ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

Pharmacokinetic Evaluation of Two Nicotine Patches in Smokers

Clinical Pharmacology in Drug Development
2018, 7(5) 506–512

DOI: 10.1002/cpdd.431

Scott Rasmussen[1], Kathleen Halabuk Horkan[2], and Mitchell Kotler[3]

Abstract

Smoking continues to be a major preventable cause of early mortality worldwide, and nicotine replacement therapy has been demonstrated to increase rates of abstinence among smokers attempting to quit. Nicotine transdermal systems (also known as nicotine patches) attach to the skin via an adhesive layer composed of a mixture of different-molecular-weight polyisobutylenes (PIBs) in a specific ratio. This randomized, single-dose, 2-treatment, crossover pharmacokinetic (PK) trial assessed the bioequivalence of nicotine patches including a replacement PIB adhesive (test) compared with the PIB adhesive historically used on marketed patches (reference). The test and reference patches were bioequivalent, as determined by the PK parameters of C_{max} and AUC_{0-t}. In addition, the parameters T_{max} and $t_{1/2}$ did not significantly differ between the 2 patches, supporting the bioequivalence finding from the primary analysis. The tolerability profiles of the patches containing the replacement and previously used PIB adhesives were similar; application-site adverse events did not significantly differ between test and reference patches. Overall, these data establish the bioequivalence of the nicotine patch with the replacement PIB adhesive formulation and the previously utilized PIB adhesive formulation.

Keywords

tobacco dependence, smoking cessation, nicotine replacement therapy, bioequivalence, nicotine transdermal system

Smoking harms nearly every organ in the body and causes disease at the cellular and molecular levels; damage caused by smoking can lead to cancer, cardiovascular disease, respiratory disease, reproductive effects, and other conditions.[1] According to the World Health Organization, tobacco kills up to half of users, directly resulting in more than 5 million deaths per year.[2] Although a recent Gallup poll showed that 74% of smokers would like to quit,[3] the rapid delivery of nicotine to the brain and ability to easily titrate the dose make smoking highly addictive and contribute to the difficulties associated with quitting.[4]

When inhaled, the acidic pH of cigarette smoke causes most of the nicotine that is delivered to be ionized and thus poorly permeable across cell membranes.[5,6] Buffering of ionized nicotine to a physiologic pH in the lung promotes rapid nicotine absorption at a rate that approximates that observed on intravenous administration.[7] After absorption, nicotine is rapidly metabolized via the cytrochrome P450 enzyme system to cotinine, predominantly by cytochrome 2A6, but also to lesser degrees by cytochromes 2B6 and 2E1,[8] and 70% to 80% of nicotine is converted to cotinine in humans.[4] Although cotinine has a longer half-life (~16 hours) than nicotine (~2 hours), nicotine concentrations achieved during smoking typically range between 20 and 40 ng/mL, and remain constant over a 24-hour period after only 6 to 8 hours of smoking because of nicotine accumulation.[4,9]

Once absorbed, nicotine has a large volume of distribution, reflecting its lipid solubility and uptake by various tissues. Metabolically, the total clearance of nicotine averages 1200 mL/min[4]; changes in hepatic blood flow contribute to marked interindividual differences in nicotine clearance.[7] Nicotine is excreted mainly via the kidney in a pH-dependent process, in which the total plasma clearance of nicotine rises at urinary pH < 5.[5]

Clinical practice guidelines consistently recommend nicotine replacement therapy (NRT) as a first-line

[1] Early Clinical Development, QuintilesIMS, Overland Park, KS, USA
[2] GlaxoSmithKline Consumer Healthcare, Warren, NJ, USA
[3] Accenture, Berwyn, PA, USA

Submitted for publication 6 July 2017; accepted 30 November 2017.

