Clinical Pharmacology in Drug Development
2021, 10(3) 260–271

DOI: 10.1002/cpdd.846

Safety, Tolerability, and Dose Proportionality of a Novel Transdermal Fentanyl Matrix Patch and Bioequivalence With a Matrix Fentanyl Patch: Two Phase 1 Single-Center Open-Label, Randomized Crossover Studies in Healthy Japanese Volunteers

Ulrike Lorch[1], Tomasz Pierscionek[1], Anne Freier[2], Christopher S. Spencer[2], and Jörg Täubel[1,3]

Abstract

Two open-label, single-dose, randomized crossover studies were conducted in healthy Japanesemen to (1) assess dose proportionality of 5 doses (1.38, 2.75, 5.5, 8.25, and 11.0 mg) of Lafenta, a novel matrix-type transdermal fentanyl patch with a rate-controlling membrane; and (2) compare patch bioequivalence (11.0 mg) with a commercially available reference patch (Durotep MT Patch [16.8 mg]). Pharmacokinetics, adhesion performance, residual fentanyl, and safety parameters were assessed. Increases in mean $AUC_{0\text{-}t}$ and C_{max} after application of the test patch were dose proportional. The test patch (11.0 mg) was bioequivalent to the 16.8-mg reference patch in terms of mean $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}. Residual fentanyl levels 72 hours postapplication were lower in the test than in the reference patch. Differences in adhesion performance between the test and the reference patch did not affect delivery efficacy and reliability of the novel matrix patch. Safety findings were in line with previous experiences with fentanyl. Both studies showed low variation in fentanyl exposure and delivery via the test patch. The test patch provided equivalent fentanyl exposure at a lower dose than the reference patch formulation with lower variability and the potential to lower medicinal waste.

Keywords

bioequivalence, dose proportionality, fentanyl, Japanese, pharmacokinetic, phase 1, transdermal patch

Pain can be classified in several ways, including physiology (eg, nociceptive, neuropathic, and psychogenic pain) and location (eg, chest, back). Its nature can also be described as acute or chronic. Acute pain has a defined location in the body and a fixed duration. It is usually managed more effectively with analgesics than chronic pain. Conversely, chronic pain is defined as pain that lasts "beyond the expected period of healing"[1] and often shows a poor response to standard analgesics such as paracetamol. This makes effective pain management difficult to achieve for both patients and doctors and can adversely affect a patient's mental state and daily activities.[2,3] Consequently, chronic pain is an area of interest in the development of effective and targeted treatments. The synthetic opioid fentanyl has emerged as one of the most potent analgesics used to treat both acute and chronic pain.

Fentanyl is a potent agonist of mu-opioid receptors[4] and a powerful analgesic. It is approximately 100

[1]Richmond Pharmacology Ltd., St George's University London, London, UK
[2]Richmond Research Institute, London, UK
[3]St George's University London, London, UK

Submitted for publication 17 February 2020; accepted 7 June 2020.

Corresponding Author:
Jörg Täubel, MD, FFPM, Richmond Pharmacology Ltd., St George's University London, Cranmer Terrace, London, UK
(e-mail: j.taubel@richmondpharmacology.com)

times more potent than morphine, with a rapid onset and short duration of action.[5] As fentanyl has a high first-pass metabolism that significantly reduces its bioavailability,[6] alternative administration routes have been introduced. Intravenous fentanyl is now used extensively for anesthesia and analgesia in operating theaters and intensive care units and to relieve pain in cancer patients and those suffering from other forms of chronic pain. Because of its highly lipophilic nature,[7] fentanyl can be delivered transdermally in the form of an adhesive patch. This provides significant advantages for chronic pain management[8] including the slowed release of fentanyl at a constant rate.[9,10] Several transdermal patch formulations are now available commercially, and their use has increased in recent years.

The first transdermal patch formulations of fentanyl were based on "reservoir" technology, whereby liquid fentanyl was contained in a drug reservoir above a rate-controlling membrane, a release liner, and an adhesive layer.[11] These were well tolerated by patients and provided acceptable pain control. However, their potential limitations included a risk of drug leakage and a greater potential for abuse because of ease of drug extraction.[12] As development continued, various prototypes of transdermal patch systems were created based on plastic/silicone matrix technology, which prevented extraction and allowed for controlled drug release. However, fentanyl abuse and rates of accidental overdose have increased in recent years. Coupled with the drug's potentially life-threatening side effects,[13-16] the development of safe, effective, and tamper-proof formulations of transdermal fentanyl is of paramount importance.

A novel fentanyl transdermal matrix patch with a rate-control membrane has been developed. Its membrane allows a more gradual release rate of fentanyl compared with other commercially available transdermal patches. Constant serum fentanyl concentrations from the patch are sustained over 3 days.[17] Clinical trials involving healthy European volunteers showed that the novel fentanyl patch was equivalent to a conventional reservoir fentanyl patch in terms of transdermal delivery and was bioequivalent to a commercially available fentanyl matrix patch.[11,18,19] The patch was shown to be as safe and effective as standard oral or transdermal opioid treatments used by European patients with chronic cancer pain in an open, randomized, parallel-group multicenter study.[20] To be able to conduct further trials in Japanese patients, a phase 1 study to evaluate the safety and pharmacokinetics of the patch was required.

We performed 2 studies to (1) examine the dose proportionality of the test patch's pharmacokinetic parameters after administration of 5 single doses in healthy Japanese male volunteers, and (2) compare the bioequivalence between the test and the reference patch Durotep, a matrix patch commercially available in Japan. The tolerability and safety profiles of the test patch were also evaluated. Because the test patch contained a smaller amount of fentanyl compared with the reference patch (11 vs. 16.8 mg), the amount of residual drug after use was lower.

Materials and Methods

Study Volunteers

Japanese men aged 20-45 years (inclusive) with a body mass index (BMI) between 18.0 and 27.0 kg/m^2 (inclusive) who were deemed to be healthy according to the study's eligibility criteria were deemed suitable for inclusion in the trial. To ensure that the study population was representative of the Japanese population, volunteers had to be Japanese passport holders, be descended from 4 Japanese grandparents, and to have not lived outside Japan for more than 5 years before screening. Furthermore, volunteers were required to have healthy skin and an absence of tattoos, sunburn, or significant birthmarks in the area where the test and reference products were applied. Volunteers also agreed to avoid unprotected sex, use specific contraceptive methods, and refrain from donating sperm until 3 months after drug application. All volunteers signed informed consent forms written in English and translated into Japanese.

