GSK1265744 Pharmacokinetics in Plasma and Tissue After Single-Dose Long-Acting Injectable Administration in Healthy Subjects

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Background: GSK1265744 (744) is an HIV-1 integrase inhibitor in clinical development as a long-acting (LA) injectable formulation. This study evaluated plasma and tissue pharmacokinetics after single-dose administration of 744 LA administered by intramuscular (IM) or subcutaneous injections.

Methods: This was a phase I, open-label, 9-cohort, parallel study of 744 in healthy subjects. 744 was administered as a 200 mg/mL nanosuspension at doses of 100–800 mg IM and 100–400 mg subcutaneous.

Results: Eight (6 active and 2 placebo) male and female subjects participated in each of the first 7 cohorts. All 8 subjects, 4 males and 4 females, received active 744 LA in cohorts 8 and 9 and underwent rectal and cervicovaginal tissue sampling, respectively. Plasma pharmacokinetic sampling was performed for a minimum of 12 weeks or until 744 concentrations were ≤0.1 μg/mL. Rectal and cervicovaginal tissue biopsies were performed at weeks 2 and 8 (cohort 8) and weeks 4 and 12 (cohort 9). 744 LA was generally safe and well tolerated after single injections. A majority of subjects reported injection site reactions, all graded as mild in intensity. Plasma concentration–time profiles were prolonged with measureable concentrations up to 52 weeks after dosing. 744 LA 800 mg IM achieved mean concentrations above protein adjusted-IC90 for approximately 16 weeks. Rectal and cervicovaginal tissue concentrations ranged from <8% to 28% of corresponding plasma concentrations.

Conclusions: These data suggest 744 LA injection has potential application as a monthly or less frequent HIV treatment or prevention agent.

Key Words: GSK1265744, pharmacokinetics, tissue penetration, single dose

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INTRODUCTION

Despite tremendous strides in the treatment of HIV infection, there remains a need for simple, effective, and well-tolerated regimens. Long-acting (LA) injectable antiretrovirals may provide significant advantages in adherence and patient convenience for both treatment and prevention of HIV infection. GSK1265744 (744), a potent HIV integrase inhibitor, has produced significant −2.2 to −2.5 $\log_{10}$ reductions in HIV RNA after short-term oral monotherapy at doses of 5 and 30 mg once daily in treatment-naive HIV-1–infected subjects[1] and produced complete virologic suppression (plasma HIV-1 RNA <50 copies/mL) in 87% of treatment-naive patients receiving once daily oral doses of 10–60 mg with 2 nucleoside reverse transcriptase inhibitors for 24 weeks.[2] 744 is also under development as a nanosuspension for injection based on its inherent characteristics of very low aqueous solubility, low metabolic clearance, and daily oral dose of ≤30 mg/d.[3] The objective of this study was to describe the safety, tolerability, and pharmacokinetics (PK) of single doses of 744 LA injection in healthy subjects.

METHODS

This was a phase 1, single-center, parallel, 9-cohort, randomized, single-dose dose-escalation study in healthy, HIV-seronegative adults. Cohorts 1–7 were placebo controlled (6 active and 2 placebo), and cohorts 8 and 9 were open label. All subjects signed written informed consent, and the protocol was approved by the Independent Investigational Review Board, Inc, Plantation, FL.

Cohorts 1–4 evaluated intramuscular (IM) doses of 100, 200, 400, and 800 mg, respectively. Cohorts 5–7 evaluated subcutaneous (SC) doses of 100, 200, and 400 mg, respectively. 744 LA was administered as a 200 mg/mL nanosuspension. IM doses of 100–800 mg were injected into gluteal muscle at a maximum volume of 2 mL/injection using 25 gauge 1.5″ needles, and SC doses of 100–400 mg were injected into the abdominal region at a maximum volume of 1 mL/injection using 25 gauge 5/8″ needles. Dosing between cohorts was staggered to allow for real-time evaluation of plasma concentrations before dose escalation. After reviewing data following the first 7 cohorts, the protocol was amended to include 2 additional cohorts of 400 mg IM to evaluate the effect of splitting the dose into 2 injections (200 mg × 2; cohort 8) versus a single injection (400 mg × 1; cohort 9)

and to enable preliminary evaluation of 744 partitioning into rectal and female genital tract tissue.