Corresponding Author:
Scott Rasmussen, Vice President for Medical Research, Early Clinical Development, QuintilesIMS, 6700 W. 115th Street, Room 3524, Overland Park, KS 66211
(e-mail: scott.rasmussen@quintilesims.com)

option for treating nicotine dependence.[10] NRT is available in multiple formulations including gums, lozenges, inhalers, nasal sprays, and nicotine transdermal systems (NTSs; also known as nicotine patches). All forms of NRT are designed to deliver nicotine to the user to reduce the intensity of nicotine withdrawal symptoms during the quitting process and have been consistently shown to increase abstinence rates among those attempting to quit.[10] NTSs have been shown to be effective in increasing rates of long-term abstinence in users[10] and have other advantages including over-the-counter access, an improved safety profile, sustained drug delivery, and low cost compared with other forms of NRT.[11,12] Because nicotine can be readily absorbed through the skin, NTSs are designed to mimic the blood nicotine profile of a typical smoker, although at lower levels.[13] The slow release of nicotine in NTSs provides steady-state levels of nicotine without the need to redose throughout the day.[13]

NTSs have been marketed worldwide by GlaxoSmithKline Consumer Healthcare under several brand names (NicoDerm CQ, Niquitin CQ, Nicabate) and attach to the skin via an adhesive layer composed of polyisobutylenes (PIBs) of 2 molecular weights in a specific ratio. Because of the discontinuation of production of these PIBs by the manufacturer, ExxonMobil (XOM), a replacement PIB adhesive layer with physical characteristics similar to the original adhesive has been sourced from BASF. The primary goal of the present study was to establish whether patches using the replacement adhesive layer from BASF (test patch) were bioequivalent to the discontinued XOM adhesive (reference patch). Bioequivalence was determined with respect to the pharmacokinetic (PK) parameters of the area under the plasma nicotine concentration–time curve from time 0 to the last quantifiable sample (AUC_{0-t}) and the maximal measured plasma nicotine concentration (C_{max}). Secondary objectives included assessing and comparing the parameters of the area under the plasma nicotine concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), time to maximum observed plasma nicotine concentration (T_{max}), and apparent terminal elimination half-life of drug ($t_{1/2}$). Finally, the comparative safety and tolerability of the test and reference patches were assessed.

Methods

Study Design

This was a single-center, randomized, open-label, single-dose, 2-treatment, 2-period (2-way) crossover study conducted between March 6, 2012, and March 30, 2012, in healthy smokers at the Celerion facility in Lincoln, Nebraska. This study was registered at ClinicalTrials.gov (NCT01702519) and was conducted according to the International Conference on Harmonisation Topic 6 Guideline for Good Clinical Practice, the laws and regulations of the United States, and the Declaration of Helsinki. Institutional review board review and approval of the research protocol and informed consent form were provided by Chesapeake Research Review, Inc. (Columbia, Maryland). Subjects were informed about the study both verbally and in writing, and written informed consent was obtained from all subjects prior to any study procedures.

The study included a screening visit followed by 2 treatment periods. Each treatment period lasted approximately 56 hours and consisted of a baseline phase, treatment phase, and posttreatment confinement. The screening visit was conducted 2 to 21 days before the first treatment period, during which potential subjects were informed verbally and in writing about the purpose and conduct of the study. Demographic information, medical history, smoking history, and concomitant medication use were obtained from each subject, and inclusion/exclusion criteria were assessed. All subjects underwent physical examination to confirm general good health. The baseline phase of each treatment period included the period from subject check-in at the study facility (at least 24 hours before administration of the study treatment) to the time immediately before dosing. Study personnel confirmed subject compliance with inclusion and exclusion criteria and lifestyle restrictions (detailed below), recorded concomitant medication use, and any adverse events (AEs) and collected urine samples for laboratory testing. The treatment phase lasted 24 hours from administration of the test or reference nicotine patch. Expired carbon monoxide (CO) testing was carried out approximately 30 minutes prior to dosing. Subjects remained at the study facility for 8 hours following the removal of the patch (posttreatment confinement phase). A washout period of at least 24 hours separated the 2 treatment periods. Smoking was not permitted during the treatment period, but was allowed during the washout period. The Biostatistics Department of GlaxoSmithKline Consumer Healthcare provided the study randomization schedule.