Volunteers with a clinically significant medical condition or relevant medical history or those with a history of alcohol excess and/or drug abuse were not included in the study. Volunteers who had taken any prescription or over-the-counter medications (excluding vitamins) within 7 days of dosing or who had consumed alcohol or caffeine within 48 hours before dosing were excluded from the study. Volunteers who were vegetarians, vegans, had medical dietary restrictions, had undergone an inappropriately strict diet within 28 days of dosing, or who were otherwise deemed unsuitable by the investigator were also excluded from the study. Other exclusion criteria included any presence or clinical history of asthma, bradyarrhythmia, hepatic or renal disorders, other system organ-specific disorders, and skin hypersensitivity or relevant atopy.

Study Design

We present data from 2 crossover clinical trials that each involved 30 volunteers. Study 1 assessed the dose proportionality of a single-dose administration of the 72-hour test patch (Eudra/CT no. 2011-004713-16). Study 2 examined the bioequivalence of the test patch compared with a commercially available fentanyl transdermal matrix patch (Durotep MT Patch, Janssen Pharmaceutical K.K., Tokyo, Japan; Eudra/CT no. 2011-002031-25).

Table 1. Random Allocation

Sequence	12.5 μg/h (1.38 mg)	25 μg/h (2.75 mg)	50 μg/h (5.5 mg)	75 μg/h (8.25 mg)	100 μg/h (11.0 mg)
1	X	X	X		
2	X	X		X	
3	X	X			X
4	X		X	X	
5	X		X		X
6	X			X	X
7		X	X	X	
8		X	X		X
9		X		X	X
10			X	X	X

In vitro release testing was conducted before the start of both studies to confirm the quality and the drug-release profiles of both the test and references patches (Supplementary Materials 1). The reference patch released 80% of fentanyl in 3 hours, whereas the test patch with a novel rate control membrane released fentanyl at a constant rate, taking 19 hours for 80% to be released.

To prevent adverse drug reactions and prevent the emergence of symptoms associated with fentanyl use, the opioid antagonist naltrexone was administered in a dose regimen proven to be safe in healthy volunteers.[21,22] Both studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Study 1 was approved by the Plymouth Independent Ethics Committee (Plymouth, Devon, UK) in 2011; study 2 was approved by the National Health Service National Research Ethics Service London-Surrey borders (London, UK) in 2011. Both studies were conducted at Richmond Pharmacology Ltd. (London, UK).

Study 1: Dose Proportionality. This was a single-center phase 1 open-label, single-dose, randomized, 3-period, 10-sequence, 5-treatment crossover study using a balanced incomplete block design. Thirty volunteers received 3 of the following 5 test patch applications: 1.38 mg × 1 patch (release rate, 12.5 μg/h), 2.75 mg × 1 patch (release rate, 25 μg/h), 5.5 mg × 1 patch (release rate, 50 μg/h), 8.25 mg × 1 patch (release rate, 75 μg/h), and 11.0 mg × 1 patch (release rate, 100 μg/h). Volunteers were admitted to the unit 1 day before patch application and were discharged 6 days after the patch had been applied. Each volunteer was randomly allocated to 1 of 10 randomization sequences as described in Table 1 and received 3 patches of different doses in sequence (from a lower to a higher dose) during the 3 periods. The patch was applied on day 1 and remained in place for 72 hours, followed by a 72-hour observation period. Each period was followed by a washout of at least 11 days between removal of 1 patch and application of the next. A follow-up visit was conducted 7 to 10 days after discharge from the last admission (period 3).

Study 2: Bioequivalence. This was a single-center phase 1 open-label, single-dose, randomized, 2-period crossover study. Volunteers were admitted to the unit 1 day before patch application and were discharged 6 days after the patch was applied. The study was divided into a screening phase (up to 28 days before dosing) followed by period 1 (72-hour treatment followed by a 72-hour observation period). After an 11-day washout period, volunteers returned to the unit to receive the alternate treatment using the same design (period 2). Thirty volunteers (15 in each treatment sequence) received either the test patch (11.0 mg × 1 patch; release rate, 100 μg/h) or the reference patch (16.8 mg × 1 patch, release rate, 100 μg/h) on day 1 of each period. A follow-up visit was conducted 7 to 10 days following discharge from period 2.

Naltrexone Treatment. The narcotic antagonist naltrexone (50-mg tablet) was administered 2 hours before patch application and every 12 hours until 22 hours after patch removal in both studies to prevent side effects related to opioid administration.

Pharmacokinetic Analysis

In both studies blood samples were collected in 7.5-mL lithium/heparin S-Monovette tubes (Starstedt, Germany) at 16 points for each period: before application (predose and before naltrexone administration) and 6, 12, 18, 24, 30, 36, 48, 60, 72, 78, 84, 96, 108, 120, and 144 hours postapplication. Samples were stored in ice-water baths immediately after collection. Subsequently, samples were centrifuged at 4°C at 1500*g* for 15 minutes. The plasma supernatant was transferred into 2 aliquots in 3.6-mL Nunc tubes (Merck, formerly

Sigma-Aldrich, Germany), and these aliquots were stored at −20°C until shipment.

Plasma fentanyl concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method by CRS Clinical Research Services Mannheim GmbH (Grünstadt, Germany). Fentanyl-D5 was used as the internal standard. A solid-phase extraction method was applied (Strata-X-C33μ strong cation; Phenomenex, Torrance, California) to isolate the analytes. For the chromatographic measurement, a HTC PAL Autosampler (CTC Analytics, Zwingen, Switzerland) was used with a Kinetex XB-C18100 Å 2.6-μm column (Phenomenex, Torrance, California). Data were recorded using Analyst, version 1.4.2 (ABSciex, Warrington, UK). Mobile phase A consisted of 2.5 L of acetonitrile, and mobile phase D was composed of 1.6 L of H_2O with 1.82 g of ammonium acetate and 0.4 L of acetonitrile with 4 mL of formic acid. The gradient table can be found in Supplementary Materials 2 (Table 1). The mass spectrometer (API 4000/API 5000) ionization mode was API-ES (positive only) to monitor for *m/z* 337.20 (188.00 amu, fentanyl) and *m/z* 342.30 (188.00 amu (internal standard); see Supplementary Materials 2. The lower limit of quantification was 50.00 pg/mL for both the bioequivalence and the dose proportionality studies. At 50.00 pg/mL, precision was 2.78%, and accuracy was −0.08%. Between-sequence precision ranged from 3.03% to 4.70%, and accuracy ranged from 3.04% to 6.33%. Within-sequence precision ranged from 1.98% to 4.86%, and within-sequence accuracy ranged from -0.63% to 7.88%. Additional information on sample preparation and measurement are available in the Supplementary Materials 2.