Subject Criteria

Subject eligibility was determined by medical history, physical examination, and laboratory screening tests. Healthy volunteers of either sex aged between 18 and 55 years inclusive, with a body mass index within the range, 18.5–31.0 kg/m^2 (inclusive) were eligible to participate in this study. Male subjects with female partners of child-bearing potential agreed to use specified contraception methods from the time of the first dose of study medication until the investigational product was undetectable. Female subjects were required to be of non-childbearing potential. Female subjects participating in cohort 8 or 9 were required to have an intact uterus and cervix without lesions, to be negative for sexually transmitted diseases and to abstain from use of intravaginal products and sexual activity for 72 hours before specimen collection. Male subjects in cohorts 8 or 9 were required to be free of rectal disease and to abstain from use of intrarectal products and anal sexual activity for 72 hours before specimen collection.

Subjects were ineligible for a positive prestudy hepatitis B surface antigen, a positive hepatitis C antibody result within 3 months of screening, a positive test for HIV antibody, history of liver disease or known hepatobiliary abnormalities, electrocardiogram abnormalities, or a history of tobacco/nicotine use for 6 months before study start. Subjects with underlying skin conditions or tattoos at the location of injection sites were excluded from the study. Pregnant or lactating females were not eligible. Use of prescription or nonprescription drugs, including vitamins and herbal and dietary supplements, was precluded within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever was longer) before the first dose of study medication, unless in the opinion of the Investigator and the Medical Monitor, the medication would not have interfered with the study procedures or compromised subject safety.

Safety evaluations, including adverse event (AE) assessments, vital signs, laboratory testing, and electrocardiograms, were performed at regular intervals throughout the study. Injection site examination included an assessment of pain, tenderness, pruritus, warmth, infections, rash, erythema, swelling, induration, and nodule (granulomas or cysts). If present, each of these injection site reactions (ISRs) were graded on a scale of 1–4 with 1 being mild (no or minimal limitation) and 4 being severe (inability to perform basic self-care functions or hospitalization other than emergency department required for management). Subjects completed an ISR diary until the last study visit.

Plasma and Tissue Sampling

Blood samples (2 mL) were collected in K_3EDTA tubes for determination of plasma 744 concentrations at predose and at 4, 8, and 12 hours after dose on day 1; on days 2–7, 10, and 14; at weeks 3–6, 8, 10, and 12, with monthly follow-up PK visits after week 12 until plasma concentrations were $\leq$0.1 μg/mL, or sufficient data were collected to characterize individual PK parameters. The plasma was separated from blood cells by refrigerated (4°C) centrifugation at 1500–2000*g* for a minimum of 10 minutes within 1 hour of blood collection. Supernatant plasma ($\leq$500 μL) was transferred to a 1.4-mL Matrix tube, and the remaining plasma was transferred into a 1.8-mL Nunc tube and stored at −30°C or below before shipment.

Tissue biopsies were obtained from subjects in cohort 8 at weeks 2 and 8 and in cohort 9 at weeks 4 and 12. Female subjects underwent 1 cervical tissue biopsy per visit, with the second occurring approximately 180° from the original biopsy site. Two vaginal tissue biopsies were collected during each procedure, 1 distally on 1 side and proximally on the other, reversing at the second biopsy visit. All biopsies were approximately 4 mm × 2 mm × 2 mm in size. Male subjects underwent flexible sigmoidoscopy to collect 2 biopsies per visit, which were obtained circumferentially at a standard level of 10–30 cm from the anal margin to avoid potential regional variation. Each biopsy was approximately 2–3 mm^3 (average 10–12 mg each). Biopsy sites were to be macroscopically normal in appearance. Tissue samples were rinsed in cold saline, blotted dry, weighed, then placed into 1.8-mL cryovials, placed on dry ice immediately after collection, and stored at −70°C or colder until shipment.