Study Subjects

Current smokers between 19 and 55 years of age with a body mass index ranging from 19 to 27 kg/m^2 were chosen as the subject population for this bioequivalence study because they are the target population for the NRT product containing the replacement PIB adhesive and because the pharmacodynamics of nicotine delivery by NTSs differ between smokers and nonsmokers.[12] Subjects were eligible for this study if they self-reported smoking more than 10 cigarettes per day for the 6 months preceding the study. Subjects were

otherwise in generally good health (assessed during screening by medical history, physical examination, electrocardiogram, and laboratory testing); women were required to use an accepted form of birth control, be surgically sterile, or be postmenopausal. Subjects were excluded if they were pregnant or breastfeeding, had any disease or medical condition that might interfere with transdermal absorption of the study treatments, or had a medical history of recent or severe cardiovascular risk factors. Subjects who were unable to abstain from using tobacco products during each study period, were allergic to or intolerant of any of the study materials, or who took liver enzyme inducers/inhibitors within 30 days, NRT within 21 days, prescription drugs within 14 days, or over-the-counter or herbal supplements within 48 hours of study treatment were not eligible for study inclusion. Subjects with positive testing for hepatitis B, hepatitis C, or human immunodeficiency virus, a history of drug or alcohol abuse within 2 years of screening, or positive urinalysis results for drugs, alcohol, or anemia were excluded.

Several lifestyle restrictions were required for study participation. Subjects were prohibited from using tobacco products during the treatment periods; smoking abstinence was verified by assessing the levels of exhaled CO in each subject before administering the study treatment and at 4 random times during the treatment phase of each period. Subjects who exhaled CO levels greater than 10 parts per million were withdrawn from the study.

In addition, consuming alcohol within 48 hours of receiving a study treatment was prohibited, as was the consumption of beverages containing caffeine or xanthine during each study period. No showering was permitted while wearing the patch and for 8 hours after patch removal. Lotion application to the upper back or arms during each treatment period was not allowed. Finally, subjects were required to fast for at least 8 hours before and 4 hours after receiving the study treatment; otherwise, standardized meals were provided to subjects by study-site personnel.

Study Treatments

The test treatment was a 21-mg nicotine clear patch made with the replacement PIB adhesive from BASF, and the reference treatment was a 21-mg nicotine clear patch made with the original PIB adhesive from XOM (both patches supplied by GlaxoSmithKline Consumer Healthcare Clinical Supplies, Parsippany, New Jersey).

Analytical Measurements and Evaluations

Pharmacokinetic Assays. Blood samples for PK analysis were collected from each subject immediately before patch application and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 25, 26, 28, and 32 hours following patch application. Patches were removed from subjects after collection of the 24-hour sample. Approximately 5 mL of blood was collected for each PK sample, and a total of approximately 200 mL of blood was collected from each participant over the course of the study. Samples were collected by direct venipuncture into ethylenediaminetetraacetic acid (EDTA) tubes. Blood samples were centrifuged at 3000 revolutions per minute for 15 minutes at 4°C or room temperature to isolate plasma, and approximately 2 mL of plasma was aliquoted and stored at −20°C until analysis.

Plasma nicotine levels were determined by analyzing plasma samples with a proprietary, fully validated liquid chromatography–tandem mass spectrometry method at Celerion (Lincoln, Nebraska). In brief, an aliquot of human plasma (EDTA) containing the analyte (nicotine) and internal standard (d_3-nicotine) were extracted using a solid-phase extraction procedure. The extracted samples were analyzed using high-performance liquid chromatography (Merck KGaA, Chromolith Performance Si, 100 × 4.6 mm; 2 columns in series; or Phenomenex, Onyx Monolithic Si, 100 × 4.6 mm; 2 columns in a series) and mobile phase (60:40 MeOH:90 mM HCOONH4, pH 3.0 w/ HCOOH) equipped with AB | MDS Sciex API 5000 triple quadrupole mass spectrometer using an electrospray ionization source. Positive ions were monitored in the multiple reaction monitoring mode. The peak area of mass-to-charge ratio (m/z) 136.2 → 130.0 nicotine product ion was measured against the peak area of the m/z 166.2 → 132.0 of the internal standard. A weighted linear regression curve (1/x2) was determined to best represent the concentration/detector–response relationship for nicotine. The lower limit of quantitation (LLOQ) for this method was 0.500 ng/mL. A total of 3 sample batches were used to test precision and accuracy in nicotine concentration results. Acceptance criteria for the inter- and intrabatch precision evaluations were a coefficient of variation and bias ≤15% for low, medium, and high standards and ≤20% for the LLOQ standard.