The following pharmacokinetic parameters were derived from plasma fentanyl concentrations by noncompartmental procedures: maximum observed plasma fentanyl concentration (C_{max}), time of occurrence of C_{max} (t_{max}), area under the plasma concentration-time curve from time zero to the last sampling point ($AUC_{0\text{-}t}$) and to infinity ($AUC_{0\text{-}\infty}$), mean retention time, elimination rate constant (k_{el}), and corresponding half-life ($t_{\frac{1}{2}}$).

Residual Fentanyl and Patch Adhesion Performance

Residual fentanyl in used patches after their removal at 72 hours was measured at LTS (Lohmann Therapie-Systeme) AG (Andernach, Germany). The delivered dose was calculated as the difference between the nominal fentanyl content of an unused patch and the determined amount of residual fentanyl in the patch removed.

Adhesion performance of patches was evaluated at every blood collection point. Adhesion scoring was measured on a scale of 0 (≥90% adhered [essentially no lifting off the skin]) to 4 (0% adhered-patch detached [patch lifting completely off the skin]). In cases in which the patch had come away from the skin, the removal time was recorded.

Safety

Safety evaluations included the measurement of vital signs (blood pressure, pulse rate, respiration rate, tympanic body temperature), clinical laboratory tests (hematology, serum biochemistry, urinalysis, and urine microscopy), electrocardiogram parameters, telemetry, 24-hour Holter recordings, pulse oximetry, and topical skin assessments. Adverse events were monitored and recorded throughout the study from the time of patch application until the end of the study and were summarized according to the Medical Dictionary for Regulatory Activities, version 14.1.

Statistical Analyses

Study 1: Dose Proportionality. Statistical analysis was performed in the safety population (all volunteers who had received at least 1 dose of fentanyl) and in the pharmacokinetic population (those in the safety population who had evaluable pharmacokinetic data). Twenty-nine of the 30 volunteers who enrolled in study 1 completed the study. One volunteer withdrew consent before treatment period 2 after completing period 1. The biometrical evaluation was carried out by the Department Clinical Data Management of CRS Clinical Research Services Mannheim GmbH using SAS software, version 9.2 of the SAS System for Microsoft Windows. Demographic, safety, adhesion performance, residual fentanyl amount, and pharmacokinetic data were summarized using descriptive statistics. For pharmacokinetic parameters and concentrations, arithmetic and geometric means and standard deviations ([SDs] dispersion factor), and geometric coefficient of variation (CV) were calculated. Dose proportionality was explored using a power model[23] on log-transformed pharmacokinetic parameters. For dose-proportionality assessments across the complete dose range, a factor of 2 in exposure was considered acceptable to conclude dose proportionality. The limits of the critical interval for slope were defined as 0.5 and 2. Pharmacokinetic parameters and dose were log(e)-transformed before fitting an analysis of covariance model with fixed-effect terms for dose and period and a random effect for volunteers using PROC MIXED in PC SAS version 9.2.

Study 2: Bioequivalence. Demographic, safety, adhesion performance, residual fentanyl amount, and pharmacokinetic data were summarized using descriptive statistics. Bioequivalence between the test and reference formulations was assessed by calculation of 90% confidence intervals (CIs) for the test:reference ratio of the

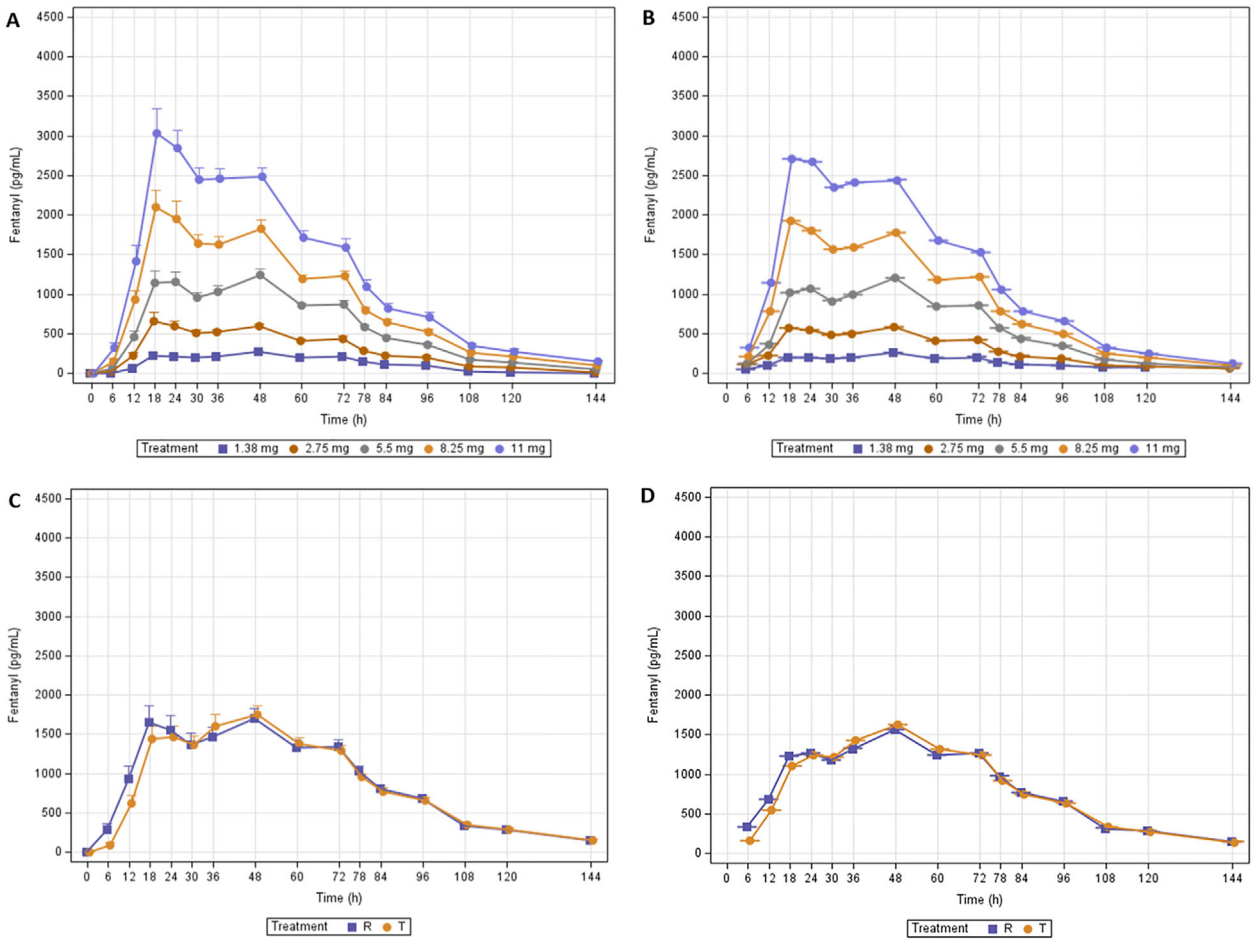

Figure 1. Plasma concentrations of the fentanyl-versus-time profile (arithmetic and geometric mean concentrations plus or minus the standard error). (A, C) Arithmetic mean concentration, (B, D) geometric mean concentration. h, hour; T, test patch (11.0 mg × 1 patch); R, reference patch (16.8 mg × 1 patch). Release rate for both patches: 100 μg/h.

