Original Manuscript

Single-Dose Bioequivalence of Two Mini Nicotine Lozenge Formulations

Clinical Pharmacology in Drug Development
2018, 7(5) 498–505

DOI: 10.1002/cpdd.415

Scott C. Rasmussen[1], William D. Becker[2], and Gilbert M. Shanga[2]

Abstract

Diverse nicotine replacement therapy options may improve consumer usage. This study was conducted to establish the bioequivalence of a new cherry-flavored mini lozenge with that of a currently marketed mint-flavored mini lozenge. The rate (C_{max}) and extent (AUC_{0-t}) of plasma nicotine absorption were compared after administration of 2- and 4-mg doses of each lozenge in healthy adult smokers (n = 43). The bioequivalence of each respective dose was established based on the 90% confidence interval for the ratio of geometric means for both C_{max} and AUC_{0-t} lying within the range of 0.80 to 1.25. Adverse-event profiles were similar between formulations.

Keywords

tobacco use cessation products, tobacco, smoking cessation, smoking, nicotinic agonist, nicotine replacement therapy

Even after decades of research, the list of known harms caused by smoking continues to grow. Smoking damages nearly every organ of the body, causing health problems including cardiovascular disease, respiratory disease, cancer, and fertility problems in women.[1] According to the World Health Organization, smoking kills 6 million people per year, including more than 600 000 people who die as a result of secondhand smoke exposure.[2]

Smoking-related toxicity is caused by various components contained within tobacco smoke; however, it is the delivery of nicotine that leads to and sustains addiction in smokers.[3] Nicotine binds stereoselectively to nicotinic acetylcholine receptors and mediates release of dopamine in several brain areas, including the mesolimbic pathway connecting the ventral tegmental area of the midbrain to the nucleus accumbens; this pathway is involved in drug-induced reward. In addition, nicotine induces the release of several other neurotransmitters (eg, norepinephrine, acetylcholine, serotonin, glutamate, gamma-aminobutyric acid, and endorphins) that mediate various physiological responses. Regular use of nicotine leads to dependence; once dependent, reduction in or abstinence from nicotine intake causes a well-recognized withdrawal syndrome.[3] Despite findings that abstinence from smoking produces immediate and long-term health benefits,[1] the reinforcing effects of nicotine, negative consequences of nicotine withdrawal, and conditioned responses derived from smoking-associated stimuli perpetuate nicotine addiction and hamper efforts to quit in habitual smokers.[3]

The pharmacokinetics and metabolism of nicotine have been described elsewhere in detail.[3–6] In brief, nicotine intake via cigarette smoke is associated with rapid absorption through the lungs at a rate similar to that found after intravenous administration.[4–6] Nicotine undergoes rapid and extensive metabolism in the liver to cotinine.[5] This is primarily a consequence of cytochrome P450 (CYP) 2A6 enzymatic activity, but also to a lesser degree by the actions of CYP2B6 and CYP2E1.[3] With a half-life of ~16 hours, cotinine is widely used as an indicator of tobacco use.[3] Although the half-life of nicotine is ~2 hours, nicotine accumulates within the body over 6 to 9 hours of smoking and results in a constant 24-hour nicotine exposure, with average nicotine concentrations in a

[1] Celerion, Inc., Lincoln, NE, USA
[2] GlaxoSmithKline Consumer Healthcare, Warren, NJ, USA

Submitted for publication 19 April 2017; accepted 3 October 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)

typical day ranging from 20 to 40 ng/mL.[4,6] Cotinine undergoes further metabolism via CYP2A6 to trans-3′-hydroxycotinine.[3] Glucuronidation, via uridine 5′-diphospho-glucuronosyltransferase (UGT) 1A4, 1A9, and 2B10, serves as a minor pathway for nicotine and cotinine metabolism, although in those with genetic polymorphisms conferring low CYP2A6 activity, it may be a major pathway for the clearance of nicotine from the body.[3] Genetic polymorphism in CYP2A6 and UGT activity are substantial and are associated with individual variability in nicotine metabolism. For example, nicotine metabolism is faster in whites and Hispanics than in Asians and African Americans. Women metabolize nicotine faster than men; metabolism of nicotine is even further accelerated in women who take oral contraceptives containing estrogen and in those who are pregnant.[3]