The minimum requirements for validation included an assessment of accuracy, precision, selectivity, sensitivity, matrix effect, stability (long-term, freeze-thaw, short-term, postpreparative, and long-term stability for stock solutions), and response function; all validation requirements were met.

Safety Assessments. All AEs, defined as any untoward medical occurrence in subjects that was temporally associated with the use of the test or reference treatments, were recorded from the start of the administration of the first study treatment until 5 days after the last administration using the Medical Dictionary for Drug Regulatory Affairs version 15.0. AEs were classified

Table 1. Topical Effect Rating Scale

Score	Erythema	Edema	Extent of Erythema, Papules, and Pustules	Itching
0	None	None	None	None
1	Barely perceptible redness	≤50% of occluded area	≤50% of occluded area	Mild
2	Definite redness	>50% of occluded area	>50% of occluded area	Moderate
3	"Beet" redness	100% of occluded area	100% of occluded area	Severe

as serious (SAEs) if they resulted in death, were life-threatening, required hospitalization or prolonged existing hospitalization, or resulted in disability or incapacity. Abnormal results from laboratory tests and vital sign assessments that were considered by the investigator to be clinically significant were reported as AEs. AEs were graded for intensity and assessed for their relationship to the study treatment, and those that occurred during the washout period were attributed to the previously administered treatment. To avoid any potential bias, a blinded rater evaluated subject skin within 1 hour before patch application and used a 4-point topical effect rating scale (Table 1) to assess the topical effect of patches 8 hours after removal.

Data Analysis

The sample size for this study was calculated based on the ratio of geometric means (log scale) of the PK parameters with 2 one-sided tests. An enrollment goal of 40 subjects was set to ensure at least 32 would complete both treatment periods to reach a 5% significance level. The per-protocol (PP) population was used for the primary analysis and included subjects who were randomized, received at least 1 study treatment, provided sufficient PK data (as determined by the pharmacokineticist), had no major protocol deviations, and had the patch attached to the skin for at least 20 hours in a given treatment phase. Finally, treatment safety was evaluated using the safety population, which was determined separately for each treatment period in the study and consisted of subjects who were randomized and received at least 1 dose of the study treatment.

Statistical Analysis. Baseline data, relevant screening data, and demographic characteristics were recorded for all randomized subjects. Bioequivalence of the 2 patches was established if the 90% confidence interval (CI) for the ratio of the geometric means of AUC_{0-t} and C_{max} was within the standard acceptable bioequivalence limits of 0.80–1.25.

All PK parameters, including AUC_{0-t}, C_{max}, $AUC_{0-\infty}$, T_{max}, and $t_{1/2}$, were calculated using unadjusted nicotine concentrations as well as baseline-adjusted nicotine concentrations. Baseline-adjusted nicotine concentrations were calculated using the apparent terminal elimination rate constant (K_{el}) calculated from the subject's own data as follows: $C(t)_{adjusted} = C(t)_{observed} - C(0)e^{-Kel\,(t)}$, where (t) is the time adjusted and C(0) is the baseline nicotine concentration.

Nicotine concentrations below the limit of quantification were recorded as 0 if they occurred before the first quantifiable concentration and recorded as "missing" if they occurred thereafter. Analysis of variance was conducted separately for each log-transformed PK parameter (AUC_{0-t} and C_{max}) using a mixed model with sequence, period, and treatment as fixed effects and subjects nested in sequence as a random effect. Least-squares estimates of the treatment effects and the 90%CI for the treatment differences were calculated. The treatment difference and its 90%CI were exponentiated to obtain the ratio of the geometric means between the test and reference product and its 90%CI.