Bioanalytical Methods

Plasma 744 concentrations were determined using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay with a TurboIonSpray (AB Sciex, Framingham, MA) interface and positive ion multiple reaction monitoring after extraction from plasma by protein precipitation using acetonitrile. Data were acquired and processed using the proprietary software application Analyst (Version 1.4.2, MDS Sciex, Framingham, MA, USA) and the Study Management System, SMS2000 (Version 2.3, GlaxoSmithKline, Middlesex, UK). The internal standard was [$^{13}C^2H_2{}^{15}N$]-744. This method was validated over the range 10–10,000 ng/mL. Three concentrations of quality control (QC) samples were included in each run at 30, 800, and 8000 ng/mL. Based on the results of the analysis of QC samples, the bias ranged from 0.7% to 4.9%, and precision ranged from 5.4% to 5.7%.

Human tissue samples were analyzed for 744 using a validated HPLC-MS/MS assay with a linear range of 2.5–1000 ng/mL using a 25-mL aliquot of human tissue homogenate. 744 was extracted from human tissue homogenate by protein precipitation using acetonitrile containing [$^{13}C^2H_2{}^{15}N$]-744 as the internal standard. The homogenate concentration results (nanograms per milliliter) for the analyzed sample aliquots were converted to nanograms per gram based on the weight of biopsy tissue. 744 QC samples were prepared in rat intestinal tissue homogenate at 3 concentrations (7.5, 80, and 800 ng/mL), which spanned the calibration range of the method. Based on the results of the analysis of QC samples, the bias ranged from −1.1% to 3.7%, and precision ranged from 3.0% to 7.0%.

Pharmacokinetic Analysis

Individual concentration–time data were analyzed with model 200 for extravascular administration of the Phoenix

Professional software (version 5.2; Pharsight Corp., Mountain View, CA). Actual recorded times for each individual profile were used to determine plasma 744 PK parameters, which included the area under the curve from time 0 until various time points (AUC_{0-t}), area under the curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), the observed maximum plasma concentration (Cmax), the time to observed maximum plasma concentration (tmax), plasma concentration at various time points (Ct), apparent terminal phase half-life after LA injectable administration, and clearance after LA administration (CL/F). Plasma AUC values were calculated using the linear-up/log-down approach to the trapezoidal rule, and $AUC_{0-\infty}$ was determined by extrapolation using the formula $Ct/\lambda z$ and was reported only if extrapolation was $\leq$40%.

Statistical Analysis

Descriptive statistics were used to describe the PK and safety of 744 LA. Plasma PK parameter values and AEs were summarized by treatment. Dose proportionality was assessed using both the power model and analysis of variance. The effect of splitting injections on PK after 400 mg IM was evaluated by analysis of variance. Tissue concentrations and individual ratios of tissue:plasma concentrations were summarized by tissue type and treatment.

RESULTS

Demographics

Seventy-two subjects were enrolled and were dosed in the study. Fifty-eight subjects completed the study, and 14 subjects discontinued the study [7 (10%) subjects lost to follow-up and 7 (10%) subjects withdrew consent]. No subject withdrew from the study due to an AE. Two subjects withdrew due to transportation issues, 2 withdrew after moving away from the clinical site with inability to make the required visits, and 3 withdrew consent for unspecified reasons. The mean ($\pm$SD) age was 35.1 $\pm$ 10.4 years and the mean body mass index was 25.9 $\pm$ 3.1. Females comprised 46% (33/72) of the population, and 19% of subjects (14/72) were African American or of African heritage.