arithmetic and geometric means for $AUC_{0\text{-}t}$ and C_{max}. To be considered bioequivalent, the 90%CIs for both ratios had to be contained within the range of 80% to 125%. The 90%CIs were calculated from an analysis of variance model on the log-transformed data including terms for treatment, period, sequence, and volunteer nested within sequence. The statistical analysis for bioequivalence followed the Guideline for Bioequivalence Studies of Generic Products for Japan.

Results

Volunteer Disposition and Baseline Characteristics

Fifty-six volunteers were screened for study 1, and 48 were screened for study 2 (Supplementary Materials 1, Figure 1). Thirty Japanese male volunteers enrolled in study 1, and 29 of these completed the study; 1 volunteer withdrew consent before treatment period 2. Mean ± SD age was 29.4 ± 5.40 years, and mean BMI and body weight were 21.1 kg/m^2 and 63.27 kg, respectively (Table 2). The 17 volunteers who received the 11-mg patch during study 1 had a mean age of 29.33 years and a mean BMI of 21.1 kg/m^2. Men enrolled in study 2, and all completed the study. Mean ± SD age was 27.7 ± 5.38 years, and mean BMI and body weight were 21.4 kg/m^2 and 64.03 kg, respectively (Table 2).

Pharmacokinetic Profile

Study 1: Dose Proportionality. A total of 1392 plasma samples were analyzed from 29 volunteers. Plasma fentanyl concentrations increased after patch application, with higher concentrations observed following increasing doses. Fentanyl concentrations reached a plateau at approximately 18-48 hours before decreasing (Figure 1A,B). Mean values of $AUC_{0\text{-}t}$ and C_{max} increased with increasing dose (Table 3). Coefficient of variation was low, and there were no notable differences in volunteer variability across doses (range,

Table 2. Demographic and baseline characteristics

A. Demographic and Baseline Characteristics (Safety Populations)			
		Dose Proportionality Study, n = 30	Bioequivalence Study, n = 30
Age, years	Mean (SD)	29.4 (5.40)	27.7 (5.38)
	Min-Max	20-45	21-40
Sex, %	Male	30 (100.0)	30 (100.0)
	Female	0 (0.0%)	0 (0.0%)
Height, m	Mean (SD)	1.73 (0.05)	1.73 (0.06)
	Min-Max	1.7-1.9	1.6-1.8
Weight, kg	Mean (SD)	63.27 (6.00)	64.03 (7.60)
	Min-Max	53.0-75.0	55.0-90.0
BMI, kg/m^2	Mean (SD)	21.1 (1.91)	21.4 (2.00)
	Min-Max	18.5-24.9	18.1-26.9
B. Demographic and Baseline Characteristics (11-mg Test Patch Only)			
		Dose Proportionality Study, n = 17	Bioequivalence Study, n = 30
Age, years	Mean (SD)	29.4 (4.70)	27.7 (5.38)
	Min-Max	23-41	21-40
Sex, %	Male	17 (100.0)	30 (100.0)
	Female	0 (0.0%)	0 (0.0%)
Height, m	Mean (SD)	1.74 (0.02)	1.73 (0.06)
	Min-Max	1.7-1.8	1.6-1.8
Weight, kg	Mean (SD)	63.83 (1.75)	64.03 (7.60)
	Min-Max	61-65.7	55.0-90.0
BMI, kg/m^2	Mean (SD)	21.1 (0.84)	21.4 (2.00)
	Min-Max	20.2-22.2	18.1-26.9

SD, standard deviation; m, meter; kg, kilogram; BMI, body mass index.

17.8%-29.9% for $AUC_{0\text{-}t}$ and 28.8%-49.3% for C_{max}). Median t_{max} was 48.0 hours for fentanyl 1.38 mg and 24.0 hours for all other doses.

Dose proportionality for the test patch after single-point administration was explored over the dose range of 1.38 to 11.0 mg. Slope values and 90%CIs were 1.0666 and 0.9847-1.1485, respectively, for $AUC_{0\text{-}t}$ and 1.0314 and 0.9116-1.1513, respectively, for C_{max} (Figure 2A). As the 90%CIs for the slopes were contained completely within the defined critical range, dose proportionality was concluded for $AUC_{0\text{-}t}$ and C_{max}. This was supported by regression plots for $\log(AUC_{0\text{-}t})$ and $\log(C_{max})$ versus log(dose); see Figure 2B.

Study 2: Bioequivalence. Plasma fentanyl concentrations increased after application of both patches and reached a plateau of approximately 1100 to 1600 pg/mL 18-72 hours before decreasing (Figure 1C,D). Fentanyl plasma concentration profiles for the test and reference patches were comparable.

Pharmacokinetic parameters were very similar for both patches, as shown in Table 3. Ratios of these parameters and their 90%CIs fell within the 80.0% to 125.0% bioequivalence range (Table 4), confirming bioequivalence of the test patch and the reference patch.

The differences in the pharmacokinetic parameters for the test patch between the dose-proportionality and the bioequivalence studies are considered because of interindividual differences. The individual concentrations of fentanyl (11 mg) versus time for both the bioequivalence and dose-proportionality studies are presented in Supplementary Materials 1.

