Allometric Scaling of Testosterone Enanthate Pharmacokinetics to Adolescent Hypogonadal Males (IM and SC Administration)

Maria G. Vogiatzi,[1] **Jonathan S. Jaffe,**[2] **Takugo Amy,**[3] **and Alan D. Rogol**[4]

[1]Adrenal and Puberty Center, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA 19104-4399, USA
[2]Clinical Development and Medical Affairs, Antares Pharma Inc, Ewing, NJ 08628, USA
[3]Department of Pharmacokinetics, Synteract Inc, a Syneos Health Company, Morrisville, NC 27560, USA
[4]Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22903, USA

Correspondence: Maria G. Vogiatzi, MD, Adrenal and Puberty Center, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA 19104-4399, USA. Email: vogiatzim@email.chop.edu.

Abstract

Context: Intramuscular (IM) testosterone enanthate (TE) and testosterone pellets were US Food and Drug Administration approved before 1962 for pediatric use but not studied in controlled trials in adolescents.

Objective: An analysis using nonlinear mixed effect (NLME) modeling was designed to evaluate the adult pharmacokinetics (PK) of subcutaneous (SC) and IM TE. This model was used to simulate SC and IM TE administration in adolescents of different weight groups.

Methods: Data from adult male patients in a phase 2 trial were used to characterize the PK of TE using population PK modeling for SC and IM administration: Allometry was used to scale PK parameters from the adult model to simulate adolescent (aged 12 to < 18 years) serum testosterone levels at body weights of 30, 40, 50, and 60 kg after weekly, every-other-week (EOW), and monthly SC and IM administration of 12.5, 25, 50, 75, and 100 mg TE regimens.

Results: The final data set included 714 samples from 15 patients receiving 100 mg SC TE and 123 samples from 10 patients receiving 200 mg IM TE. In simulated populations, average serum concentration SC:IM ratios were 0.783, 0.776, and 0.757 at steady state for weekly, EOW, and monthly dosing groups, respectively. Simulated regimens of 12.5 mg SC TE monthly produced serum testosterone levels representative of early puberty and simulated pubertal stage progression following multiple subsequent testosterone dose increases.

Conclusion: SC TE administration achieved a testosterone exposure-response relationship similar to IM TE in simulated adolescent hypogonadal males, which may reduce size of fluctuations in serum T and related symptoms.

Key Words: subcutaneous, testosterone, pharmacokinetics, hypogonadism, adolescent

Abbreviations: %RSE, percentage relative SE; BMI, body mass index; BSA, body surface area; CDGP, constitutional delay of growth and puberty; Cl, central clearance; EOE, every other week; HR, heart rate; IM, intramuscular; K_a, absorption rate constant; NLME, nonlinear mixed effect; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics; SC, subcutaneous; TE, testosterone enanthate; V, volume of distribution.

Normal male pubertal maturation occurs between ages 9 and 14 years, after which puberty is considered delayed [1]. Delayed puberty affects approximately 2% of adolescents and has been associated with considerable psychosocial distress [1, 2]. Delays in puberty due to hypogonadism or constitutional delay in males may be treated with testosterone, which is used to promote the development of secondary sexual characteristics, growth, and normal bone and muscle mass [3, 4]. Although many testosterone formulations are approved for the treatment of hypogonadism in adult men, only intramuscular (IM) testosterone enanthate (TE) and testosterone pellets have been approved for adolescent males. These approvals were issued before the 1962 Kefauver-Harris Drug Control Act requiring that drugs prove safe and efficacious [5-7]. It is unclear whether there was clinical trial evidence supporting the safety and efficacy of these drugs at the time

of their approval, and the US Food and Drug Administration has cautioned that evidence for IM TE and testosterone pellets may not align with current pediatric drug-approval standards [5]. Furthermore, improper use of testosterone therapies approved for adult males in adolescent males may lead in the latter group to disproportionate advancements in bone maturation, fusion of the epiphyseal growth centers, and early termination of linear growth [6, 7].

Testosterone therapy in adolescent males with delayed puberty starts with the administration of small doses of testosterone, typically IM TE, to induce puberty. In hypogonadism, doses are gradually increased to reach adult male testosterone replacement over a course of approximately 3 years and in a process that mimics physiologic male pubertal progression [1]. Intramuscular TE injections are easy to titrate, and TE given IM is the most commonly used preparation for induction

and progression of puberty [8]. However, the injections can be painful, may require frequent office visits if not self-administered, and may be associated with nonphysiologic fluctuations in serum testosterone levels [3, 7]. Many new testosterone formulations have been developed to overcome difficulties with administration and adverse events, but these are supported only by expert opinion and are not evidence based [3, 4]. Oral testosterone esters and transdermal testosterone gel have been used for puberty induction. However, the use of oral therapy has been limited by concerns about bioavailability and difficulties with dose titration, while the use of transdermal testosterone gel in pediatrics is limited by dosing variability [1, 9]. Since there is little evidence to guide optimal testosterone dosing in adolescent males, efficacy and safety of testosterone administration may be supported by extrapolation from adult pharmacokinetics (PK) data, which have previously been used to augment pediatric drug development [4, 5, 10]. Extrapolation of adult data and scaling to pediatric patients may be completed through the use of allometry, which is the study of how the characteristics of living creatures change with size [11]. Differences in physiology and biochemistry lead to different rates of metabolism and renal clearance of drugs in different age groups of pediatric patients compared to adults. These differences necessitate the use of allometric modeling to scale drug clearance from adults to pediatric patients.

The goal of the present study is to design a nonlinear mixed effect (NLME) model to characterize the PK of IM and subcutaneous (SC) TE in adult patients with hypogonadism, to identify potential covariates affecting the PK of TE, and to scale these data to adolescent patients. Adult models were allometrically scaled to adolescent patients (aged 12 to < 18 years) at typical body weights of 30, 40, 50, and 60 kg after weekly, every-other-week (EOW), and monthly IM and SC administration of 12.5, 25, 50, 75, and 100 mg TE regimens to project an optimal dose and schedule for adolescent patients with hypogonadism whose pubertal maturation is induced with testosterone.

Materials and Methods

Study Design

This PK study is an analysis of data from a previously published 3-arm, open label, multidose, parallel-group phase 2 study (NCT01887418) [12]. The phase 2 study design was approved by the institutional review boards of participating centers and conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice Guidelines. Informed consent was obtained from all patients.

Eligible patients for the phase 2 study were 18- to 75-year-old men with a history of physician-diagnosed hypogonadism of any etiology and serum testosterone less than 300 ng/dL recorded on 2 occasions at least 1 week apart. Patients were excluded if they had testosterone levels greater than 300 ng/dL or any clinically significant medical condition that made the patient an unsuitable candidate. Untreated patients were randomly assigned to receive 50 or 100 mg SC TE weekly for 6 weeks and compared to a reference group of patients already treated with IM TE at steady state who received 200 mg IM TE once on day 1. For patients receiving SC TE, 7-day PK profiles were collected at weeks 1 and 5, and full PK profiles were generated after the sixth dose. Predose trough

and 24-hour postdose samples were collected weekly. Patients receiving IM TE had PK profiles collected through week 4. A prespecified serum testosterone reference range of 300 to 1100 ng/dL was used. Testosterone was quantified using sensitive and specific liquid chromatography-tandem mass spectrometry assays that were developed, validated, and performed by MedPace Bioanalytical Laboratories.