Safety

Thirty-eight (79%) of 48 subjects receiving an IM injection and 22 (92%) of 24 subjects receiving a SC injection reported at least 1 AE. A higher percentage of AEs identified as ISRs occurred in subjects receiving 744 than placebo. In subjects receiving IM injections, 33 (83%) of 40 subjects receiving 744 reported an AE compared with 5 (63%) of subjects receiving placebo, whereas in subjects receiving SC injections, 17 (94%) of 18 subjects receiving 744 reported an AE compared with 5 (83%) of 6 subjects receiving placebo. Most frequent ($\geq$2 subjects in any dose cohort) AEs that occurred while on therapy by treatment are shown in Table 1.

Serious adverse events were reported in 2 subjects during the study. One subject (cohort 5, 100 mg SC) developed a methicillin-resistant *Staphylococcus aureus* osteomyelitis of the right calcaneus, which required hospital admission for surgical intervention. The investigator considered that there was no reasonable possibility that the osteomyelitis may have been caused by study drug. This serious adverse event resolved after 68 days, and the subject completed the study per protocol.

Another subject (cohort 8, 400-mg IM single injection) developed grade 2 (moderate) uterine fibroids 21 days after receiving study drug. The subject continued to have pain underwent an elective hysterectomy, which resolved the pain. The investigator considered that there was no reasonable possibility that the serious adverse event may have been caused by the study drug.

Injection Site Reactions

The most frequently described ISR-related AE was pain, followed by erythema and nodule formation. There were no grade 2 to 4 ISRs and no subject discontinued from the study as a result of an ISR. In addition, no subjects required any symptomatic treatment for ISRs.

The most common IM-related AEs were pain, erythema, and nodule formation at the site of injection. Pain was described in 50%, 83%, 64%, 63%, and 83% of subjects receiving 744 IM 100-mg, 200-mg, 400-mg, 400-mg split, and 800-mg split injections, respectively, relative to 25% of placebo subjects describing pain. Pain did not seem to be substantially more common with an increasing volume of injection (0.5 vs 2 mL) or with split versus single injection. The mean duration of pain was 2.3–12.4 days across dosing arms. Erythema was described in 33%, 0%, 14%, 0%, and 17% of subjects receiving 744 IM 100-mg, 200-mg, 400-mg, 400-mg split, and 800-mg split injections, respectively, relative to 0% of subjects receiving IM placebo injection. Rates of erythema do not seem to be associated with dose or split versus unsplit injections. The mean duration of erythema ranged from 4 to 14.5 days across dosing arms. Nodules were described clinically as typically painless areas of firm tissue, which resolved in all cases over time. Nodules after IM injection were described in 17%, 0%, 21%, 13%, and 17% of subjects receiving 744 IM 100-mg, 200-mg, 400-mg, 400-mg split, and 800-mg split injections, respectively, relative to 0% of subjects receiving IM placebo injection. The average nodule size was 1.5 cm (range, 0.5–3.0), and the average duration of a nodule was 24 days (range, 2–66 days).

The most common SC-related AEs were pain, erythema, and nodule formation at the site of injection. Pain was described in 50%, 100%, and 83% of subjects receiving 744 SC 100-mg, 200-mg, or 400-mg split injections, respectively, relative to 33% of placebo subjects describing pain. Pain was more common with an increasing volume of injection, 0.5 mL versus 1 mL. The mean duration of pain ranged from 7 to 12 days. Erythema was described in 33%, 83%, and 67% of subjects receiving 744 SC 100-mg, 200-mg, or 400-mg split injections, respectively, relative to 17% of subjects receiving SC placebo injection. The mean duration of erythema ranged from 2 to 10.7 days. Rates of erythema at the injection site were higher after SC injection than IM injection. Nodules were described clinically as typically painless areas of firm

TABLE 1. Summary of Most Frequent (≥2 Subjects in Any Arm) AEs on Therapy by Treatment (Safety Population)

