Comparative Bioavailability of Hydroxyprogesterone Caproate Administered via Intramuscular Injection or Subcutaneous Autoinjector in Healthy Postmenopausal Women: A Randomized, Parallel Group, Open-label Study

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ABSTRACT

Purpose: The purpose of this study was to evaluate the bioavailability of hydroxyprogesterone caproate (HPC) administered as a subcutaneous injection in the back of the upper arm using a prefilled autoinjector syringe with a 27-gauge needle compared with standard intramuscular injection in the gluteus maximus using a 21-gauge needle.

Methods: Healthy postmenopausal women 50 to 75 years old were randomized in a parallel group design to receive a single SC injection of 1.1 mL (275-mg total dose) of preservative-free HPC administered using an autoinjector in the back of the upper arm or a single IM injection of 1 mL (250-mg total dose) of preservative-free HPC administered in the gluteus maximus. Blood samples were collected through 1008 hours (42 days) after injection. The primary measures were the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Secondary measures were T_{max}, k_e, $t_{½}$, and injection site reactions captured as a treatment-emergent adverse event.

Findings: The pharmacokinetic population consisted of 90 individuals; 45 received subcutaneous administration and 45 received intramuscular administration. Geometric mean whole blood concentrations of HPC were comparable between administration regimens. Subcutaneous administration resulted in a higher geometric mean C_{max} than intramuscular administration (7.88 vs 6.91 ng/mL), but median T_{max} values were comparable (48.1 vs 49.7 hours). The least square geometric mean ratios for AUC_{0-168}, AUC_{0-t}, and $AUC_{0-\infty}$ were 102.89%, 110.25%, and 113.51%, respectively, with all 90% CIs within the 80.0% to 125.0% window that defined bioequivalence. The ratio for C_{max} was 113.95% with a 90% CI of 91.94% to 141.23% but with substantial overlap of individual values between administration regimens. The geometric mean $t_{½}$ of HPC was 212 hours for the subcutaneous administration and 188 hours for the intramuscular administration. The most common treatment-emergent adverse event was injection site pain (subcutaneous, 37.3%; intramuscular, 8.2%), described as mild (85%) to moderate (15%).

Implications: Administration of HPC by SC injection of 1.1 mL (275 mg) via autoinjector is bioequivalent to IM injection of 1.0 mL (250 mg). ClinicalTrials.gov identifier: NCT02940522. (*Clin Ther.* 2017;39:2345–2354) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: bioavailability, hydroxyprogesterone caproate, pharmacokinetic properties, route of administration, subcutaneous.

INTRODUCTION

Preterm birth, defined as delivery before 37 weeks' gestation, results in substantial mortality and morbidity burdens in the United States. Not only is preterm birth considered the leading cause of infant death in the United States,[1] but it is also associated with an increased risk of long-term sequelae (physical, cognitive, and social disabilities) among survivors relative to full-term birth.[2–4] The most recent US

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estimates indicate that there has been a slight increase in preterm births that represent the first increase in the preterm birth rate since 2007.[5]

Previous pregnancy history provides an indication of the risk for preterm birth (ie, women who have had a prior preterm birth have a 2.5-fold greater risk for a subsequent preterm birth than those with no such history).[6,7] Prevention of recurrent preterm birth among individuals at risk improves immediate neonatal outcomes[8] and may be expected to also improve long-term outcomes. However, there are limited preventive measures, and among the available options, the effectiveness of lifestyle modification and cervical cerclage is unclear and may be dependent on other factors that can include clinical, cultural, and societal variables.[9,10]

One measure that has demonstrated efficacy in clinical trials to reduce the risk of recurrent preterm birth is the use of hydroxyprogesterone caproate (HPC or 17-OHP),[8,11] which is thought to support gestation and inhibit uterine activity.[12] Although it can reduce recurrent preterm birth in women with a history of spontaneous preterm delivery and improve outcomes among neonates,[8] it has been available for intramuscular administration only, and it has been suggested that alternate routes of administration may be advantageous.[12]

A US Food and Drug Administration (FDA)–approved formulation of HPC* is currently available and is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[13] Administration of this formulation of HPC is as a 1-mL (250-mg) solution via IM injection in the upper outer quadrant of the gluteus maximus muscle using a syringe with a 21-gauge needle.[13] The administration regimen also requires that health care professionals draw the drug from a vial using a large-gauge needle and then switch needles to administer the dose with a smaller-gauge needle.[13] This method is subject to several limitations, including human error when drawing up the dose in the syringe and an increased risk of needlestick injury. Additionally, needle phobia may be a deterrent to patient adherence with the weekly dosing regimen.