Pharmacokinetics Analysis

Data sets for adult patients receiving 200 mg IM TE and 100 mg SC TE were formatted to work with Phoenix NLME (v-8.1), which was used to conduct exploratory analyses. The data of adult patients receiving 50 mg SC TE were excluded because of high variability, possibly due to postdose endogenous testosterone production. One concentration time point was removed from the SC data set at 9 hours post dose as an outlier for being out of central range. Testosterone PK data were analyzed using an NLME modeling approach, and population PK models were developed in Phoenix NLME. The fit of this model was assessed based on various criteria, including successful minimization and covariance steps, precision in parameter estimates, visual inspection of goodness-of-fit plots, −2 log-likelihood ratio test, Akaike information criterion, and Bayesian information criterion as well as scientific plausibility. This model was qualified using a visual predictive check and nonparametric bootstrap analysis. Evaluation of multiple compartment models with different error models are shown in Supplemental Tables 1 and 2 for SC and IM models, respectively [13]. A one-compartment model with multiplicative error was deemed best fit for both models. Although a 2-compartment multiplicative model showed a statistically significant lower −2 log-likelihood ratio test value for the IM model, the difference was deemed marginal and not in line with the SC model.

Stepwise covariate modeling was used to assess age, body weight, body mass index (BMI), and heart rate (HR) as potential covariates in this model.

After scaling and evaluation of the adult models, mean PK parameters were allometrically scaled to simulate average serum testosterone levels at steady state in adolescent (aged 12 to < 18 years) weight groups of 30, 40, 50, and 60 kg following weekly, EOW, and monthly IM and SC administration of 12.5, 25, 50, 75, and 100 mg TE regimens. Allometric scaling of clearance and volume was completed according to a standard exponent model, where $\text{Clearance}_{\text{pediatric}} = \text{Clearance}_{\text{adult}} * \left(\frac{\text{Pediatric Body Weight}}{\text{Adult Body Weight}}\right)^{0.75}$ and Volume of Distribution $= \text{Vd}_{\text{adult}} * \left(\frac{\text{Pediatric Body Weight}}{\text{Adult Body Weight}}\right)$, and where mean adult body weights for SC and IM dosing groups from the phase 2 study (93.16 and 90.35 kg, respectively) were used [12, 14]. The standard 0.75 exponent was considered valid because the target age group was older than 5 years. Previous studies have found that estimating pediatric clearance based on body weight taken to the power of 0.75 produces acceptable results for small molecules [14, 15]. Steady-state PK was defined as PK following 5 model-determined half-lives (97% of steady state achieved). Half-life was calculated from volume of distribution and clearance as $t_{1/2} = \frac{\ln(2) * V_d}{CL}$. For SC TE simulations, all weight groups were found to reach steady state by dose 3 for monthly, dose 5 for EOW, and dose 9 for weekly simulations. The output was plotted on time (h)

vs average plasma concentration during a dosing interval (C_{ave}, ng/dL) line graphs to show simulated PK profiles in adolescent patients, which were used to evaluate possible regimens for the treatment of hypogonadal adolescent males. Evaluated PK parameters in adolescent simulations after each dosing interval included C_{ave}, time to C_{ave} (T_{ave}), maximum concentration (C_{max}), and time to C_{max} (T_{max}). To describe approximate puberty status after simulated testosterone dosing in adolescent males, the following serum testosterone levels were used: less than 10 ng/dL, lack of puberty; 10 to 149 ng/dL, early puberty; 150 to 249 ng/dL, midpuberty; 250 to 1200 ng/dL, advanced puberty. These puberty ranges and their associated serum testosterone levels are based on approximate serum testosterone in ascending Tanner genital stages [5].

Results

Patient Population

The data set included 714 samples from 15 adult patients receiving 100 mg SC TE and 123 samples from 10 adult patients receiving 200 mg IM TE. Predose testosterone serum concentrations and baseline adult patient demographics were previously reported [12]. Notably, the mean predose total testosterone (SD) serum concentrations for adult patients receiving 100 mg SC TE and 200 mg IM TE were 232.8 ng/dL (75.61) and 642.5 ng/dL (271.80), respectively. Predose serum testosterone concentrations were higher in the IM TE group because these patients were on a steady-state TE replacement before PK studies.

Pharmacokinetic Parameters

Following both forward selection and backward elimination, the stepwise covariate modeling returned with HR as a significant covariate for the SC model and found no significant covariates in the IM model. Given that HR did not show a similar influence between the SC and IM model, and the clinical limitations and applicability of HR, it was decided against including the covariate in either model. Therefore, the inclusion of age, body weight, or BMI covariates would not likely provide better predictions in pediatrics.

Visual inspection of observed concentration vs individual predicted concentration both for SC and IM (Supplementary Figs. 1 and 2) showed good adherence to line of unity with little bias [13]. Similarly, conditional weighted residuals vs time for SC and IM models (Supplementary Figs. 3 and 4) generally lies between 2 and −2 with an even distribution, indicating acceptable fit [13]. Furthermore, visual predictive check for SC and IM models (Supplementary Figs. 5 and 6) show that most observed data lie within the fifth and 95th percentile of the simulated PK [13].

Percentage relative SE (%RSE) of PK parameters was found to be generally small for the SC model, with %RSE of 25.2%, 13.0%, 8.9%, and 6.5% for absorption rate constant (K_a), volume of distribution (V), central clearance (Cl), and residual variability, respectively, indicating good precision (Supplementary Table 3) [13]. The IM model showed higher variability than the SC model with values of 71.3%, 18.0%, 20.4%, and 12.6% for K_a, V, Cl, and residual variability, respectively, indicating reasonable precision (Supplementary Table 3) [13]. These %RSE values along with satisfactory goodness-of-fit plots give confidence in the fit of both the IM

and SC models. Additional results supporting model validation including bootstrap analyses (Supplementary Tables 4 and 5) and simulated population predictions (Supplementary Figs. 7 and 8) are reported in the supplementary materials [13].

Adult models were allometrically scaled to adolescent patients based on weight groups of 30, 40, 50, and 60 kg, and the final population PK model fixed-effect parameter estimates for SC and IM TE dosing in adolescents are available in Table 1; K_a for SC TE was estimated to be 0.09 hour^{-1}. Simulated concentrations for IM TE groups were proportionally larger than SC TE, with SC TE C_{ave} values approximating 75% of IM TE values in adolescents. Steady-state C_{ave} SC:IM ratios were 0.783, 0.776, and 0.757 for weekly, EOW, and monthly dosing groups, respectively. SC and IM TE reached C_{max} at similar times, as steady-state T_{max} SC:IM ratios were 1.02, 1.07, and 1.00 for weekly, EOW, and monthly dosing groups, respectively. Steady-state C_{max} was lower for SC than IM TE; average C_{max} SC:TE ratios were 0.782, 0.779, and 0.766 for weekly, EOW, and monthly dosing groups, respectively.