	Treatment									
	IM (Gluteal)						SC (Abdominal)			
Most Frequent AEs	100 mg, N = 6	200 mg, N = 6	400 mg, N = 14	400 mg (200 × 2), N = 8	800 mg (400 × 2), N = 6	PBO, N = 8	100 mg, N = 6	200 mg, N = 6	400 mg (200 × 2), N = 6	PBO, N = 6
Any event, n (%)	5 (83)	5 (83)	12 (86)	6 (75)	5 (83)	5 (63)	5 (83)	6 (100)	6 (100)	5 (83)
Any ISR	3 (50)	5 (83)	9 (64)	5 (63)	5 (83)	2 (25)	5 (83)	6 (100)	6 (100)	3 (50)
Any non-ISR	5 (83)	2 (33)	8 (57)	5 (63)	5 (83)	5 (63)	4 (67)	6 (100)	6 (100)	4 (67)
ISRs										
Erythema	2 (33)	0	2 (14)	0	1 (17)	0	2 (33)	5 (83)	4 (67)	1 (17)
Nodule	1 (17)	0	3 (21)	1 (13)	1 (17)	0	3 (50)	5 (83)	6 (100)	0
Pain	3 (50)	5 (83)	9 (64)	5 (63)	5 (83)	2 (25)	3 (50)	6 (100)	5 (83)	2 (33)
Non-ISRs										
Nausea	0	0	2 (14)	2 (25)	0	0	1 (17)	0	0	0
Vomiting	0	0	2 (14)	1 (13)	0	1 (13)	1 (17)	0	0	0
Non-ISR pain	0	0	2 (14)	0	0	1 (13)	0	0	0	0
Increased blood CPK	2 (33)	0	0	0	0	0	0	0	0	0
Back pain	0	0	3 (21)	0	1 (17)	0	1 (17)	0	0	0
Headache	1 (17)	2 (33)	4 (29)	4 (50)	1 (17)	3 (38)	3 (50)	5 (83)	0	1 (17)
Cough	2 (33)	1 (17)	0	0	0	2 (25)	0	0	1 (17)	2 (33)
Oropharyngeal pain	0	0	1 (7)	0	1 (17)	1 (13)	0	0	0	2 (33)
Rhinorrhea	0	0	0	0	0	0	0	0	2 (33)	1 (17)
Sneezing	0	0	1 (7)	0	0	0	0	0	2 (33)	1 (17)
Erythema	0	0	0	1 (13)	0	0	0	2 (33)	0	0

tissue, which resolved in all cases over time. Nodules after SC injection were described in 50%, 83%, and 100% of subjects receiving 744 SC 100-mg, 200-mg, or 400-mg split injections, respectively, relative to 0% of subjects receiving SC placebo injection. The average nodule size was 2.1 cm (range, 0.5–3.0), and the mean duration of a nodule was 72 days (range, 2–195 days). Nodules were more common after SC injection than after IM injection.

Non-ISR Adverse Events

AEs that were not related to ISRs occurred with low frequency, and there was no obvious relation to dose. The only drug-related non-ISR AEs that occurred in more than 1 subject was headache, reported in 4 subjects (7%).

Pharmacokinetics

Plasma 744 PK parameters are summarized in Table 2, and mean concentration–time profiles are shown graphically for cohorts 1–7 in Figure 1. Absorption of 744 from depot injection sites began within 4 hours, the first sampling time, after LA administration as no lag time was observed in any subject. Plasma concentration–time profiles were consistent with LA administration, with low Cmax values, prolonged median tmax values ranging from 6 to 69 days, and measureable concentrations in some subjects to approximately 1 year after dose. In addition, the apparent terminal phase $t_{1/2}$ after LA administration, which reflects the rate-limiting step of absorption from the depot site rather than elimination from plasma, is prolonged, with geometric mean values ranging from 25 to 54 days. Using a power model, PK parameters seemed to increase proportionally to dose after unsplit SC administration (100 and 200 mg) and split IM administration (400 and 800 mg) but less than proportionally to dose after unsplit IM administration (100, 200, and 400 mg IM). Administration of the dose as 2 separate injections (dose splitting)—400 mg (200 mg × 2) IM and SC as well as 800 mg (400 mg × 2) IM—achieved geometric mean Cw4 above the protein-adjusted IC90. Splitting 400 mg IM into 2 IM injections resulted in a >2-fold increase in plasma 744 $AUC_{0–W4}$, Cmax, and C_{W4} relative to unsplit administration with GLS mean ratios (90% confidence interval) of 2.22 (1.53 to 3.23), 2.03 (1.37 to 3.00), and 2.34 (1.60 to 3.42), respectively (Fig. 2). Dose splitting did not affect 744 $AUC_{0–\infty}$ [GLS mean ratio (90% confidence interval) 1.01 (0.730 to 1.41)].