Although the achievement of smoking abstinence can be a formidable task, surveys indicate that a large majority of smokers would like to quit smoking; the US Surgeon General, citing data from the 2010 National Health Interview Survey, reported that 68.9% of current US adult smokers had an interest in quitting smoking.[7] In support of those findings, a 2016 Gallup poll found that 74% of current smokers expressed a desire to quit.[8] Clinical practice guidelines recommend nicotine replacement therapy (NRT) as a first-line option for smoking cessation. These therapies deliver nicotine via various modalities, reducing the withdrawal symptoms associated with smoking cessation. Specific delivery methods available in the United States include NRT via transdermal patch, gum, lozenge, inhaler, and nasal spray, with varying pharmacokinetic properties.[9,10] However, it has been previously reported that physicians underuse NRTs as an aid to smoking cessation.[11] In addition, some smokers have negative attitudes toward NRT, including perceptions of ineffectiveness, which may translate to a general lack of use of these products.[12,13] Furthermore, many smokers dislike existing medication options because of side effects (eg, nausea or local irritation).[10,11] These issues illustrate the need for the development of additional NRT options to support attempts at quitting for those who wish to stop smoking.

Nicotine lozenges have been shown to more than double the odds of abstinence 1 year after smoking cessation.[14] One currently marketed formulation is a mint-flavored mini lozenge (GlaxoSmithKline Consumer Healthcare, Parsippany, New Jersey). This mint-flavored mini lozenge delivers the same levels of nicotine as larger lozenges but has a quicker dissolution time, which makes it more convenient to use and may thereby increase patient adherence.[10] The mini lozenges have also been shown to be more effective than conventional lozenges in reducing the urge to smoke.[15]

The development of new NRT products that provide a more pleasant experience may increase utilization by consumers. Having a greater variety of options available may also improve smokers' chances of successfully quitting by providing a greater feeling of control and investment in the process.[10] In an effort to provide additional treatment options for those who wish to stop smoking and are unsatisfied with current options, a new cherry-flavored nicotine mini lozenge has been developed.

The primary objectives of this study were to determine whether the new nicotine cherry-flavored mini lozenges (2- and 4-mg doses) were bioequivalent to the currently marketed 2- and 4-mg nicotine mint-flavored mini lozenges in terms of the rate and extent of nicotine absorption. Secondary objectives were to compare the cherry-flavored mini lozenges with the mint-flavored mini lozenges in terms of area under the plasma concentration–time curve (AUC) extrapolated to infinity ($AUC_{0-\infty}$), time to maximum absorption (T_{max}), and elimination parameters ($t_{1/2}$ and K_{el}) and to evaluate comparative safety and tolerability.

Methods

Study Subjects

Healthy subjects aged 19 to 55 years with a body mass index (BMI) of 19 to 27 kg/m^2 (inclusive) who had smoked cigarettes for the preceding 12 months and routinely smoked their first cigarette of the day within 30 minutes of awakening were eligible for this study. Subjects agreed to abstain from smoking or the use of other tobacco products during each study session. Women were required to be practicing an acceptable method of birth control, be surgically sterile, or be postmenopausal. Potential subjects were excluded if they were pregnant or breastfeeding, had a medical history that might have compromised their safety or the validity of the results, had used tobacco products other than cigarettes within 21 days of the beginning of the study, had an allergy or intolerance to any of the study materials, tested positive for hepatitis B, hepatitis C, or human immunodeficiency virus, had recently donated blood or plasma, or had a history of drug or alcohol abuse within 2 years of screening. Alcohol abuse was defined as daily consumption of more than 2 drinks (360 mL of beer, 150 mL of wine, or 40 mL of distilled spirits with 40% alcohol by volume). Urine drug screens tested for levels of alcohol, cannabinoids, amphetamines, cocaine, ecstasy, methamphetamine, and opiates; any patients testing positive were excluded. In addition, treatment with any known enzyme-altering agents (eg, barbiturates, phenothiazines, cimetidine, theophyllines) within 30 days, use of any over-the-counter medication

(including herbal supplements) within 48 hours, or prescription medication use within 14 days of the study, with the exception of hormonal contraceptives or hormone replacement therapy, was exclusionary.