Simulated C_{ave} for weekly, EOW, and monthly regimens of 12.5, 25, 50, 75, and 100 mg in each of the adolescent weight groups predicted higher serum testosterone concentrations in lighter- compared to heavier-weight groups and reliable increases in C_{ave} (Figs. 1-5).

Simulated regimens of SC and IM TE given 12.5, 25, 50, 75, and 100 mg weekly, EOW, and monthly produced steady-state C_{max} and C_{ave} values indicative of early, mid-, and advanced puberty in all weight groups (Fig. 6).

Some simulated weight groups receiving regimens of SC TE 12.5 to 75 mg produced steady-state C_{ave} values suggestive of mid-puberty. All weight groups receiving regimens of SC TE 12.5 mg EOW and 12.5 and 25 mg monthly produced simulated steady-state C_{ave} values suggestive of early puberty. For IM TE, some simulated regimens of 12.5 to 50 mg produced steady-state C_{ave} values suggestive of mid-puberty. Early puberty steady-state C_{ave} values were reported in simulations of IM TE given 12.5 mg EOW in patients 50 to 60 kg, monthly in patients 30 to 60 kg, and 25 mg monthly in patients 40 to 60 kg. No simulations for SC or IM TE in any weight groups receiving any dose or interval produced steady-state C_{ave} values indicative of a lack of puberty.

Some simulated steady-state C_{max} concentrations were indicative of patients in mid-puberty both for SC and IM TE regimens of 12.5 and 25 mg. For SC TE, simulated early puberty steady-state C_{max} values resulted from 12.5 mg EOW in 50 to 60 kg patients and 12.5 mg monthly in 40 to 60 kg patients. Only 12.5 mg monthly in patients 50 to 60 kg produced steady-state C_{max} values indicative of early puberty in IM TE simulations.

Table 1. Population pharmacokinetics fixed-effect parameter estimates for subcutaneous and intramuscular testosterone enanthate in adults

	SC TE (97.5% CI)	IM TE (97.5% CI)
K_a, h^{-1}	0.09 (0.0457 to 0.135)	0.08 (−0.0342 to 0.201)
V, L	23 800 (17 800 to 29 900)	13 800 (8840 to 18 700)
Cl, L/h	60.8 (50.3 to 71.3)	50.6 (30.1 to 71.0)