*Trademark: Makena® (AMAG Pharmaceuticals Inc, Waltham, Massachusetts).

An autoinjector was developed for subcutaneous dosing of HPC to improve administration by enhancing ease of administration by health care professionals and potentially increasing patient adherence to treatment based on attributes of the autoinjector. These properties were designed to reduce needle phobia by using a smaller needle size for injection into the subcutaneous compartment as opposed to the deeper intramuscular space as well as incorporating a needle shield that prevents the patient from seeing the needle and reduces the risk of inadvertent needlestick injuries. Although the pharmacokinetic (PK) profile of HPC using the standard injection regimen has been well characterized,[14–16] different routes of administration may affect the PK profile. Therefore, the purpose of the current analysis was to assess the bioavailability of subcutaneous administration with a specific focus on determining bioequivalence with that of intramuscular administration.

METHODS

Study Design

This prospective, multicenter, open-label, single-dose study was of parallel-group design to compare the bioavailability of preservative-free HPC administered subcutaneously using an autoinjector with that of the preservative-free standard formulation administered by manual intramuscular injection in healthy postmenopausal women. The study was conducted between September 20 and December 21, 2016, at 5 study sites in the United States. The protocol was approved by an independent institutional review board (IntegReview Institutional Review Board, Austin, Texas), and the study was conducted in accordance with the Declaration of Helsinki (third revision); all participants provided written informed consent before participation.

Dosing and initial assessment was performed on an inpatient basis at the clinic study site, with participants remaining at the site from a least 10 hours before the planned injection time to approximately 24 hours after dosing to obtain adequate time points for collection of blood for PK analysis and to monitor tolerability. Once discharged, participants returned to the clinic for 11 outpatient visits during 42 days for additional blood draws and tolerability monitoring.

Participants were randomized to receive open-label drug exposure with 1.1 mL (275-mg total dose) of

preservative-free HPC administered via SC injection using an autoinjector to the back of the upper arm (triceps area) or 1 mL (250-mg total dose) of preservative-free HPC administered via a manual IM injection to the upper outer quadrant of the gluteus maximus. Drug administration was performed after a fast of at least 10 hours. The intramuscular dose was given via a 1.5-in, 21-gauge needle, with preparation of the syringes within 2 hours before dosing. The autoinjector is a single-use, fixed-dose device that contains a prefilled syringe with a 27-gauge, 10-mm, thin-wall needle that features automated delivery of the drug when triggered by pushing the device onto the skin. The needle is hidden within the safety guard, and as the autoinjector is activated, the needle automatically inserts into the skin. When the autoinjector is fully depressed, the medication is delivered; the needle returns to its original location after the injection and is locked in place to prevent unintentional needlesticks. The single-use disposable autoinjector is intended to be applied only by health care professionals. Investigational products were administered under direct supervision of the investigator or designee. Adherence was verified by the clinical study monitor or designee, who checked all drug supplies and records for completeness and accuracy.

An HPC dose of 250 mg administered IM once weekly is currently recommended by the Society for Maternal-Fetal Medicine for reducing risk of recurrent preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[17] Dose selection for subcutaneous administration (ie, 275 mg) was based on a preliminary assessment that suggested that subcutaneous injection of this dose in the back of the upper arm (triceps area) using a conventional needle and syringe results in total drug exposure over time that is similar to a 250-mg IM injection in the gluteus maximus.

Study Participants

For inclusion, individuals were required to be healthy postmenopausal (naturally or surgically) women between 50 and 75 years old with a body mass index of ≥18 kg/m^2. Postmenopausal was defined as follicle-stimulating hormone levels >40 mIU/mL and one of the following: at least 1 year of natural spontaneous amenorrhea; at least 6 weeks after surgical bilateral oophorectomy, with or without hysterectomy; or hysterectomy (without oophorectomy). Postmenopausal women were selected because administration of HPC may affect menstrual cycles. Exclusion criteria included but were not limited to currently taking any estrogen or progesterone hormone replacement therapy; history or evidence of disease or medical conditions that would place the individual at undue risk of toxic or adverse events; poorly controlled diabetes (hemoglobin A_{1c} >8%); receipt of any prescription or over-the-counter medications that are known to alter CYP3A4 or CYP3A5 levels[18]; any estrogen, progestin, or selective estrogen receptor modulator treatment without sufficient washout (2–6 months, depending on treatment); history of excessive alcohol consumption or treatment for drug or alcohol addiction within the past 12 months; and use of tobacco products within the past 30 days. Additionally, caffeine, xanthine, alcohol, and grapefruit products were not permitted during the inpatient period.