Residual Fentanyl Amount

For all doses in study 1, approximately 20%-30% of the nominal fentanyl content remained in patches removed 72 hours after application. In the 11-mg

Table 3. Descriptive Statistics of Pharmacokinetic Parameters of Fentanyl

	Dose-Proportionality Study Test Patch — Fentanyl Dose (mg)					Bioequivalence Study	
Pharmacokinetic Characteristic of Fentanyl	1.38, n = 18	2.75, n = 17	5.5, n = 18	8.25, n = 17	11.0, n = 17	Test Patch 11.0 mg (Test Treatment), n = 30	Reference Patch, n = 30
AUC_{0-t} (pg·h/mL)							
Mean ± SD	17.0 ± 5.1	41.2 ± 9.1	82.0 ± 19.5	127.7 ± 28.6	180.6 ± 32.2	126.0 ± 40.9 (32.5)	129.4 ± 53.6
(CV)	(29.9)	(23.3)	(23.8)	(22.4)	(17.8)		(41.4)
C_{max} (pg/mL)							
Mean ± SD	296 ± 92.6	761 ± 375	1384 ± 479	2257 ± 852	3372 ± 971	1959 ± 824 (42.1)	1993 ± 1052
(CV)	(31.3)	(49.3)	(34.6)	(37.8)	(28.8)		(52.8)
t_{max} (h)							
Median	48.0	24.0	24.0	24.0	24.0	48.0	48.0
Min-Max	18.0-71.9	18.0-71.9	18.0-48.0	18.0-48.0	18.0-48.0	18.0-71.9	18.0-71.9

C_{max}, maximum concentration; T_{max}, time to reach C_{max}; AUC_{0-t}, area under the concentration-time curve from time zero to time t; SD, standard deviation; CV, coefficient of variation; h, hour; reference patch, Durotep MT Patch 16.8 mg.

(highest) dose group, 21.3% of the fentanyl content remained after patch removal. CVs for the residual fentanyl were low among the different doses, ranging from 27.45 to 45.55 (Table 5A). In the bioequivalence study, mean delivered dose was similar for the 2 treatments: 7.46 mg for the test patch and 6.96 mg for the reference patch (Table 5B and Figure 3A,B). The test patch contained 11.0 mg of fentanyl, and the reference patch contained 16.8 mg of fentanyl. Thus, mean residual fentanyl was 32% for the test patch and 59% for the reference patch. Coefficient of variation for the delivered fentanyl amount observed among volunteers was approximately 10% lower for the novel membrane patch than for the reference patch (14.92 versus 24.14, respectively; Table 5B).

Adhesion Analysis

In the dose-proportionality study, most of the test patches had ≥75% surface area adhesion (some edges lifting off the skin to essentially no liftoff from the skin) for all doses and at all assessment times. In period 1 of the bioequivalence study, 9 of the test patches (60%) and 13 of the reference patches (87%) adhered ≥90% 4 days after application. In period 2, 6 of the test patches (40%) and all the reference patches adhered ≥90%. Although there were slight differences in patch adhesion between the test and reference patches—-the outer edges of the test patch peeled away slightly during the application period—this had no impact on the delivery performance and lower variability of the test patch. Test patch adherence appeared to be slightly better in study 1 (conducted in winter) than in study 2 (conducted in summer).

Safety

No serious, severe, or significant adverse events occurred during either study, and no volunteer discontinued the study prematurely on account of an adverse event.

Study 1: Dose Proportionality. Nineteen of the 30 volunteers (63.3%) reported 58 adverse events. Similar numbers of volunteers experienced adverse events across doses: 7 volunteers each for 1.38, 2.75, 5.5, and 8.25 mg (38.9%-41.2%) and 9 volunteers (52.9%) for the 11.0-mg dose. The most frequent adverse events were nausea, abdominal pain, headache, constipation, and a decrease in appetite (Supplementary Materials 1, Table 1). All 19 volunteers experienced a minimum of 1 adverse event assessed as at least possibly related to the test patch. All adverse events resolved by the end of the study.

Study 2: Bioequivalence. Sixteen of the 30 volunteers (53.3%) who received the test patch and 14 of the 30 volunteers (46.7%) who received the reference patch experienced adverse events. The most frequent adverse events were nausea, dizziness, somnolence, and headache after the application of the test patch and nausea, dizziness, decreased appetite, and application-site pruritus after application of the reference patch (Supplementary Materials 1, Table 2). Most volunteers experienced mild adverse events (15 of the 16 volunteers after the test patch treatment and 13 of the 14 volunteers after the reference patch treatment); 1 volunteer experienced moderate constipation after the test patch,