Abbreviations: Cl, central clearance; IM, intramuscular; K_a, absorption rate constant; SC, subcutaneous; TE, testosterone enanthate; V, volume of distribution.
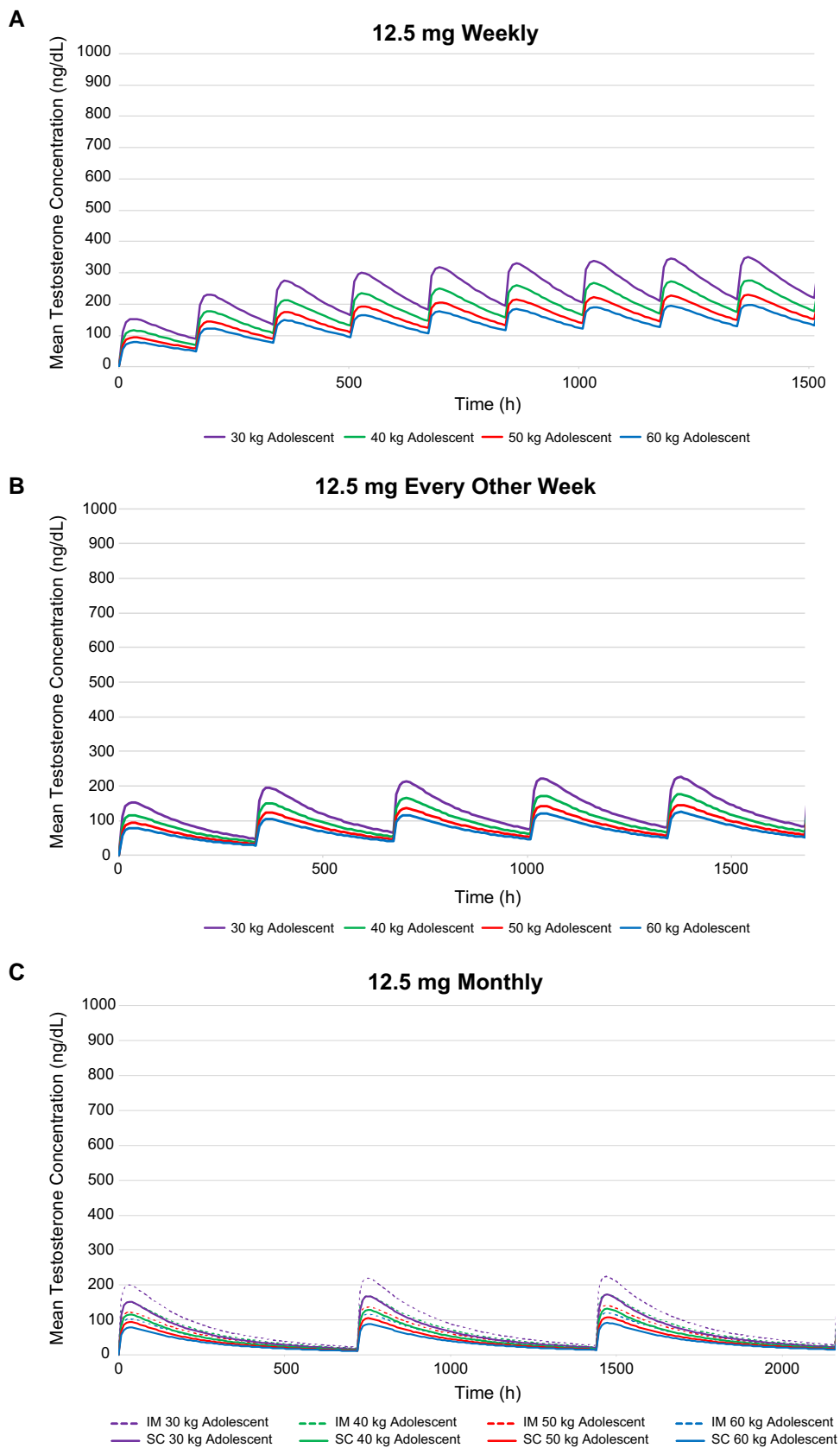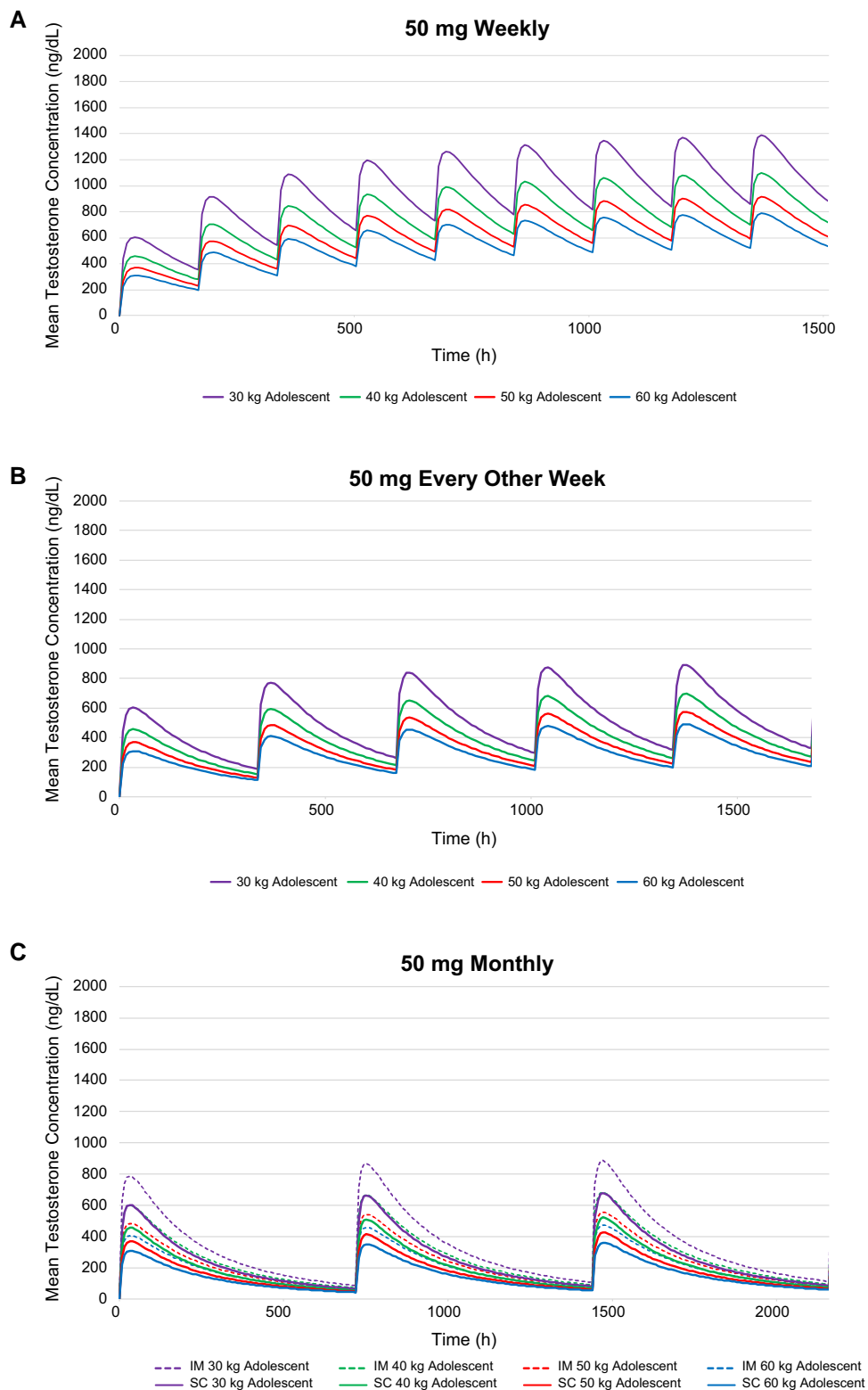
Figure 1. 12.5 mg subcutaneous (SC) testosterone enanthate (TE). A, 12.5 mg SC TE weekly. B, 12.5 mg SC TE every other week. C, 12.5 mg SC and intramuscular (IM) TE monthly. Modeled dose, formulation, and interval are shown with mean testosterone concentration cut-off at steady state.
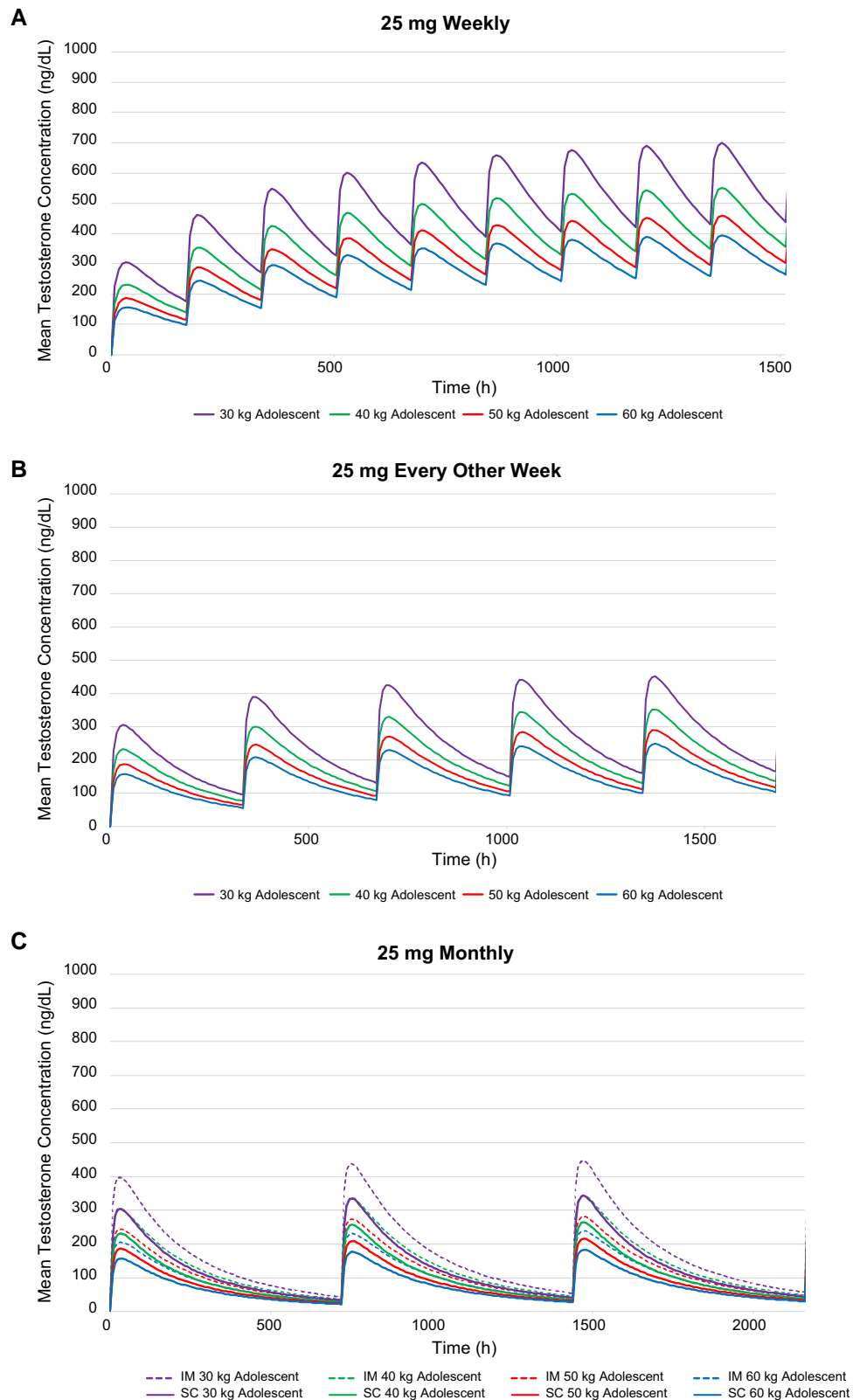
Figure 2. 25 mg subcutaneous (SC) testosterone enanthate (TE). A, 25 mg SC TE weekly. B, 25 mg SC TE every other week. C, 25 mg SC and intramuscular (IM) TE monthly. Modeled dose, formulation, and interval are shown with mean testosterone concentration cut-off at steady state.