Study Design

This was a single-center (Celerion, Lincoln, Nebraska), randomized, open-label, single-dose, 4-way crossover study in which otherwise healthy smokers received a single dose of each of the 4 study treatments — 2-mg nicotine mini cherry lozenge, 2-mg nicotine mini mint lozenge, 4-mg nicotine mini cherry lozenge, and 4-mg nicotine mini mint lozenge — in a randomized sequence. All study treatments were provided by GlaxoSmithKline Consumer Healthcare (Parsippany, New Jersey). The final protocol was reviewed and approved by the Celerion institutional review board (Lincoln, Nebraska), and the study was conducted according to Good Clinical Practice (International Council for Harmonisation 1996), the laws and regulations of the country in which the research was conducted, and the Declaration of Helsinki. All participants provided written informed consent prior to any study procedures.

Participants were confined to the study facility for approximately 48 hours, including a 36-hour predosing baseline phase and a 12-hour postdosing treatment phase, during which participants were required to abstain from smoking. During the study session, the investigator or designated site personnel placed a single lozenge (either mini lozenge or standard lozenge) in the subject's mouth to be dissolved. The subject was instructed to move the lozenge from one side of the mouth to the other periodically to facilitate dissolution; subjects were instructed not to chew or swallow the lozenge. The lozenge dose, initial dose time, and complete dissolution time, as confirmed by study-site personnel, were captured. Study sessions were separated by at least a 48-hour washout period. Study subjects were prohibited from consuming alcoholic beverages within 24 hours of each study session and caffeine- and xanthine-containing beverages during study sessions and were required to fast for at least 8 hours before and 1 hour after dosing. In addition, prescription and over-the-counter medications were restricted before and during each study session.

Potential study subjects first underwent a screening assessment 2 to 21 days before the first study session. Screening assessments included medical history, physical examination, electrocardiogram, and clinical laboratory tests to verify study participants were in good general health with no clinically significant abnormalities. During the initial baseline phase of each study session, study subjects underwent inclusion/exclusion criteria confirmation, concomitant medication and adverse event (AE) assessments, completion of a meal record, and laboratory testing for pregnancy, drug and alcohol use, and expired carbon monoxide (CO). During the treatment phase, subjects underwent expired CO assessments, treatment administration, serial blood collections, meal record completion, and assessments of concomitant medications and AEs. An expired CO level of $\leq$10 ppm indicated compliance with the nonsmoking restriction. Subjects with an expired CO level $>$ 10 parts per million (ppm) were to be discontinued from the study.

Pharmacokinetic Measurements and Evaluations

Blood samples were collected via indwelling cannulas or venipuncture immediately predose and 3, 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours postdose. A total of approximately 340 mL of blood was taken from each subject. Blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 3000 rpm for 15 minutes. Plasma was then drawn off and stored at -20°C within 2 hours of collection and until bioanalysis.

Plasma samples were analyzed for nicotine using a proprietary, fully validated method employing liquid chromatography coupled with tandem mass spectrometry at Celerion. In brief, an aliquot of human plasma (EDTA) containing each analyte (nicotine) and internal standard (d_3-nicotine) was extracted using a solid-phase extraction procedure. The extracted samples were analyzed using high-performance liquid chromatography (Merck KGaA, Chromolith Performance Si, 100 $\times$ 4.6 mm [2 columns in series] or Phenomenex, Onyx Monolithic Si, 100 $\times$ 4.6 mm [2 columns in series]) and a mobile phase (60:40 MeOH:90 mM $HCOONH_4$, pH 3.0 w/HCOOH) equipped with an AB SCIEX API 5000 or QTRAP 5500 mass spectrometer using an electrospray ionization source. Positive ions were monitored in multiple reaction monitoring mode. The peak area of mass-to-charge ratio (m/z) 163.2 $\rightarrow$ 130.0 of nicotine production was measured against a peak area of the m/z 166.2 $\rightarrow$ 132.0 of the internal standard. A weighted linear regression curve ($1/x^2$) was determined to best represent the concentration/detector response relationship for nicotine. The lower level of quantification of this method was 0.2 ng/mL. Nicotine concentration values that were below the limit of quantification or were negative following baseline adjustment were set to zero.