Calculation of $AUC_{0-\infty}$ was conducted using the same model as for the other PK parameters. Drug half-life ($t_{1/2}$) and T_{max} were analyzed using the nonparametric Wilcoxon signed rank test with a 5% significance threshold.

Potential topical patch effects including edema, erythema, itching, and extent of erythema, papules, and pustules were each analyzed separately and compared between respective patches using the Wilcoxon signed rank sum test.

Results

Subject Disposition

Of 128 potential subjects screened, 40 were randomized, and 37 completed both treatment periods. Three subjects withdrew after completing the first period (1 completed with only the reference patch and 2 with only the test patch). Reasons for subject withdrawal were protocol violation, withdrawal of consent, and failure to check in for the second treatment period. In addition, plasma nicotine concentrations in 1 subject were unexpectedly high and low over time in the second treatment period. Following a medical data review by the principal investigator and GlaxoSmithKline medical and biostatistics representatives, the nicotine concentrations for this subject during the second treatment period were deemed nonevaluable. Therefore, the PK-evaluable population consisted of 38 subjects in each treatment period.

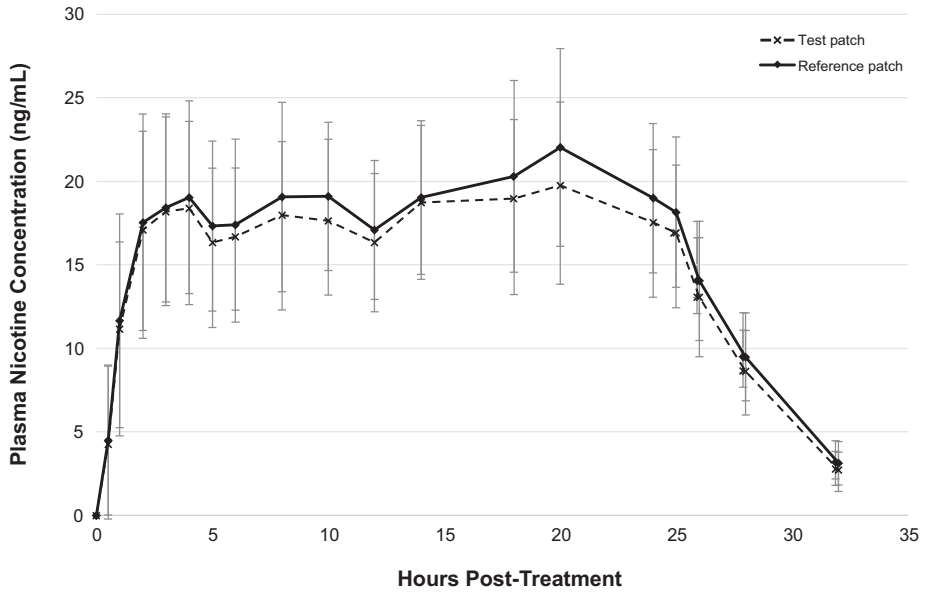

Figure 1. Baseline-adjusted mean plasma nicotine concentration follows a similar trend over time after the application of both the test and reference patches (per-protocol population; n = 38 for each treatment). Arithmetic means are plotted; error bars represent standard deviation. All values below the limit of quantitation were considered to be 0. For baseline adjustment, nicotine levels at time 0 were adjusted for the apparent terminal elimination rate constant calculated for each subject and subtracted from the observed nicotine concentration at each time.

Of the 40 randomized subjects, 28 were male (70%), 35 were white (87.5%), 3 (7.5%) were African American, and 2 (5%) were American Indian or Native Alaskan. Mean age was 33.8 years (range, 19–54 years). The mean number of years smoked was 11.0, and the mean number of cigarettes smoked daily was 17.6. No medical or surgical findings or concomitant medication use precluded participation in this study for any randomized subjects.