Taken together, these simulated results suggest that SC TE regimens of 12.5, 25, 50, 75, and 100 mg given weekly, EOW, or monthly can generate C_{ave} and C_{max} concentrations that may mimic early to advanced puberty, with most simulations producing values indicative of advanced puberty. C_{ave} and C_{max} concentrations corresponding to early puberty were reached by the SC and IM TE regimen of 12.5 mg monthly and the SC TE regimen of 12.5 mg EOW.

A

50 mg Weekly

B

50 mg Every Other Week
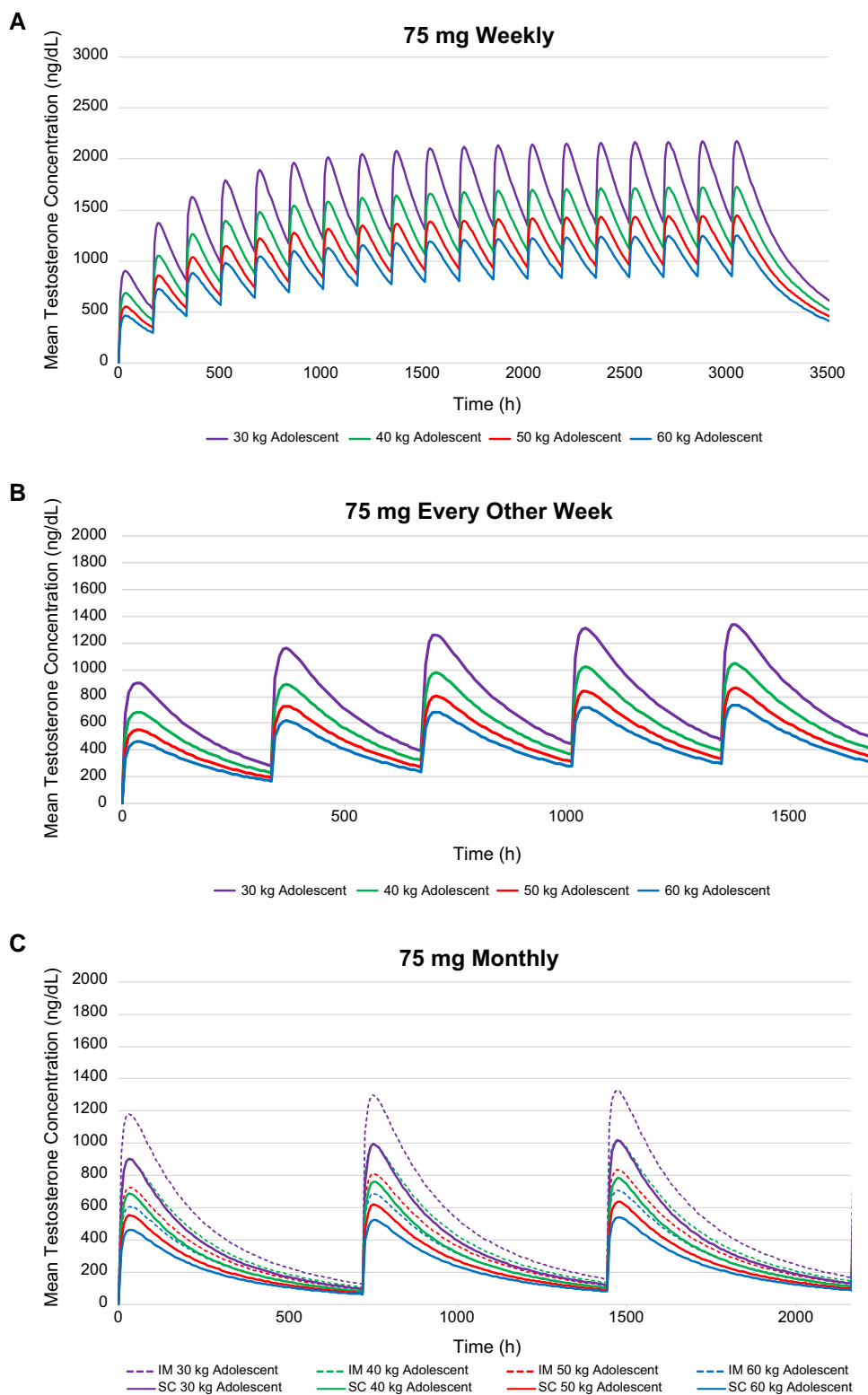

C

50 mg Monthly

Figure 3. 50 mg subcutaneous (SC) and intramuscular (IM) testosterone enanthate (TE). A, 50 mg SC TE weekly. B, 50 mg SC TE every other week. C, 50 mg SC TE and IM TE monthly. Modeled dose, formulation, and interval are shown with mean testosterone concentration cut-off at steady state.