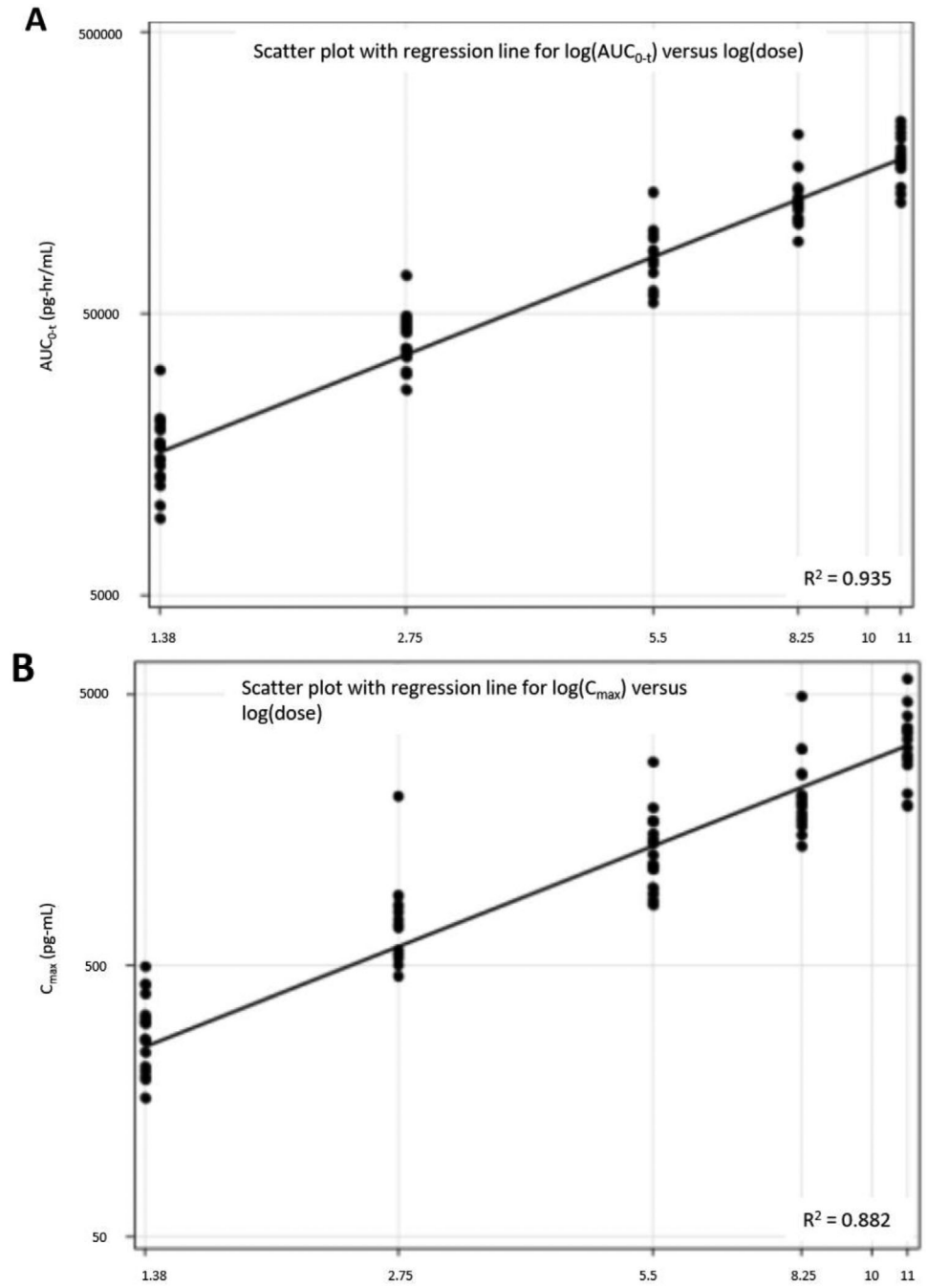

Figure 2. Analysis of dose proportionality.

and another experienced moderate nausea and vomiting after the reference patch treatment. Sixteen volunteers who received the test patch and 12 volunteers who received the reference patch experienced adverse events at least possibly related to treatment. All but 2 adverse events (both deemed mild in severity) had resolved by the end of the study. One of these was a headache that had improved, whereas the other was a red spot over the patch application site that remained unchanged at the end of the study.

Discussion

The volunteers participating in this study were healthy Japanese men. Racial and ethnic variation must be accounted for when conducting clinical trials, as genetic and epidemiological factors can affect the efficacy and safety profile of a novel device/drug formulation.[24] The bioavailability and safety results of the test patch in healthy Japanese men were very similar to those obtained from studies performed in European volunteers

Table 4. Summary of Statistical Analysis of Bioequivalence of the Test Patch and the Reference Patch

Pharmacokinetic Characteristics of Fentanyl	ANOVA CV (%)	Point Estimate of Ratio T/R (%)	90% Confidence Interval of Ratio T/R (%)
$AUC_{0-\infty}$ (pg·h/mL)	9.76	98.60	94.47-102.91
AUC_{0-t} (pg·h/mL)	11.11	99.21	94.50-104.16
C_{max} (pg/mL)	19.24	101.18	93.05-110.01

ANOVA, analysis of variance; CV, coefficient of variation; T, test patch (11.0 mg × 1 patch; release rate: 100 μg/h [test]); R, Durotep MT Patch (16.8 mg × 1 patch; release rate: 100 μg/h [reference]).

Table 5. Summary of Descriptive Statistics of Residual and Delivered Fentanyl Amount

A. Residual Fentanyl (Dose-Proportionality Study)

	Test Patch Nominal Content (mg)				
	1.38	2.75	5.5	8.25	11.0
n	18	18	18	17	17
Mean (SD)[a]	0.41 (0.131)	0.71 (0.228)	1.52 (0.448)	1.89 (0.518)	2.34 (1.070)
CV	32.04	32.40	29.44	27.45	45.55
Min-Max	0.182-0.647	0.256-1.12	0.768-2.190	0.926-2.630	0.862-4.300

B. Delivered Fentanyl (Bioequivalence Study)

	Test Patch	Reference Patch
	11.0 mg	16.8 mg
n	30	30
Mean (SD)[a]	7.46 (1.11)	6.96 (1.68)
CV	14.92	24.14
Min-Max	4.74-9.39	4.50-10.53

[a]Arithmetic mean.

with the patch, which is commercially available in the European Union.[18,19]

The 2 aforementioned studies showed that the fentanyl transdermal matrix patch with a novel rate-controlling membrane provided dose-proportional increases in exposure for a dose ranges between 1.38 and 11.0 mg. The matrix patch containing 11.0 mg of fentanyl was bioequivalent to the 16.8 mg contained in the commercially available reference patch in terms of exposure, safety profile, and tolerance. Furthermore, the test patch was previously deemed safe and efficient in managing pain among European cancer patients.[20] The lower nominal fentanyl dose (11.0 mg) of the test patch compared with the reference patch (16.8 mg) should provide an effective alternative for pain management. In both studies, the fentanyl delivered 72 hours after application of the test patch amounted to 70% to 80% of the nominal patch content. The amount of fentanyl delivered by the reference patch was 41% of the nominal patch content.

Adhesion of the test patch was slightly lower than that of the reference patch. There may be several reasons for this including skin sweating and environmental temperature changes.[25] Because room temperature was held steady during trials, it was not expected that sweat might have had an effect on test patch adhesion, as treatment sequence was randomized using the same condition for both treatments. Patch adhesion did not affect the patch's lower variability in the pharmacokinetic profile and the lower residual amount compared with the reference patch. As Jeal and Benfield[9] pointed out, under normal physiological conditions, skin temperature and blood flow have no significant effect on the absorption rate of fentanyl from a patch. In addition, sweat itself does not appear to create a barrier to drug uptake in transdermal patches.[26] It was previously observed that sweat creates an adhesion issue, but this was not observed to lead to any differences in drug uptake. Therefore, t is unlikely that variations in drug uptake and/or skin temperature are from differences in perspiration. Nevertheless, we found a slightly higher absorption of the same test patch in study 1, which was conducted in winter.