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

Safety assessments included the recording and evaluation of all AEs, either spontaneously reported by the subject at any time during the study or elicited by the investigator or investigator's designee in a standard manner. AEs were defined as any untoward medical occurrence in a subject temporally associated with administration of treatment. All AEs were assessed for severity and relatedness to the drug product. Serious AEs (SAEs) were defined as any AE that results in disability, incapacity, or death; is life threatening; requires hospitalization or prolongs existing hospitalization; or is a congenital anomaly or birth defect. Laboratory results and vital signs were evaluated at screening only; any results that were considered clinically significant by the study investigator were recorded as either an AE or SAE.

Data Analysis Methods

Enrollment of 50 subjects was planned to ensure that approximately 40 subjects would complete all 4 treatment sessions. With 40 completers, it was estimated that the power to establish bioequivalence would be >80% given true ratios ranging between 1.05 and 1.14. The intent-to-treat analysis included data from completed sessions, whereas the per-protocol analysis excluded data from sessions in which a major protocol violation occurred.

The primary pharmacokinetic (PK) parameters assessed were peak plasma nicotine concentration (C_{max}) and AUC calculated to the last point with a measurable nicotine concentration (AUC_{0-t}). Secondary PK parameters include AUC extrapolated to infinity ($AUC_{0-\infty}$), time to maximal plasma nicotine concentration (T_{max}), apparent elimination half-life ($t_{1/2}$), and apparent elimination rate constant for plasma nicotine (K_{el}). All PK parameters were calculated based on data adjusted for nicotine levels at baseline as well as unadjusted concentrations. For subjects with measurable predose nicotine levels, baseline-adjusted plasma concentrations were obtained by using the following formula: $C(t)_{adj} = C(t)_{obs} - C(0)e^{(-Kel)t}$, where t is the time point adjusted and K_{el} is the elimination rate constant for nicotine calculated from the unadjusted data. Data were excluded for periods when and subjects for whom the baseline nicotine concentration was greater than 5% of C_{max}.

A linear mixed-effects model was fitted to the log-transformed primary PK variables (AUC_{0-t}, C_{max}) as the dependent variable, with treatment and period as fixed effects and subject as a random effect. The same model was used to make 2 comparisons: 2-mg mini mint lozenge with 2-mg mini cherry lozenge and 4-mg mini mint lozenge with 4-mg mini cherry lozenge. Least-squares estimates of treatment effects were calculated, and the 90% confidence interval (CI) for the treatment difference was computed. The treatment difference and its CI were exponentiated to obtain the ratio of the geometric means between the products and its CI. Bioequivalence between 2 formulations was determined if the 90%CI for the ratio of the means for each of the PK parameters (AUC_{0-t} and C_{max}) fell within the interval of 0.80 to 1.25. The secondary parameter $AUC_{0-\infty}$ was analyzed using the same model. The secondary PK parameters K_{el}, $t_{1/2}$, and T_{max} were analyzed using a nonparametric signed rank test on the within-subject differences to compare treatments.

AEs, including severity and relationship to study treatments, were coded using the Medical Dictionary for Regulatory Activities version 14.0 and summarized by treatment. AEs that occurred during the washout period between treatments were attributed to the previously administered treatment.

Table 1. Subject Demographics

Sex, n (%)	
Male	33 (66.0)
Female	17 (34.0)
Race, n (%)	
White	43 (89.6)
Black or African American	3 (6.3)
American Indian or Alaska Native	2 (4.2)
Missing	2
Age, mean (SD), years	30.3 (9.6)
Body mass index, mean (SD), kg/m^2	23.4 (2.4)
Cigarettes smoked/day, mean (SD)	16.3 (7.7)
Time to first cigarette after awakening, mean (SD), minutes	15.2 (9.9)

Study Population

A total of 50 eligible individuals (33 men and 17 women) were enrolled to receive a randomly assigned treatment sequence, and 43 individuals (29 men and 14 women) completed all 4 study treatments. The demographic and safety analyses included all study participants. The majority of subjects were white and about 30 years old and had a BMI corresponding to a normal weight (Table 1).