Discussion

PK results from adult male patients receiving SC or IM TE in a phase 2 study were characterized and modeled, resulting in a one-compartment model with first-order absorption and elimination kinetics. The model was used to identify significant covariates that affect testosterone PK, and despite finding HR to be a significant covariate in the SC TE model, no covariates were included during PK modeling. This was due to limited clinical applicability and a lack of consistent influence of HR on SC and IM TE PK parameters. The model was then allometrically

Figure 4. 75 mg subcutaneous (SC) and intramuscular (IM) testosterone enanthate (TE). A, 75 mg SC TE weekly. B, 75 mg SC TE every other week. C, 75 mg SC TE and IM TE monthly. Modeled dose, formulation, and interval are shown with mean testosterone concentration cut-off at steady state.

scaled to adolescent male patients in weight groups of 30, 40, 50, and 60 kg, and used to simulate SC and IM TE dosing following 12.5, 25, 50, 75, and 100 mg administered weekly, EOW, and monthly. The results of these simulated SC and IM TE regimens in adolescent patients were found to predict higher mean testosterone concentrations in lighter- compared to heavier-weight groups and reliable increases in C_{ave} following increasing testosterone doses (Figs. 1-5). Simulated PK parameters for adolescent males using the adult model predicted that 12.5, 25, 50, 75, and 100 mg SC TE dosed weekly, EOW, or monthly could produce testosterone levels consistent with early, mid-, and advanced puberty, although more research on specific
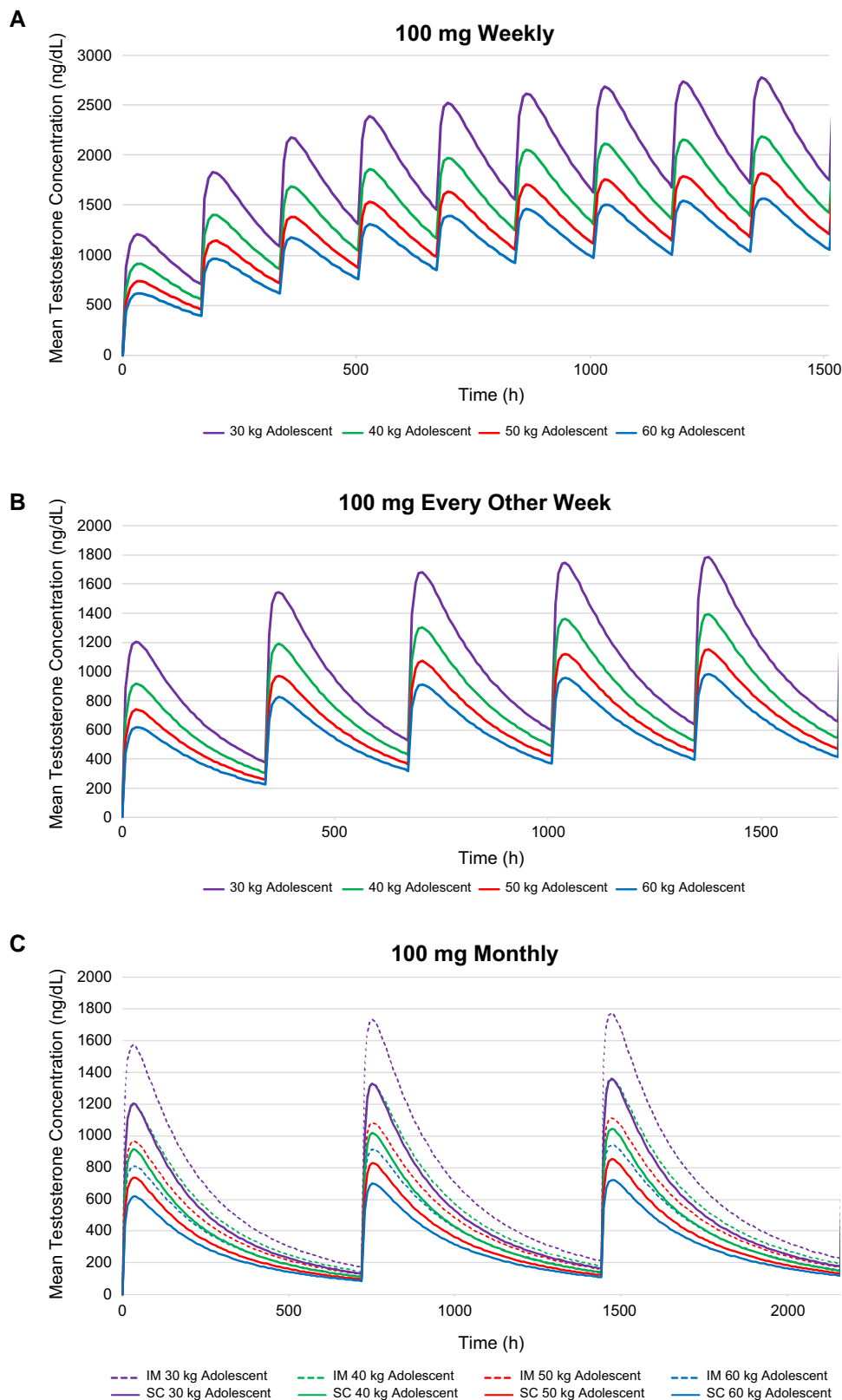
Figure 5. 100 mg subcutaneous (SC) and intramuscular (IM) testosterone enanthate (TE). A, 100 mg SC TE weekly. B, 100 mg SC TE every other week. C, 100 mg SC TE and IM TE monthly. Modeled dose, formulation, and interval are shown with mean testosterone concentration cut-off at steady state.

regimens is necessary to determine the utility of concentration-guided testosterone dosing in pediatric patients. Therefore, SC TE administered to adolescents may represent an effective and convenient treatment option for adolescent males with hypogonadism, which could reduce fluctuations in serum testosterone and related symptoms.

10-149 ng/dL	Early puberty
150-249 ng/dL	Mid-puberty
250-1200 ng/dL	Advanced puberty
>1200 ng/dL	Upper Limit of Normal

		Dose (mg)																		
		12.5				25				50				75				100			
		SC		IM		SC		IM		SC		IM		SC		IM		SC		IM	
Administration		C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}	C_{max}	C_{ave}
Weekly	30 kg	350	288	449	370	699	576	898	740	1388	1147	1775	1467	2081	1721	2663	2201	2775	2295	3550	2934
	40 kg	276	230	354	295	552	461	707	590	1096	917	1399	1170	1644	1375	2099	1756	2191	1834	2798	2341
	50 kg	230	193	294	248	459	387	588	495	912	770	1163	981	1368	1155	1745	1472	1824	1540	2326	1963
	60 kg	198	168	253	214	395	335	505	429	785	667	1000	850	1178	1001	1500	1274	1570	1335	2000	1699
EOW	30 kg	225	146	290	189	451	291	580	377	893	580	1146	748	1339	870	1719	1121	1786	1160	2292	1495
	40 kg	176	117	226	151	352	233	452	301	697	464	894	597	1046	696	1341	896	1394	929	1788	1195
	50 kg	145	98	186	127	290	196	373	253	576	390	738	502	863	585	1106	753	1151	781	1475	1004
	60 kg	124	85	159	110	248	170	318	219	492	339	630	435	738	508	945	652	985	677	1260	870
Monthly	30 kg	172	69	224	92	344	139	448	184	680	276	887	364	1020	415	1330	546	1360	553	1773	728
	40 kg	132	56	173	74	264	111	345	148	523	222	682	292	784	333	1024	439	1045	443	1365	585
	50 kg	108	47	141	62	216	94	282	124	426	187	557	247	640	280	836	370	853	374	1114	493
	60 kg	91	41	119	54	183	82	239	108	361	162	472	214	542	243	708	322	722	325	944	429

Figure 6. C_{max} and C_{ave} at steady state for weekly, EOW, and monthly SC and IM simulations. C_{ave}, Average plasma concentration during a dosing interval; C_{max}, maximum concentration for a dosing interval; EOW, every other week; IM, intramuscular; SC, subcutaneous.