Tissue concentrations by visit and overall tissue:plasma ratios are summarized in Table 3. Tissue 744 concentrations were low in comparison with corresponding blood plasma concentrations. Assuming a density of 1 g/mL, median cervical and vaginal tissue concentrations were approximately equivalent to the in vitro PA-IC90 (0.166 μg/mL) at some visits. Across visits, median cervical and vaginal tissue: plasma ratios ranged from 0.16 to 0.28. Median rectal tissue:plasma ratios were ≤0.08.

DISCUSSION

This study represents the initial description of the 744 PK profile when administered IM or SC to healthy subjects. This method of administration provides detectable plasma concentrations for up to 52 weeks and enables treatment or prevention of HIV with once-monthly or less-frequent

TABLE 2. Plasma 744 PK Parameter Summary

	Treatment							
	IM (Gluteal)					SC (Abdominal)		
PK Parameter*	100 mg	200 mg	400 mg	400 mg (200 × 2)	800 mg (400 × 2)	100 mg	200 mg	400 mg (200 × 2)
N	6	6	14	8	6	6	6	6
AUC_{0-W4}(μg·h/mL)	118 (74.9)	136 (26.0)	290 (46.2)	644 (61.7)	1497 (79.2)	90.7 (36.7)	265 (41.1)	368 (54.3)
AUC_{0-W12}(μg·h/mL)	320 (75.4)	502 (30.4)	953‡ (54.3)	1798 (50.6)	3851 (50.8)	329§ (45.5)	852§ (35.8)	1292 (61.8)
AUC_{0-t}(μg·h/mL)	607 (43.3)	1068 (37.4)	1921 (60.9)	2445 (52.7)	5651 (17.5)	433 (102)	1005 (85.7)	2402 (16.1)
$AUC_{0-\infty}$(μg·h/mL)	920‖ (12.3)	1234 (34.6)	2652‖ (29.8)	2687 (53.0)	5872 (12.6)	689§ (24.0)	1706‖ (2.6)	2734 (22.3)
Cmax(μg/mL)	0.2 (58.6)	0.3 (28.9)	0.7 (55.2)	1.4 (53.4)	3.3 (75.1)	0.2 (62.1)	0.5 (48.6)	0.9 (83.4)
Tmax†(d)	9.00 (4.0–83.0)	44.50 (27.0–170.1)	69.00 (2.0–213.0)	13.00 (4.0–84.2)	7.58 (5.0–147.0)	16.50 (4.0–55.0)	6.00 (3.0–27.0)	27.00 (3.0–83.0)
C_{W4}(μg/mL)	0.1 (82.7)	0.2 (37.0)	0.4 (54.6)	1.1 (49.3)	2.0 (76.9)	0.1 (60.8)	0.4 (69.1)	0.7 (96.6)
CL/F (L/hr)	0.1¶ (12.3)	0.1 (34.6)	0.1‖ (29.8)	0.1 (53.0)	0.1 (12.5)	0.1§ (24.0)	0.1¶ (2.6)	0.1 (22.3)
$t_{1/2}$(d)	33.3# (66.8)	53.9 (32.2)	38.3‖ (57.3)	31.7** (61.8)	25.4 (51.7)	50.4§ (76.9)	42.7‖ (53.1)	42.8 (52.0)

*Geometric mean (CV%).
†Median (range).
‡n = 13.
§n = 5.
‖n = 4.
¶n = 10.
#n = 3.
**n = 7.

injections. These prolonged exposures also pose a challenge for the conduct of studies in healthy subjects, as noted by the 20% discontinuation rate. With long follow-up periods for safety, there is an increased risk of subjects leaving the study for logistical reasons or being lost to follow-up.