Study participants smoked an average of 16.3 cigarettes per day and smoked their first cigarette an average of 15.7 minutes after awakening. There were no significant findings in any subject noted regarding physical examination, vital signs, laboratory tests, or medical history. All expired CO levels at predose and immediately after the last PK sample, as well as at random intervals, were ≤10 ppm, demonstrating smoking abstinence during testing, except for 6 subjects in period 2 with erroneous values between 7 and 11 ppm because of a malfunction that interfered with the calibration of the machine to zero between measurements. The primary investigator confirmed

Table 2. Pharmacokinetic Parameters in Subjects Taking Mini Nicotine Lozenges

	2-mg Mini Lozenges			
	Arithmetic Mean (SD)		Ratio: Cherry/Mint[a]	
Parameter	Cherry	Mint	Estimate (%)	90%CI
C_{max},[b] ng/mL	5.67 (1.5) (n = 47)	6.35 (1.4) (n = 45)	89.3	85.2–93.7
AUC_{0-t},[b] ng·h/mL	18.84 (7.1) (n = 47)	20.71 (7.4) (n = 45)	90.8	87.7–94.0
$AUC_{0-\infty}$,[b] ng·h/mL	21.03 (8.1) (n = 44)	22.66 (8.5) (n = 44)	91.6	88.2–95.0
$t_{1/2}$,[c] h	3.15 (1.0) (n = 39)	3.25 (1.1) (n = 39)		
	Median (Range)		Median Difference: Cherry-Mint	*P*[d]
T_{max},[c,e] h	0.83 (0.3–2.0) (n = 40)	0.75 (0.3–2.0) (n = 40)	0.0006	.163
	4-mg Mini Lozenges			
	Arithmetic Mean (SD)		Ratio: Cherry/Mint[a]	
	Cherry	Mint	Estimate (%)	90%CI
C_{max},[b] ng/mL	9.37 (2.6) (n = 45)	9.72 (2.7) (n = 47)	97.1	92.7–101.8
AUC_{0-t},[b] ng·h/mL	34.71 (14.5) (n = 45)	33.68 (12.2) (n = 47)	101.7	98.3–105.3
$AUC_{0-\infty}$,[b] ng·h/mL	37.48 (16.9) (n = 45)	36.08 (14.0) (n = 47)	102.1	98.5–105.8
$t_{1/2}$,[c] h	3.15 (0.8) (n = 42)	3.06 (0.7) (n = 44)		
	Median (Range)		Median Difference: Cherry–Mint	*P*[d]
T_{max},[c,e] h	0.83 (0.3–2.0) (n = 42)	0.83 (0.4–3.0) (n = 44)	0.0003	.972

PK, pharmacokinetic; SD, standard deviation; CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{0-t}, area under the plasma concentration–time curve from time zero to time of last measurable concentration; $AUC_{0-\infty}$, AUC extrapolated to infinity; T_{max}, time to maximal plasma concentration; $t_{1/2}$, apparent elimination half-life.

[a]Ratio of geometric means.

[b]Adjusted nicotine concentration.

[c]Unadjusted nicotine concentration; excludes profiles where baseline concentration was more than 5% of C_{max}.

[d]*P* value for testing the median of difference = 0 at 5% significance level.

[e]T_{max} presented as median; all others as means.

these subjects had not smoked (all personal property had been confiscated), and data for these 6 subjects were included in the analysis.

Results

Study Participant Disposition

Seven subjects discontinued participation in the study. One subject with an SAE (appendicitis) withdrew during treatment with the 4-mg mint lozenge. Two other subjects, each with mild AEs, withdrew after treatment, one after taking the 2-mg cherry lozenge and one after taking the 4-mg cherry lozenge. Four subjects withdrew consent; 2 did so after the first period (2 after taking the 2-mg mint lozenge and 1 after taking the 2-mg cherry lozenge). One additional subject withdrew consent after taking the 4-mg mint lozenge. At least 1 data period from 9 subjects was excluded from the analysis of the unadjusted PK parameters because baseline nicotine concentrations were greater than 5% of C_{max}.