Extrapolation of adult data is an important component of pediatric drug-development, but extrapolation procedures vary widely for different drug dose assessments [10, 16]. Originally, a physiologically based PK (PBPK) model was considered, as a mechanistic model would not have the model-related limitations when simulating adolescent populations. While PBPK modeling can provide accurate predictions in pediatric patients when the mechanisms involved with PK are well characterized, there are insufficient testosterone data in adolescents to derive a PBPK model, and in vitro experimentation and model building can be costly. Considering the abundance of observed adult PK data, the more simplistic and generalized method was to produce an adult population PK model allometrically scaled to adolescent weight groups to gain insight into adolescent PK parameters and serum testosterone following simulated SC and IM TE regimens. Allometric scaling cannot be reliably used in all cases, such as where relevant metabolizing enzymes have not fully matured. However, allometric scaling has been found to reasonably estimate pediatric PK parameters in small molecules when there is an abundance of adult PK data and mechanistic approaches are not feasible [14]. The allometric power function we use is the industry standard method for most small molecule drugs [14]. Caution is advised for allometric scaling when dealing with very young age groups (< 2 years, and less so < 5 years); however, given that the target groups are all adolescents, we felt that allometry was appropriate.

Allometric body scaling from adults to pediatric patients was completed using body weight, rather than body surface area (BSA) or BMI, for several reasons. BSA is mathematically derived from body weight and is most often calculated using the Du Bois and Du Bois formula. However, other equations that produce differing values are often used to determine BSA, making this a less attractive option for modeling [17]. Furthermore, BSA can be approximated using *body weight*$^{0.67}$, which already takes the form of an allometric equation [18]. Historically, *body weight*$^{0.67}$ had been used because of its relationship with surface area until research showed that using a fixed exponent of 0.75 better represented the basal metabolic rate of patients. In pediatric patients older than 5 years, the use of 0.75 produced similar results to other exponents, with 81% of pediatric patients receiving a prediction error of less than 50% [15]. Little research has been completed on BMI in allometric equations for pediatric scaling. However, as BMI is a measure of body shape and not body size, it would likely be unsuitable as a parameter for allometric scaling. Considering the reported results, if BMI had a significant effect on the clearance of testosterone, it would have been determined as a significant covariate during the stepwise covariate search while building the adult model.

Serum testosterone monitoring is not typically performed in adolescents receiving testosterone, making it difficult to compare these results to current and relevant clinical work [1, 19]. To address this concern, one mini-review on testosterone therapy in adolescents proposed concentration-guided testosterone replacement therapy for achieving physiologic testosterone levels for the induction the of puberty in patients with constitutional delay of growth and puberty (CDGP): Tanner II (60-150 ng/dL), Tanner III (150-250 ng/dL), Tanner IV (250-500 ng/dL), Tanner V (500-750 ng/dL) [19]. Modeling indicates that some of the simulated SC and IM TE regimens reported here may produce physiologic levels of testosterone typical of Tanner IV to V and therefore induce puberty in these patients, although more research on specific testosterone regimens is necessary to determine the effect of concentration-guided testosterone dosing on pediatric patient Tanner stages.

Another mini-review identified and summarized studies on testosterone therapy in adolescent males with CDGP and hypogonadism [4]. There were 2 prospective controlled trials and 4 uncontrolled or retrospective studies that evaluated IM TE regimens in adolescents for puberty induction. Evaluated IM TE regimens in these studies included 200 mg every 3 weeks for 4 doses, 100 mg monthly for 6 months, 125 mg every 6 weeks for 3 doses, 33 to 50 mg monthly for 20 months, and 50 mg monthly for approximately 1 year [20-25]. Together, these results indicated that differing IM TE regimens would induce puberty in adolescent males with

CDGP or hypogonadism. Although linear growth increased in the patients studied, the variability in testosterone regimens and the short duration of administration does not allow us to reach any conclusions about a disproportionate advancement in bone maturation and early termination of linear growth.

Considering the results of this PK analysis, one may propose the use of SC TE 12.5 mg monthly as appropriate for puberty initiation as both C_{ave} and C_{max} values correspond to those seen in early puberty. While dosing regimens modeled for monthly and EOW administration produced unphysiological testosterone concentrations, these regimens were used as a starting point to understand adolescent testosterone PK. These dosing regimens are used by pediatric endocrinologists initiating testosterone therapy in adolescents and are increased to adult dosing regimens of weekly or biweekly administration as adolescents go through pubertal maturation [1]. The results of these dosing regimens provide important context for IM and SC dosing, as adolescent patients tend to prefer nondaily testosterone formulations such as IM and SC, which produce variable and unphysiological testosterone PK in adolescents. While transdermal testosterone may be more physiological, it does not show individual pulsations or diurnal variation. Despite this, all forms of testosterone are unphysiological, and many have been used for testosterone therapy in hypogonadal men and boys. The use of IM TE at 12.5 mg monthly, as well as the SC and IM TE regimen of 25 mg monthly, may result in C_{max} values that reach mid- and advanced puberty, especially in the lighter-weight adolescents, a fact that may lead to undesirable rapid skeletal maturation during puberty induction. As the simulated adolescent C_{max} and C_{ave} values for SC TE were found to be approximately 75% of the respective IM TE values, the use of SC TE may assist with a more gradual and physiologic advancement of pubertal development compared to IM TE. The use of average testosterone exposures over a dosing interval may be limited in clinical applicability, but these methods were necessary to determine total exposure and provide practical context for IM and SC dosing in adolescent patients.

This paucity of data, coupled with a lack of evidence-based guidelines for the treatment of hypogonadism in adolescents, suggest that additional clinical trials are required to explore treatment regimens for adolescents requiring testosterone therapy [4]. Furthermore, individual patient factors and treatment goals must be considered when selecting testosterone therapy in adolescents [1].

As a model created to provide simulated SC and IM TE regimens in adolescents, our findings have several limitations that should be carefully considered when addressing clinical applicability. This model was generated from men with physician-diagnosed hypogonadism of any etiology and not organic testosterone deficiency, which may explain the high variability in PK data for patients receiving 50 mg SC TE, who may have experienced postdose endogenous testosterone production. Endogenous testosterone production in adult patients forming the basis of this model confounds extrapolation to adolescents with delayed puberty, where there is decreased endogenous testosterone production. Subsequent pediatric clinical trial data would provide more valuable insight as to the applicability of concentration-guided testosterone dosing in pediatric patients with delayed puberty. Despite adolescent simulations predicting higher serum testosterone concentrations in lighter- compared to heavier-weight groups with reliable increases in C_{ave}, interpretations about the testosterone exposure-response relationship cannot be determined. This relationship is a function of the allometric equations used during modeling, as smaller-weight groups will have lower clearance and volume of distribution, and thus a higher concentration. Also, the adult model did not find weight to be a significant covariate on PK parameters, further limiting interpretation of exposure-response results. Finally, the lowest monthly dose evaluated in this PK analysis may not prove to be appropriate in the smallest and least mature patients, but for a majority of adolescent patients being treated for hypogonadism, this dosing is predicted to produce typical C_{ave} exposures and permit dose progression to foster growth and maturation [5, 19].