Determination of HPC Concentrations in Whole Blood

Blood samples of approximately 5 mL for analysis of whole blood concentrations of HPC were taken during each drug exposure period at the prespecified time points of within 60 minutes before dosing and within a 10-minute window at 2, 4, 8, 12, 18, and 24 hours after dosing. Patients returned to the study center for blood to be drawn within 2 hours of scheduled postinjection time points of 48, 72, 120, 168, 216, 264, 336, 504, 672, 840, and 1008 hours. Blood samples were collected into labeled K_2EDTA tubes using standard venipuncture techniques. After mixing with the anticoagulant, samples were frozen at −20°C within 2 hours of collection and shipped in dry ice to the central bioanalytical laboratory (Covance Laboratories, West Trenton, New Jersey), where they were stored at −60°C to −80°C until analysis.

Analysis of samples was performed subsequently to method validation for whole blood samples using HPLC-MS/MS that met acceptance criteria and had a lower limit of quantitation of 0.500 ng/mL. Instrumentation included a Luna Cl8 3μ, 50 × 2.0-mm, reverse-phase HPLC column (Phenomenex, Torrance, California) incorporated with LC-20AD or LC1-0AD pumps (Shimadzu, Columbia, Maryland) and an SCL-IOA controller, and an API 5000 mass spectrometer with analyses performed using AB Sciex Analyst I.6.1 analytical software (AB Sciex Thornhill, Ontario, Canada).

Standard curve and quality control samples were generated at concentrations of 0.150, 2.00, 10.0, and 20.0 ng/mL to monitor assay performance; the reference standard was 4-pregnen-17α-ol-3,20-dione-2,2,4,6,6,21,21,21-d8 hexanoate (C/D/N Isotopes Inc, Quebec, Canada). Accuracy and precision acceptance criteria were considered met for validation and were subsequently incorporated into sample assays, if the overall mean percentage of relative SDs of the undiluted quality control samples were within ±15.0% of the nominal concentration and ≤15%, respectively, from all analytical runs.

PK evaluations

Evaluated PK parameters, calculated using noncompartmental analysis, included C_{max}, T_{max}, AUC_{0-t}, AUC_{0-168},[19] $AUC_{0-\infty}$, $t_{1/2}$, and k_e.

Tolerability

Tolerability was evaluated by the reporting of treatment-emergent adverse events (TEAEs) in all patients who were exposed to drug; TEAEs at the injection site were considered the main tolerability outcome measure, which was captured as any TEAE that occurred at the injection site or associated with the injection. The TEAEs were summarized by Medical Dictionary for Regulatory Activities version 19.0 (PSI International Inc, Fairfax, Virginia) preferred term and were determined by spontaneous reporting by the participants as well as direct observation and the use of nonleading questions by the investigator. The association of TEAEs to the study drug was determined in the opinion of the clinical investigator, and the severity of the TEAEs was graded as mild, moderate, or severe based on standard recommendations.[20] Evaluation also included clinical laboratory testing and vital signs.

Statistical Analysis

A total of 120 individuals, 60 per drug exposure group, were planned for enrollment to allow for data from at least 51 individuals per group. This sample size was determined based on a pilot study in which the between-subject %CV for the AUCs for the intramuscular injection (reference) was 30.9% and 26.5% for AUC_{0-t} and $AUC_{0-\infty}$, respectively. Although C_{max} is generally used to estimate sample sizes, because of the different curve shapes for subcutaneous and intramuscular injection, achieving bioequivalence with C_{max} was not considered feasible. Thus, the estimated sample size would have 90% power to obtain a 90% CI for the geometric mean ratios, assuming a true difference between administration regimens of ±5%.