Both biological and technical factors may explain the slight difference in the amount of fentanyl delivered in the 2 studies (mean of 8.66 mg in study 1 and mean of 7.46 mg in study 2). Niepel et al[27] previously argued that biological variation is one of the key factors

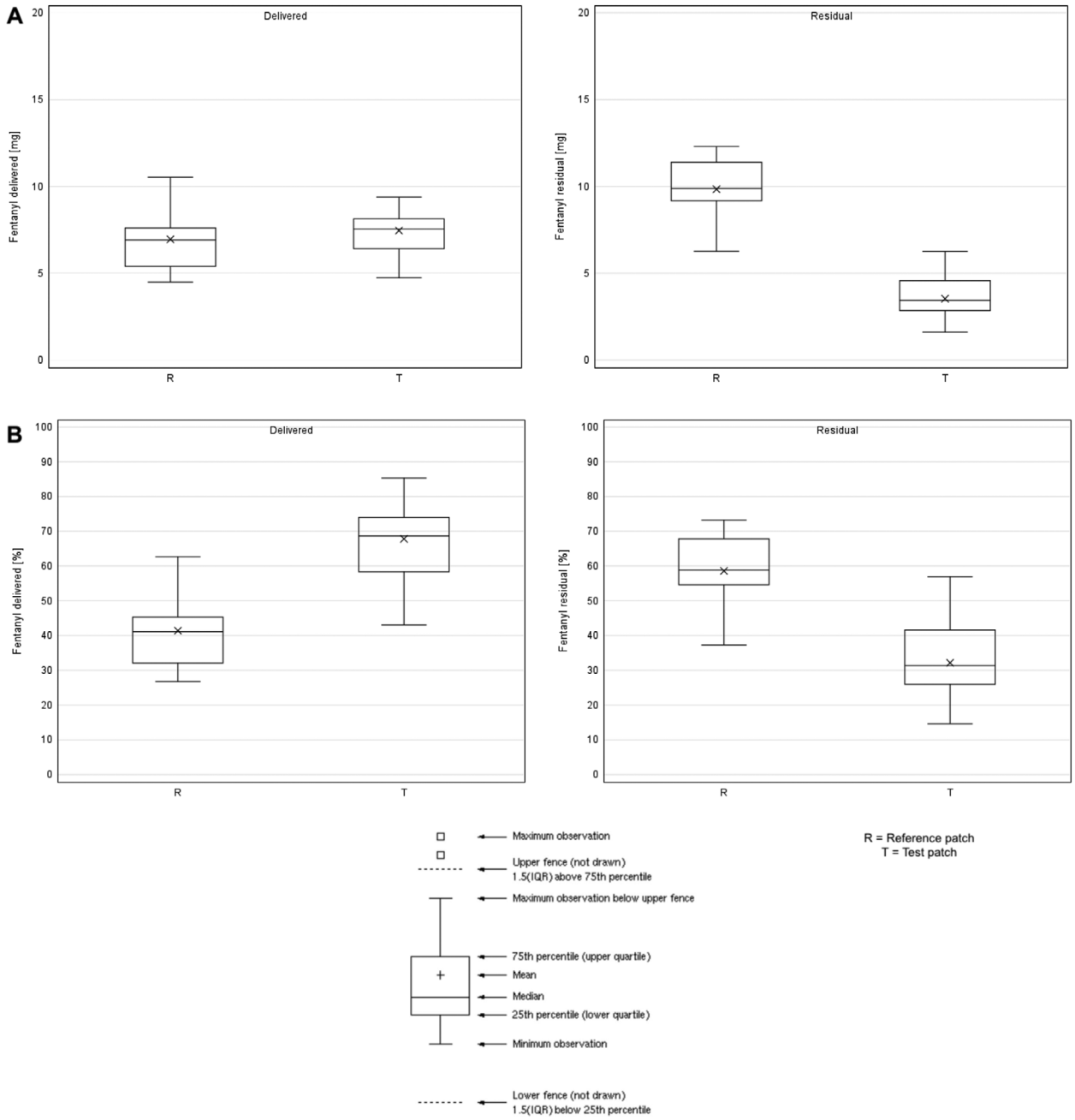

Figure 3. Comparison of delivered and residual fentanyl between test and reference patch. (A) Delivered and residual fentanyl amount in milligrams. (B) Percentage of delivered or residual fentanyl versus the nominal dose in each patch. Reference patch, 16.8 mg; test patch, 11.0 mg.

influencing reproducibility in drug research. As previously shown, drug responses markedly differ because of genetic variation among trial volunteers.[28] Other volunteer-specific factors that may have influenced drug distribution in these trials include body weight and composition. The body weight range of volunteers was slightly broader in study 2 (55.0-90.0 kg) compared with study 1 (53.0-75.0 kg). Research by Cawello et al[29] examining the pharmacokinetics of a transdermal patch for treatment of early Parkinson's disease has shown that body weight did account for differences in serum drug concentration between Japanese and white participants. In contrast, some researchers have argued that BMI, not body weight, may influence drug metabolism.[30] In the current study, BMI range was also broader in study 2 (min-max,18.1-26.9 kg/m^2) compared with study 1 (min-max, 20.2-22.2 kg/m^2). A review by Kuip et al[31] noted that absorption of fentanyl

was overall greater in patients with high versus low BMI, with adipose tissue acting as a store or buffer for the absorbed, circulating fentanyl. In cachectic patients, the concentration of fentanyl was found to be significantly lower. Volunteers with a BMI below 20 kg/m^2 in study 2 may therefore have had an effect on the mean amount of fentanyl delivered. However, because BMI was the only measure of body fat in this study, but is not an exact measure of body fat, further research is needed to gain a deeper understanding of how certain biological factors may affect transdermal fentanyl absorption and distribution. The 2 trials were performed under strict adherence to protocol to minimize technical variability, but biological differences are difficult to control for. Therefore, it is assumed that the differences observed in test patch delivery are because of biological factors.

The test patch was safe and well tolerated in both studies; its safety profile was similar to that of the reference patch. Adverse effects experienced by volunteers, such as nausea, vomiting, and headache, were consistent with those usually reported after fentanyl administration.[17-19]

Initially, the bioequivalence study was planned as a 2-stage study with stage 1 (preliminary) to confirm experimental technique and determine the number of volunteers required for stage 2 (main study). However, stage 2 was not conducted because the primary objective of demonstrating bioequivalence to the reference patch was reached in stage 1, indicating that the low variability in pharmacokinetic data and quality of results was good.

Conclusion

In conclusion, the 2 studies performed showed that the novel membrane patch was both safe and well tolerated in healthy Japanese men and provided reliable dose-dependent delivery of fentanyl with good adhesion performance. The patch provided equivalent fentanyl exposure at a lower dose than a commercially available reference patch formulation with lower variability. These data encourage the evaluation of this novel transdermal fentanyl patch in further studies in Japan.

Conflicts of Interest

Ulrike Lorch, Jörg Täubel, and Tomasz Pierscionek are employees of Richmond Pharmacology Ltd. Anne Freier and Christopher S. Spencer are employees of Richmond Research Institute. Nippon Zoki Pharmaceutical Co., Ltd obtained a marketing license for Lafenta® from the Japanese Ministry of Health, Labour and Welfare on March 26, 2019 with the intention to market Lafenta® in Japan. Ulrike Lorch and Jörg Täubel obtained permission from Nippon Zoki Pharmaceutical Co., Ltd. to use the transdermal fentanyl patch with a rate-controlling membrane, Lafenta®, in a clinical trial and to publish the results.