Conclusion

Testosterone PK following SC and IM administration of TE is best described by one-compartment models with first-order absorption and elimination kinetics in adult males. Because there are insufficient data in adolescents to derive a PK model, this male model was allometrically scaled to adolescents based on weight groups of 30 to 60 kg. For simulations in 30- to 60-kg adolescent males, SC TE C_{ave} values approximated 75% of IM TE C_{ave} values following regimens of 12.5, 25, 50, 75, and 100 mg TE administered weekly, EOW, or monthly. Therefore, SC TE administration achieved a testosterone exposure-response relationship similar to IM TE in this population of simulated adolescent hypogonadal males. This simulation provides valuable PK data for adolescents of varying weight groups following SC TE administration that may be used alongside future studies to support the use of SC TE in adolescent patients with hypogonadism. Scaling the adult model to adolescents predicted that 12.5 SC TE monthly could produce serum testosterone levels indicative of early puberty and showed pubertal stage progression following multiple subsequent testosterone doses. Therefore, SC TE may represent an effective and convenient treatment option for male adolescents with hypogonadism.

Disclosures

M.G.V. has served as a consultant for Antares Pharma, Inc and Eton Pharmaceuticals, and provided research support for Neurocrine Biosciences and Spruce. J.S.J. has served as an employee of Antares Pharma, Inc. T.A. is an employee of Synteract, Inc. A.D.R. is a consultant for Acerus

Data Availability

The data used for the analyses in this manuscript are available on request from the corresponding author.

Clinical Trial Information

This PK study is an analysis of data from a previously published [12] three-arm, open-label, multidose, parallel-group phase 2 study (No. NCT01887418) (June 26, 2013).

References

1. Mason KA, Schoelwer MJ, Rogol AD. Androgens during infancy, childhood, and adolescence: physiology and use in clinical practice. *Endocr Rev*. 2020;41(3):bnaa003.
2. Abitbol L, Zborovski S, Palmert MR. Evaluation of delayed puberty: what diagnostic tests should be performed in the seemingly otherwise well adolescent? *Arch Dis Child*. 2016;101(8):767-771.
3. Bhasin S, Brito JP, Cunningham GR, *et al.* Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.
4. Vogiatzi M, Tursi JP, Jaffe JS, Hobson S, Rogol AD. Testosterone use in adolescent males: current practice and unmet needs. *J Endocr Soc*. 2021;5(1):bvaa161.
5. US Food and Drug Administration. FDA briefing document for the discussion of issues related to the potential evaluation of efficacy and safety of testosterone replacement therapy in male boys with hypogonadism due to genetic or structural etiologies [FDA briefing document, Pediatric Advisory Committee]. April 8 2019.
6. Endo Pharmaceuticals Inc. TESTOPEL (testosterone pellets) C-III [prescribing information]. Endo Pharmaceuticals Inc; August 2018.
7. Antares Pharma I. XYOSTED (testosterone enanthate) injection, for subcutaneous use CIII [prescribing information]. Antares Pharma Inc; November 2019.
8. Drobac S, Rubin K, Rogol AD, Rosenfield RL. A workshop on pubertal hormone replacement options in the United States. *J Pediatr Endocrinol Metab*. 2006;19(1):55-64.
9. Rogol AD, Swerdloff RS, Reiter EO, *et al.* A multicenter, open-label, observational study of testosterone gel (1%) in the treatment of adolescent boys with Klinefelter syndrome or anorchia. *J Adolesc Health*. 2014;54(1):20-25.
10. Dunne J, Rodriguez WJ, Murphy MD, *et al.* Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics*. 2011;128(5):e1242-e1249.
11. Shingleton AW. Allometry: the study of biological scaling. *Nat Educ Knowl*. 2010;3(10):2.
12. Kaminetsky J, Jaffe JS, Swerdloff RS. Pharmacokinetic profile of subcutaneous testosterone enanthate delivered via a novel, prefilled single-use autoinjector: a phase II study. *Sex Med*. 2015;3(4):269-279.
13. Vogiatzi MG, Jaffe JS, Amy T, Rogol AD. Supplementary material for "Allometric scaling of testosterone enanthate pharmacokinetics to adolescent hypogonadal males (IM and SC administration)." Mendley Data. Deposited March 17, 2023. https://data.mendeley.com/datasets/rzdmvymc8w
14. Liu T, Ghafoori P, Gobburu JV. Allometry is a reasonable choice in pediatric drug development. *J Clin Pharmacol*. 2017;57(4):469-475.
15. Mahmood I. Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. *Clin Pharmacokinet*. 2014;53(4):327-346.
16. Cella M, Knibbe C, de Wildt SN, Van Gerven J, Danhof M, Della Pasqua O. Scaling of pharmacokinetics across paediatric populations: the lack of interpolative power of allometric models. *Br J Clin Pharmacol*. 2012;74(3):525-535.
17. Flint B, Hall CA. Body surface area. StatPearls. StatPearls Publishing LLC; 2022.
18. Germovsek E, Barker CI, Sharland M, Standing JF. Scaling clearance in paediatric pharmacokinetics: all models are wrong, which are useful? *Br J Clin Pharmacol*. 2017;83(4):777-790.
19. Soliman AT, De Sanctis V, Yassin M. Androgen therapy in adolescents: a review. *Andrology*. 2014;3(2):124.
20. Rosenfeld RG, Northcraft GB, Hintz RL. A prospective, randomized study of testosterone treatment of constitutional delay of growth and development in male adolescents. *Pediatrics*. 1982;69(6):681-687.
21. Wilson DM, Kei J, Hintz RL, Rosenfeld RG. Effects of testosterone therapy for pubertal delay. *Am J Dis Child*. 1988;142(1):96-99.
22. Soliman AT, Khadir MM, Asfour M. Testosterone treatment in adolescent boys with constitutional delay of growth and development. *Metabolism*. 1995;44(8):1013-1015.
23. Giri D, Patil P, Blair J, *et al.* Testosterone therapy improves the first year height velocity in adolescent boys with constitutional delay of growth and puberty. *Int J Endocrinol Metab*. 2017;15(2):e42311.
24. Bergada I, Bergada C. Long term treatment with low dose testosterone in constitutional delay of growth and puberty: effect on bone age maturation and pubertal progression. *J Pediatr Endocrinol Metab*. 1995;8(2):117-122.
25. Richman RA, Kirsch LR. Testosterone treatment in adolescent boys with constitutional delay in growth and development. *N Engl J Med*. 1988;319(24):1563-1567.