Whole blood PK parameters were summarized using descriptive statistics, and intersubject variability was described based on geometric CV. For C_{max} and AUC outcomes, natural log-transformed data were analyzed for differences between administration routes using an ANOVA model with administration regimen as the fixed effect. Results are expressed as least square means, and the ratios of the least square geometric means between subcutaneous and intramuscular administration were determined along with their 90% CIs. Because the objective was to assess bioequivalence of the higher subcutaneous dose, the data were not normalized for dose before analysis. Bioequivalence between the 2 administration routes was considered to be demonstrated if the 90% 2-sided CI for the subcutaneous-intramuscular ratio is within the predefined equivalence limits of 80.00% to 125.00% according to the general recommendations specified by the FDA.[19]

All analyses, including estimation of PK variables and statistical tests, were performed using SAS for Windows, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Participants and Disposition

A total of 120 individuals were enrolled and received HPC via subcutaneous (n = 59) or intramuscular (n = 61) administration. These individuals were primarily white (85.0%) and Hispanic or Latino (65.0%) with a mean (SD) age of 58.4 (6.1) years and body mass index of 28.2 (4.5) kg/m^2 (Table I). These characteristics were comparable between administration regimens. Of these individuals, 116 completed the study; there was one withdrawal (because of a family emergency) and 3 were lost to follow-up. Samples for full PK analysis of whole blood concentrations were available from 90 individuals, 45 in each administration regimen, and represented the primary PK population; samples from 27 individuals were incorrectly harvested as plasma, and 3 individuals (2 in the subcutaneous group and 1 in the intramuscular group) were excluded because of too many missing time points. However, samples from

Table I. Demographic characteristics.*

Characteristic	Total (N = 120)	Subcutaneous Injection (n = 59)	Intramuscular Injection (n = 61)
Age, mean (SD), y	58.4 (6.1)	59.7 (6.2)	57.0 (5.7)
Race			
American Indian or Alaska Native	2 (1.7)	1 (1.7)	1 (1.6)
Black or African American	16 (13.3)	10 (16.9)	6 (9.8)
White	102 (85.0)	48 (81.4)	54 (88.5)
Ethnicity			
Hispanic or Latino	78 (65.0)	40 (67.8)	38 (62.3)
Not Hispanic or Latino	42 (35.0)	19 (32.2)	23 (37.7)
Weight, mean (SD), kg	71.1 (12.5)	70.9 (14.3)	71.2 (10.7)
Height, mean (SD), cm	158.6 (7.4)	157.4 (6.7)	159.8 (7.9)
Body mass index, mean (SD), kg/m^2	28.2 (4.5)	28.5 (4.9)	28.0 (4.1)

*Data are presented as number (percentage) unless otherwise indicated.

all randomized participants, considered the secondary PK population, were used in a post hoc sensitivity analysis, performed using the same analytic method as the main analysis, regardless of whether collected as blood or plasma.

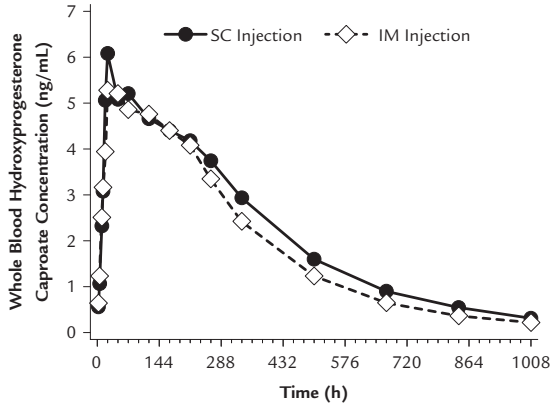

Figure 1. Geometric mean whole blood concentrations of hydroxyprogesterone caproate after administration of an SC dose of 1.1 mL (275 mg) in the back of the upper arm using an autoinjector and administration of an IM dose of 1.0 mL (250 mg) in the gluteus maximus to healthy postmenopausal women.