Pharmacokinetic Results

The mean baseline-adjusted plasma nicotine concentration-versus-time curves for the test and reference patch treatments in the PP population are shown in Figure 1. Baseline (predose) plasma nicotine concentrations were nonzero in a total of 6 study subjects (15%), 4 subjects in 1 treatment period and 2 subjects in both treatment periods. All nonzero baseline measurements were <5% of C_{max}, which was considered within acceptable limits, and therefore none of these subjects were excluded from analysis.

Mean nicotine concentrations were similar in the 2 treatments at all times, indicating that both treatments have the same trend of nicotine concentration from baseline until 32 hours after application. The calculated values for the PK parameters of C_{max} and AUC_{0-t} using baseline-adjusted data are summarized in Table 2. The confidence intervals for the ratios of the geometric means for both C_{max} and AUC_{0-t} were within the limits of 0.80–1.25, demonstrating bioequivalence of the test and reference treatments. These results were not significantly altered when unadjusted nicotine concentrations were analyzed, further supporting the bioequivalence of the 2 patches.

Analysis of the PK parameter $AUC_{0-\infty}$, derived from adjusted nicotine concentrations, also supported bioequivalence of the test and reference treatments. Nonparametric analyses of the parameters of $t_{1/2}$ and T_{max} are also summarized in Table 2. No significant median differences between the test patch and reference patch were observed for any of these parameters.

Safety Evaluation

A total of 40 subjects had at least 1 patch application for the full 24 hours. In total, 37 subjects received both treatments; 1 subject only received the test patch, and 2 subjects only received the reference patch. No AEs were reported during the baseline period prior to administration of the study treatments. Overall, 31 treatment-emergent AEs were reported by 22 subjects with the test patch (57.9%), and 41 treatment-emergent AEs were reported by 26 subjects with the reference patch (66.7%). All AEs were mild in intensity and typical for NTSs, with the most frequently reported AE being application-site erythema. AEs occurring in 2 or more subjects are listed by treatment in Table 3. No SAEs occurred during the study, and no subjects withdrew from the study because of AEs. Blinded

Table 2. Pharmacokinetic Parameters Based on Baseline-Adjusted Plasma Nicotine Concentrations (PP Population)

Parameter		Test Patch (n = 38)	Reference Patch (n = 38)	Ratio of Geometric Means (Test/Reference)	90%CI
C_{max} (ng/mL)	Arithmetic mean (SD)	22.31 (4.99)	23.50 (5.92)	0.962	0.923–1.002
	Geometric mean	21.83	22.69		
AUC_{0-t} (ng·h/mL)	Arithmetic mean (SD)	494.54 (115.08)	528.43 (129.76)	0.946	0.912–0.982
	Geometric mean	483.17	510.64		
$AUC_{0-\infty}$ (ng·h/mL)	Arithmetic mean (SD)	505.13 (118.94)	541.15 (134.85)	0.945	0.910–0.980
	Geometric mean	493.51	522.48		
$t_{1/2}$	Arithmetic mean (SD)	2.60 (0.34)	2.70 (0.43)		
		Median (Min–Max)		Difference: Test−Reference	
		Test Patch (n = 38)	Reference Patch (n = 38)	Median	*P*
T_{max}	Median (min–max)	10 (0.5–24.0)	18 (2.0–24.0)	−1.9951	.0689

AUC_{0-t}, area under the plasma nicotine concentration–time curve from time 0 to the last quantifiable sample; $AUC_{0-\infty}$, area under the plasma nicotine concentration–time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximal measured plasma nicotine concentration; PP, per protocol; SD, standard deviation; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to maximum observed plasma nicotine concentration.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥2 Subjects With Any Treatment

Adverse Event	Test Patch (n = 38)	Reference Patch (n = 39)
At least 1 adverse event, n (%)	22 (57.9)	26 (66.7)
Application-site erythema, n (%)	15 (39.5)	20 (51.3)
Application-site pruritus, n (%)	5 (13.2)	7 (17.9)
Headache, n (%)	2 (5.3)	4 (10.3)
Abnormal dreams, n (%)	0	4 (10.3)

assessment of the topical effects of the nicotine patches revealed no significant differences between the test and reference patches in terms of edema (0% vs 0%), erythema (39.5% vs 48.7%), extent of erythema, papules or pustules (39.5% vs 48.7%), and itching (0% vs 2.6%).