744 was generally safe and well tolerated when administered as a single or separate IM injection from 100 to 800 mg and as a single SC injection from 100 to 400 mg. ISRs were reported by most subjects; however, they were all mild (grade 1) in severity. In addition, ISRs were self-limited, no subjects required symptomatic treatment, and there were no withdrawals due to ISRs. The incidence of ISRs seemed to be related to active drug as a higher percentage of AEs occurred in subjects who received 744 than placebo. Both routes of administration had similar ISR profiles although erythema and nodules were more common after SC injection than after IM injection. Further data on safety and tolerability with repeat doses and in HIV-infected subjects will better characterize the acceptability of monthly injections. There were no substantial differences in reporting of non-ISR AEs between 744 and placebo and AEs not associated with ISRs occurred with low frequency.

The rate of absorption is slower than the rate of elimination after LA administration with prolonged apparent terminal half-lives of 25–54 days, reflecting rate-limited absorption, as compared with the terminal phase elimination

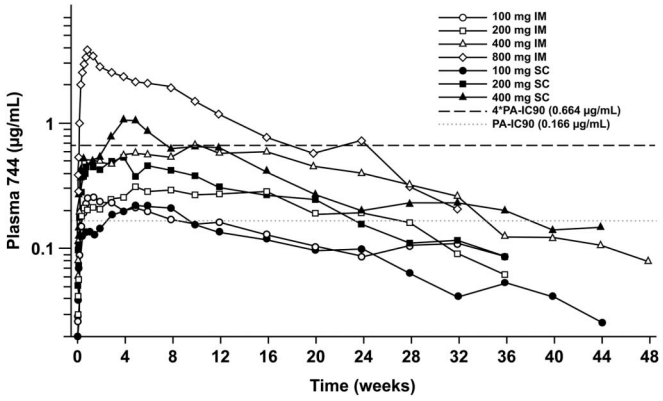

FIGURE 1. Mean plasma 744 concentration–time profiles after single-dose LA injections in healthy subjects (cohorts 1–7). PA-IC90 is the protein-adjusted concentration that inhibits viral replication by 90%. Figure reproduced with permission from Ref. 3. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

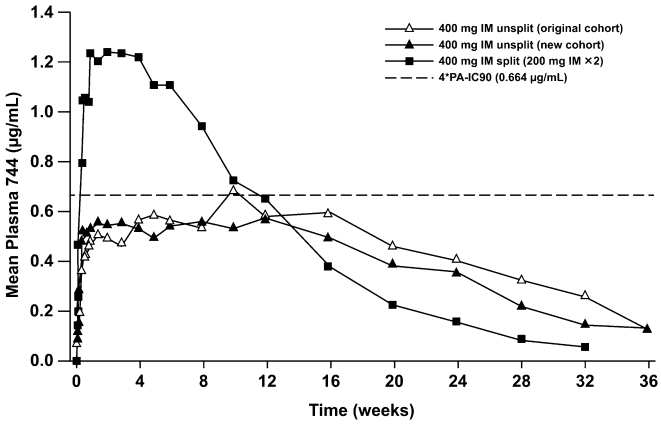

FIGURE 2. Comparison of mean 744 concentration–time profiles after 400 mg IM unsplit (cohorts 3 and 8) and split (cohort 9). PA-IC90 is the protein-adjusted concentration that inhibits viral replication by 90%.