PK results

As shown in Figure 1, after a single dose of HPC, both routes of administration resulted in similar absorption, with a geometric mean whole blood concentration-time profile for the 275-mg SC dose that was comparable to the 250-mg IM dose except for a transiently higher concentration at 24 hours in the subcutaneous group. The subcutaneous administration was characterized by a higher geometric mean C_{max} relative to intramuscular administration, 7.9 and 6.9 ng/mL, respectively, at a similar median t_{max} (48.1 vs 49.7 hours) (Table II). Drug exposure over time, expressed as AUC (Table II), was slightly but consistently lower with intramuscular administration, by 2.8%, 9.3%, and 11.9% for $AUC_{0–168}$, $AUC_{0–t}$, and $AUC_{0–\infty}$, respectively. The $t_{½}$ was 212 hours (8.8 days) for subcutaneous administration and 185 hours (7.7 days) for intramuscular administration, with a k_e of 0.0033 and 0.0038 h^{-1}, respectively (Table II).

The 90% CIs for the geometric mean ratios were within the equivalence window of 80% to 125% for $AUC_{0–168}$ (102.89%; 90% CI, 87.50%–121.00%), $AUC_{0–t}$ (110.25%; 90% CI, 100.90–120.46) and $AUC_{0–\infty}$ (113.51%; 90% CI, 103.38–124.62%). Although the upper bound of the 90% CI exceeded the 125.00% equivalence window for C_{max} (Figure 2), there was almost complete overlap between the 2

Table II. Whole blood pharmacokinetic properties after single-dose administration of hydroxyprogesterone caproate for the main pharmacokinetic population.

Variable	Geometric Mean (Geometric %CV)	
	Subcutaneous Injection (n = 45)	Intramuscular Injection (n = 45)
C_{max}, ng/mL	7.9 (71.9)	6.9 (62.9)
t_{max}, h[*]	48.1 (18.0-342)	49.7 (2.0-336)
AUC_{0-168}, ng•h/mL	813 (41.5)	790 (55.5) 2.8
AUC_{0-t}, ng•h/mL	2313 (23.5)	2098 (27.7)
$AUC_{0-\infty}$, ng•h/mL	2469 (22.8)[†]	2175 (27.8)[‡]
$t_{1/2}$, h	212 (29.1)[†]	185 (25.5)[‡]
k_e, h^{-1}	0.0033 (29.1)[†]	0.0038 (25.5)[‡]

[*]Median (range).
[†]n = 39.
[‡]n = 41.

administration regimens, with only 3 individuals outside the range (Figure 3A), and was generally similar to $AUC_{0-\infty}$, which also indicated nearly complete overlap between administration routes (Figure 3B).

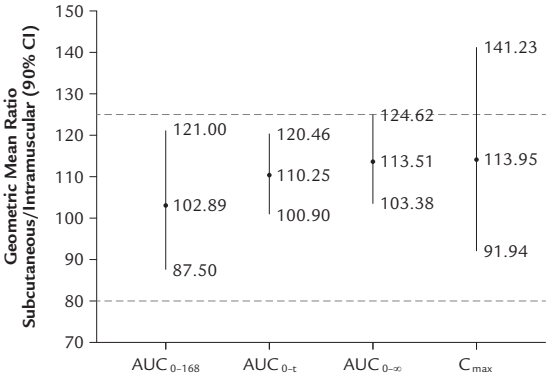

Figure 2. Geometric mean ratios of hydroxyprogesterone caproate in whole blood for AUC_{0-t}, AUC_{0-168}, $AUC_{0-\infty}$, and C_{max} (log-transformed data) after single doses administered by subcutaneous and intramuscular injection. A 90% CI for a given ratio within the predefined interval of 80% to 125% (dotted lines) was considered to indicate bioequivalence.

Results of the post hoc sensitivity analysis of the secondary PK population were concordant with the primary results, including for the geometric mean ratios and their 90% CIs, which for the secondary PK population were 115.75 (90% CI, 96.57–138.73) for C_{max}, 107.07 (90% CI, 92.63–123.77) for AUC_{0-168}; 103.09 (90% CI, 103.09–120.88) for AUC_{0-t}, and 114.38 (90% CI, 105.17–124.39) for $AUC_{0-\infty}$.