Discussion

The results of this study demonstrate the bioequivalence of the test NTS patch made with a replacement PIB adhesive manufactured by BASF to the NTS patch made with the previous PIB adhesive manufactured by XOM, as determined by the PK parameters of C_{max} and AUC_{0-t}. The PK parameters $AUC_{0-\infty}$, T_{max}, and $t_{1/2}$ showed no statistically significant differences between the 2 patches, supporting the primary results. NTS patches made with the previous PIB adhesive from ExxonMobil were available in 21-, 14-, and 7-mg doses and had demonstrated linear nicotine elimination kinetics in a previous trial[14]; therefore, based on the bioequivalence established with the 21-mg patches in this study, bioequivalence can also be assumed for the 14- and 7-mg dose patches made with the replacement PIB adhesive from BASF compared with the 14- and 7-mg patches made with the previous PIB adhesive. Treatment-emergent AEs associated with both patches were similar, typical for NTSs and mild in intensity, and no serious SAEs were reported, indicating that the test patch has a safety profile similar to the reference patch.

Acknowledgments

Medical writing assistance was provided by Peloton Advantage and was funded by GlaxoSmithKline Consumer Healthcare. GlaxoSmithKline Consumer Healthcare provided a full review of the article.

Declaration of Conflicting Interests

Dr. Rasmussen and Ms. Halabuk Horkan report no conflicts. Dr. Kotler was employed by GlaxoSmithKline Consumer Healthcare at the time this study was conducted.

Funding

This study was sponsored by GlaxoSmithKline Consumer Healthcare.

References

1. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the*

Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
2. World Health Organization. Tobacco Fact Sheet. 2016. http://www.who.int/mediacentre/factsheets/fs339/en/. Accessed October 2, 2017.
3. Tobacco and smoking. 2016. http://www.gallup.com/poll/1717/tobacco-smoking.aspx. Accessed October 2, 2017.
4. Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol*. 2009;(192):29–60.
5. Svensson CK. Clinical pharmacokinetics of nicotine. *Clin Pharmacokinet*. 1987;12(1):30–40.
6. Zevin S, Gourlay SG, Benowitz NL. Clinical pharmacology of nicotine. *Clin Dermatol*. 1998;16(5):557–564.
7. Hukkanen J, Jacob P 3rd, Benowitz, NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev*. 2005;57(1):79–115.
8. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57–71.
9. Tutka P, Mosiewicz J, Wielosz M. Pharmacokinetics and metabolism of nicotine. *Pharmacol Rep*. 2005;57(2):143–153.
10. Pack QR, Jorenby DE, Fiore MC, et al. A comparison of the nicotine lozenge and nicotine gum: an effectiveness randomized controlled trial. *WMJ*. 2008;107(5):237–243.
11. Schnoll RA, Goelz PM, Veluz-Wilkins A, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med*. 2015;175(4):504–511.
12. Yun HY, Seo JW, Choi JE, Baek IH, Kang W, Kwon KI. Effects of smoking on the pharmacokinetics and pharmacodynamics of a nicotine patch. *Biopharm Drug Dispos*. 2008;29(9):521–528.
13. Le Houezec J. Role of nicotine pharmacokinetics in nicotine addiction and nicotine replacement therapy: a review. *Int J Tuberc Lung Dis*. 2003;7(9):811–819.
14. Gorsline J, Gupta SK, Dye D, Rolf CN. Steady-state pharmacokinetics and dose relationship of nicotine delivered from Nicoderm (Nicotine Transdermal System). *J Clin Pharmacol*. 1993;33(2):161–168.