Funding

Nippon Zoki Pharmaceutical Co., Ltd., funded the studies reported.

Data Sharing

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

References

1. Turk DC, Okifuji A. Pain terms and taxonomies of pain. In: Fishman SC, Ballantyne JC, Rathmell JP, eds. *Bonica's Management of Pain*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2010:13-23.
2. Main CJ, Spanswick CC. *Pain Management: An Interdisciplinary Approach*. 1st ed. London: Churchill Livingstone; 2000.
3. Apkarian AV, Sosa Y, Krauss BR, et al. Chronic pain patients are impaired on an emotional decision-making task. *Pain*. 2004;108(1-2):129-136.
4. Maguire P, Tsai N, Kamal J, Cometta-Morini C, Upton C, Loew G. Pharmacological profiles of fentanyl analogs at mu, delta and kappa opiate receptors. *Eur J Pharmacol*. 1992;213(2):219-25.
5. Poklis A. Fentanyl: a review for clinical and analytical toxicologists. *J Toxicol Clin Toxicol*. 1995;33(5):439-447.
6. Labroo RB, Paine MF, Thummel KE, Kharasch ED. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual variability in disposition, efficacy, and drug interactions. *Drug Metab Dispos*. 1997;25(9):1072-1080.
7. Roy SD, Flynn GL. Solubility and related physicochemical properties of narcotic analgesics. *Pharm Res*. 1988;5(9):580-586.
8. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy and quality of life. *J Pain Symptom Manage*. 1997;13(5):254-261.
9. Jeal W, Benfield P. Transdermal fentanyl. A review of its pharmacological properties and therapeutic efficacy in pain control. *Drugs*. 1997;53(1):109-138.
10. Lane ME. The transdermal delivery of fentanyl. *Eur J Pharm Biopharm*. 2013;84(3):449-455.
11. Marier JF, Lor M, Potvin D, DiMarco M, Morelli G, Saedder EA. Pharmacokinetics, tolerability, and performance of a novel matrix transdermal delivery system of fentanyl relative to the commercially available reservoir formulation in healthy subjects. *J Clin Pharmacol*. 2006;46(6):642-653.

12. Prodduturi S, Sadrieh N, Wokovich AM, Doub WH, Westenberger BJ, Buhse L. Transdermal delivery of fentanyl from matrix and reservoir systems: effect of heat and compromised skin. *J Pharm Sci*. 2010;99(5):2357-2366.
13. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths–United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016;64(50-51):1378-1382.
14. Fox LM, Hoffman RS, Vlahov D, Manini AF. Risk factors for severe respiratory depression from prescription opioid overdose. *Addiction*. 2018;113(1):59-66.
15. Frank RG, Pollack HA. Addressing the fentanyl threat to public health. *N Engl J Med*. 2017;376(7):605-607.
16. Raffa RB, Pergolizzi JV, LeQuang JA, Taylor R, Colucci S, Annabi MH. The fentanyl family: a distinguished medical history tainted by abuse. *J Clin Pharm Ther*. 2017;43(1):154-158.
17. Hair PI, Keating GM, McKeage K. Transdermal matrix fentanyl membrane patch (Matrifen®) in severe cancer-related chronic pain. *Drugs*. 2008;68(14):2001-2009.
18. Marier JF, Lor M, Morin J, et al. Comparative bioequivalence study between a novel matrix transdermal delivery system of fentanyl and a commercially available reservoir formulation. *Br J Clin Pharmacol*. 2007;63(1):121-124.
19. Kress HG, Boss H, Delvin T, et al. Transdermal fentanyl matrix patches matrifen and durogesic DTrans are bioequivalent. *Eur J Pharm Biopharm*. 2010;75(2):225-231.
20. Kress HG, Von der Laage D, Hoerauf KH, et al. A randomized, open, parallel group, multicenter trial to investigate analgesic efficacy and safety of a new transdermal fentanyl patch compared to standard opioid treatment in cancer pain. *J Pain Symptom Manage*. 2008;36(3):268-279.
21. Lor M, Di Marco M, Marier J, et al. Pharmacokinetics, safety and tolerability of a novel 100 μg/h transdermal fentanyl patch co-administered with 100 mg oral naltrexone in healthy males. *Clin Pharmacol Ther*. 2005;77(2):P76-P76.
22. Darwish M, Tempero K, Kirby M, Thompson J. Pharmacokinetics and dose proportionality of fentanyl effervescent buccal tablets in healthy volunteers. *Clin Pharmacokinet*. 2005;44(12):1279-1286.
23. Gough K, Hutchison M, Keene O, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/pharmacokinetics UK joint working party. *Drug Inf J*. 1995;29(3):1039-1048.
24. Taylor AL, Wright JT Jr. Should ethnicity serve as the basis for clinical trial design? Importance of race/ethnicity in clinical trials: lessons from the African-American Heart Failure Trial (A-HeFT), the African-American Study of Kidney Disease and Hypertension (AASK), and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Circulation*. 2005;112(23):3654-3660; discussion 3666.
25. Cilurzo F, Gennari CGM, Minghetti P. Adhesive properties: a critical issue in transdermal patch development. *Expert Opin Drug Deliv*. 2011;9(1):33-45.
26. Solassol I, Caumette L, Bressolle F, et al. Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients. *Oncol Rep*. 2005;14(4):1029-1036.
27. Niepel M, Hafner M, Mills CE, et al. A multi-center study on the reproducibility of drug-response assays in mammalian cell lines. *Cell Syst*. 2019;9(1):35-48.e5.
28. Madian AG, Wheeler HE, Jones RB, Dolan ME. Relating human genetic variation to variation in drug responses. *Trends Genet*. 2012;28(10):487-495.
29. Cawello W, Kim SR, Braun M, Elshoff J-P, Ikeda J, Funaki T. Pharmacokinetics, safety and tolerability of rotigotine transdermal patch in healthy Japanese and Caucasian subjects. *Clin Drug Investig*. 2013;34(2):95-105.
30. Paulzen M, Haen E, Stegmann B, et al. Body mass index (BMI) but not body weight is associated with changes in the metabolism of risperidone; a pharmacokinetics-based hypothesis. *Psychoneuroendocrinology*. 2016;73:9-15.
31. Kuip EJM, Zandvliet ML, Koolen SLW, Mathijssen RHJ, van der Rijt CCD. A review of factors explaining variability in fentanyl pharmacokinetics; focus on implications for cancer patients. *Br J Clin Pharmacol*. 2016;83(2):294-313.

Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.