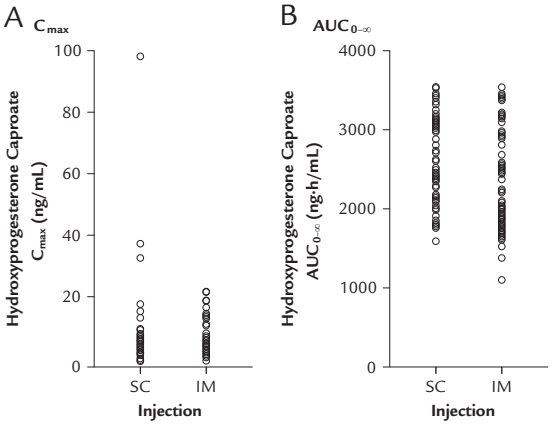

Figure 3. Individual values after subcutaneous or intramuscular administration of hydroxyprogesterone caproate to healthy postmenopausal women. (A) C_{max}. (B) $AUC_{0-\infty}$.

Tolerability

There were 57 TEAEs reported in 32 individuals (54.2%) in the subcutaneous group and 31 TEAEs in 23 individuals (37.7%) in the intramuscular group (Table III); all TEAEs were of mild or moderate severity. There were no serious TEAEs, and none resulted in study withdrawal. Among the TEAEs, 45 in 27 individuals (45.8%) in the subcutaneous group were considered related to study drug, and 23 in 18 individuals (30.5%) were considered related to the autoinjector study device. In the intramuscular group, 16 of the TEAEs in 15 individuals (24.6%) were considered related to study drug, and 1 TEAE was considered related to the manual injection study device (Table III).

Among the most common TEAEs (Table III), defined as occurring in ≥1 individual in either administration regimen, those that were more common in the subcutaneous group included injection site pain (37.3% vs 8.2%) that was primarily attributable to a stinging sensation, diarrhea (5.1% vs 1.6%), and hot flush (3.4% vs 1.6) (Table III); upper respiratory tract infections were more frequent in the intramuscular group, and the frequency of the other common TEAEs were similar between administration regimens. Although duration of the injection site pain was generally short, the overall range of duration was 3 minutes to approximately 7 days for the subcutaneous injection and 1 minute to approximately 2 days for intramuscular injection. There were no clinically significant changes in vital signs or laboratory values.

For the 3 individuals with elevated C_{max} values, there were no injection site reactions or other TEAEs as a result of the high HPC concentrations, and only 1 of these individuals had any TEAEs (abdominal discomfort and laceration that were neither drug nor device related).

Table III. Treatment-emergent adverse events (TEAEs).

	Subcutaneous injection (n = 57)		Intramuscular injection (n = 60)	
Event	Number (%) of subjects	Number of events	Number (%) of subjects	Number of events
Any TEAE	32 (54.2)	57	23 (37.7)	31
TEAEs by severity				
Mild	27 (45.8)	38	17 (27.9)	22
Moderate	14 (23.7)	19	9 (14.8)	9
Severe	0	0	0	0
Serious TEAEs	0	0	0	0
Withdrawal due to TEAEs	0	0	0	0
Drug-related TEAEs	27 (45.8)	45	15 (24.6)	16
Device-related TEAEs	18 (30.5)	23	1 (1.6)	1
Most common TEAEs*				
Injection site pain†	22 (37.3)	25	5 (8.2)	6
Headache	9 (15.3)	9	10 (16.4)	10
Dizziness	1 (1.7)	1	1 (1.6)	1
Diarrhea	3 (5.1)	3	1 (1.6)	1
Nausea	1 (1.7)	1	1 (1.6)	1
Upper respiratory tract infections	1 (1.7)	1	3 (4.9)	3
Hot flush	2 (3.4)	2	1 (1.6)	1

*Occurring with a frequency ≥ 1 subject with either route of administration.
†Majority due to burning/stinging.

DISCUSSION

The desired goals of developing an autoinjector for subcutaneous administration of HPC include increased convenience of administration and potential reduction in injection-related pain or anxiety, without compromising bioavailability and other PK characteristics on which efficacy is dependent. The results of this study confirm the equivalent bioavailability between the 2 dosing regimens.