TABLE 3. Summary of 744 Tissue Concentrations by Visit and Overall Tissue:Plasma Ratios by Tissue Type*

	400 mg IM Unsplit (Cohort 8) (n = 4/Visit)			400 mg IM Split (2 × 200 mg IM, Cohort 9) (n = 4/Visit)		
Tissue Type	**Week 2 (μg/g)**	**Week 8 (μg/g)**	**Overall Tissue:Plasma**	**Week 4**	**Week 12**	**Overall Tissue:Plasma**
Cervical	0.081 (NQ-0.17)	0.096 (0.06–0.19)	0.20 (0.0–0.40)	0.177 (0.07–0.50)	0.133 (NQ-0.21)†	0.16 (0.0–0.4)
Vaginal	0.121 (NQ-0.18)	0.184 (0.09–0.44)	0.28 (0.0–0.7)	0.155 (NQ-0.90)	0.181 (NQ-0.35)	0.19 (0.0–0.7)
Rectal	NQ (NQ-0.10)	NQ (NQ-0.05)	0.00 (0.0–0.1)	0.079 (NQ-0.20)	0.063 (NQ-0.08)	0.08 (0.0–0.2)

*Median (range).
†n = 3.
NQ, nonquantifiable concentration measured as below the lower limit of quantitation (50 μg/g).

$t_{1/2}$ of approximately 40 hours after oral administration. LA 744 administered as 2 separate injections—400 mg (200 mg × 2) IM and SC as well as 800 mg (400 mg × 2) IM—achieved geometric mean C648 hours (4 weeks) above the protein adjusted-IC90, consistent with the trough concentrations observed in HIV-infected subjects who achieved a mean 2.2-$\log_{10}$ reduction in viral load at day 10 after 5-mg oral once-daily monotherapy.[1] These exposures and elimination rates after IM or SC injections suggest that a dosing frequency of once monthly or longer is possible for HIV treatment. The PK profile also supports an ongoing study as a pre-exposure prophylaxis agent with an even longer interval between doses.[4]

Plasma 744 PK parameters increased less than proportionally to dose after single, unsplit injections from 100 to 400 mg IM; plasma PK parameters seemed to increase proportionally to dose after split injections from 400 mg (2 × 200 mg) IM to 800 mg (2 × 400 mg) IM and after 100–400 mg SC. Splitting 400 mg IM into two 200-mg IM injections increased Cmax and partial areas ($AUC_{0–W4}$ and $AUC_{0–W12}$) approximately 2-fold. 744 $AUC_{0–\infty}$ was unaffected, however, suggesting that dose splitting may increase the rate but not extent of absorption. The reason for the change in shape of the plasma concentration–time curve is unclear but may be related to greater perfusion with 2 depot sites or greater surface area of the drug.

Although no formal statistical analysis of 744 PK parameters by the gender was performed, there was a general trend of higher plasma exposures in female subjects after SC administration of 744 and of higher exposures in males after split IM injections. Gender differences in absorption rate after IM injections may reflect greater skin-to-muscle depth in females, which would result in an increased likelihood of delivering 744 into the SC space.[5]

After administration of 400 mg IM, tissue:plasma ratios were low: 16%–28% in cervicovaginal tissue and ≤8% in rectal tissue. These values are expected based on the high protein binding of 744 and are in a similar range as were observed for DTG.[6,7] At some visits, cervicovaginal tissue: plasma ratios exceeded the in vitro protein adjusted-IC90. As a linear relationship between tissue and plasma concentrations was observed graphically, tissue concentrations should increase at higher doses of 744 LA, which produce plasma concentrations in the target therapeutic range. The clinical significance of tissue concentrations for systemically administered antiretrovirals is currently unknown; however, 744 LA has previously been shown to prevent transmission of HIV after intrarectal viral challenges in macaques.[8]

In conclusion, 744 LA was well tolerated and produced prolonged plasma exposures after single injection. A dose of 800 mg IM achieved mean concentrations above the protein adjusted-IC90 for approximately 16 weeks, making this a viable loading dose for repeat dose regimens for monthly or bimonthly treatment of HIV infection and quarterly injections for potential pre-exposure prophylaxis in healthy subjects at risk of acquiring HIV.

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