety monitoring by capping the maximum treatable BSA <90% to ensure safety and/or by staggered enrollment of the younger pediatric cohorts after completion of systemic concentration assessments in older cohorts, which would allow utilization of the accrued data to inform the conduct of the subsequent cohorts involving younger patients.

It is important to recognize that the predictions for adults and pediatrics are applicable to 2% tofacitinib ointment and denote the worst-case scenario, as 2% ointment strength represents the highest feasible dose strength as an ointment for tofacitinib. The above predictions for pediatric subjects were made using the 50th percentile height and weight data to represent the typical subject. As the application rate was constant and the dose was a certain percent of the body size, the predicted exposures were not remarkably different when calculated for the 5th, 50th, or 95th percentile of body weight and height (Supplementary Table 1). In addition, in this study patients were required to treat their baseline affected BSA, even if disease had cleared. In clinical practice it is expected that the treated BSA would decrease over time if a treatment was effective. Further, the predictions were made outside the range of observed treated BSA values but under assumptions of linearity and allometry and provide useful information about expected exposures under alternate conditions.

Conclusions

The predicted systemic concentrations for 2% tofacitinib ointment in both adult and pediatric populations at treated BSAs ≤50% and at typical application rates of ≤3 mg/cm^2 for a mild to moderate atopic dermatitis population did not exceed those reported for the 10th percentile of observed oral tofacitinib 5-mg twice-daily doses in patients with moderate to severe plaque psoriasis. For both adult and pediatric populations with treated BSAs ≥70% and at application rates ≥3 mg/cm^2, the systemic concentrations could exceed the values for the 10th percentile observed for oral tofacitinib 5-mg twice-daily doses. Predicted systemic exposures for pediatric populations are not expected to be higher than in adults at similar percent-treated BSAs. The above results provide important insight for design considerations for future trials of topical agents and can be generalized for topical agents that have measurable linear systemic concentrations prior to conduct of definitive MUsT studies.

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Declaration of Conflicting Interests

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Data-Sharing Statement

On request and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply via a secure portal. To gain access, data requesters must enter into a data access agreement with Pfizer.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.