The primary analysis revealed that all 90% CIs of the geometric mean ratios for the AUC parameters between the subcutaneous and intramuscular groups were contained within the window of 80.00% to 125.00%. Although the geometric mean C_{max} was 14.5% higher for subcutaneous autoinjection in the upper arm relative to standard manual intramuscular administration in the gluteus maximus and the upper limit of the 90% CI exceeded the 125.00% threshold, there was substantial overlap in C_{max} between routes of administration. This overlap was similar to that observed for $AUC_{0-\infty}$. Taken together, these results indicate that there is essentially no difference in the extent of exposure between the routes of administration, thereby satisfying the criteria for bioequivalence between the 275 mg SC dose and the 250 mg IM dose.[19]

The PK characteristics observed in this study are different than what have been reported in previous analyses in terms of C_{max} and the $t_{1/2}$,[15,16] although one point of consistency is the wide intersubject variability, including %CVs in those studies up to 50% for plasma concentration. These differences in PK characteristics are likely attributable to not only the multiple dosing in the other studies but also to the populations studied; those analyses were performed in pregnant women being treated for recurrent preterm birth risk associated with singleton or twin gestation and would be expected to have a higher V_d of the drug; during pregnancy there is expansion of intravascular (plasma volume) and extravascular water content; thus, total body water may increase by up to 8 L, creating a larger space within which hydrophilic drugs may distribute, thereby increasing the V_d.[21]

One of the goals of using the subcutaneous route of administration via an autoinjector was to potentially reduce injection site pain that may be associated with a deeper intramuscular injection, as has been noted in patients with rheumatoid arthritis treated with methotrexate.[22] However, injection site pain was reported by a substantially higher proportion of individuals in the subcutaneous group relative to the intramuscular group (37.3% vs 8.2%). This incidence of pain in the subcutaneous group is consistent with the 35% that has previously been reported using the intramuscular route,[8] also suggesting that the intramuscular group in the present study reported an unusually low incidence of injection site pain. The severity of the reported injection pain was mild (85%) to moderate (15%) in nature. The subcutaneous injection site pain was predominantly described by the patients as a burning sensation, suggesting that this pain is likely attributable to nonaqueous excipients that may sting under the skin, where there are more nerve endings than deeper intramuscular, for which the pain was mainly described as "stinging, "tenderness," or "soreness." Although injection site reactions, especially the presence of pain, may affect patient adherence with treatment in the clinical setting, patients often consider other factors when making decisions regarding treatment adherence, such as the frequency of dosing, ease of use, length and width of needle, visibility of needle, and administration time, which is less with the autoinjector than the more traditional intramuscular administration of HPC. In this regard, overall, HPC was well tolerated, with a generally similar frequency of the noninjection site TEAEs between routes of administration, and all TEAEs, including injection site pain, were of mild or moderate severity.

A limitation of this study is that the population consisted of postmenopausal women instead of those of child-bearing age who may more closely approximate the target population. In this regard, age-dependent changes in CYP3A4/5 expression levels were not considered, representing another limitation of the study population. However, as mentioned above, although the PK properties of HPC may vary, depending on the population (ie, whether the woman is pregnant, nonpregnant premenopausal, or postmenopausal), we do not believe that comparison between the subcutaneous and intramuscular dosing would be population dependent. Another potential limitation is the incorrect collection of a proportion of samples, resulting in a smaller population with evaluable PK data. Nevertheless, both the primary analysis and the post hoc sensitivity analysis of the secondary PK population suggest that the 275-mg SC dose is bioequivalent to the 250-mg IM dose in terms of AUC metrics. Finally, although the study design was in accordance with FDA guidelines,[19] use of a parallel-group rather

than crossover design may also be perceived as a limitation because in a crossover-design individuals also act as their own controls.

CONCLUSIONS

This study provides PK evidence for equivalent bioavailability between a 275-mg SC dose of HPC administered into the back of the upper arm using an autoinjector and a 250-mg IM dose manually administered into the gluteus maximus. These results confirm that subcutaneous administration using the autoinjector represents an appropriate alternative to the current intramuscular dosing regimen that will provide the same systemic exposure and thus expected to have equivalent efficacy for reducing the risk of recurrent preterm singleton birth. Although injection site pain was the most common TEAE with subcutaneous administration, it was generally of mild or moderate severity, with the subcutaneous autoinjector also providing the advantages of smaller needle size, shorter administration time, and no visible needle, which is beneficial to individuals with needle phobia.

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CONFLICTS OF INTEREST

Dr Krop is an employee of AMAG Pharmaceuticals Inc, and Dr Kramer is a paid consultant to

AMAG Pharmaceuticals Inc. With the authors, AMAG Pharmaceutical Inc participated in the study design, collection, analysis, and interpretation of data and in the decision to submit the final manuscript. They also reviewed the final manuscript and have approved this for submission to *Clinical Therapeutics*. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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