Pharmacokinetic Results

Primary and (select) secondary PK parameters are summarized in Table 2 for the 2-mg mini lozenge comparisons and 4-mg mini lozenge comparisons. In the primary PK parameter comparison of the 2-mg mini lozenge formulations, the ratio of the geometric means (cherry flavored/mint flavored) and 90%CIs for C_{max} (89.3; 85.2–93.7) and AUC_{0-t} (90.8; 87.7–94.0) each fell within the 0.80 to 1.25 limits indicative of formulation bioequivalence. The 4-mg mini lozenge formulations were also found to be bioequivalent (C_{max}, 97.1; 90%CI, 92.7–101.8; and AUC_{0-t}, 101.7; 90%CI, 98.3–105.3). The mean baseline-adjusted plasma nicotine concentration-versus-time profile for each formulation is shown in Figure 1. When the data were

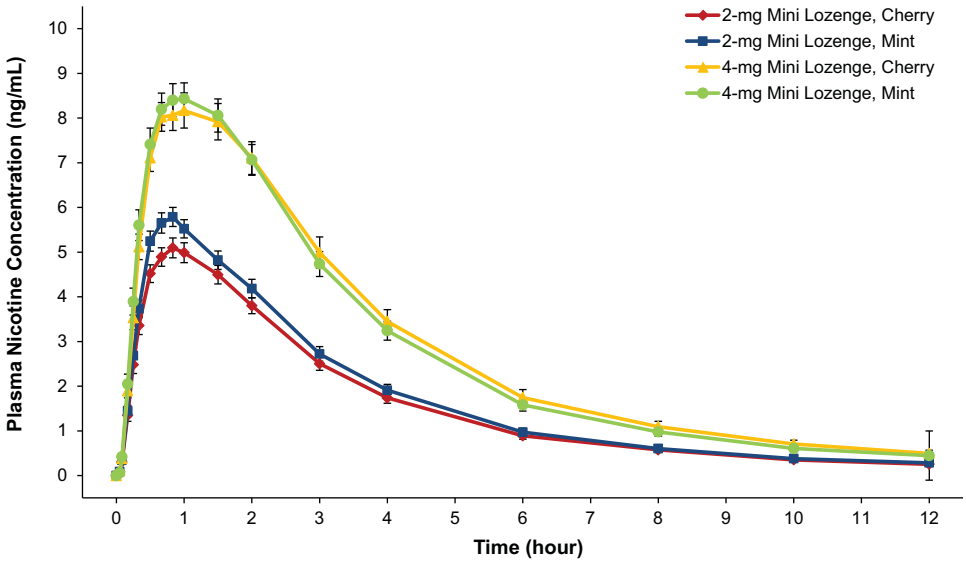

Figure 1. Plasma nicotine concentrations, presented as arithmetic means, following treatment with either flavor of the 2- and 4-mg mini nicotine lozenges. Plasma concentrations that were below the limit of quantification were set as zero for calculation of means. Error bars represent standard error of the mean.

analyzed without adjusting for baseline plasma nicotine levels, values for C_{max} and AUC_{0-t} were very similar to the baseline-adjusted results shown in Table 1, further supporting bioequivalence.

Evaluation of the secondary PK parameter $AUC_{0-\infty}$ revealed that the geometric mean ratio (90%CI) for the 2-mg cherry-flavored mini lozenge versus the 2-mg mint-flavored mini lozenge was 91.6 (88.2–95.0); the geometric mean ratio (90%CI) for the 4-mg cherry-flavored mini lozenge versus the 4-mg mint-flavored mini lozenge was 102.1 (98.5–105.8). Both comparisons added additional support to bioequivalence findings for the primary PK parameters. Nonparametric analysis of T_{max}, $t_{1/2}$, and K_{el} showed that median differences between the 2-mg cherry-flavored and 2-mg mint-flavored mini lozenges and between the 4-mg cherry-flavored and 4-mg mint-flavored mini lozenges were not statistically different from zero (Table 2).

Finally, the dissolution times of the mini lozenges were similar for both the 2-mg (cherry flavored, 22.3 minutes; mint flavored, 23.2 minutes) and 4-mg (cherry flavored, 24.6 minutes; mint flavored, 22.2 minutes) formulations.

Safety Evaluation

Safety profiles were similar for the respective dose strengths of the cherry-flavored mini lozenge and the mint-flavored mini lozenge. AEs occurred in about 8% more subjects taking the 4-mg mini lozenges than in those taking the 2-mg mini lozenges (Table 3).

Overall, 75 AEs were reported by 28 subjects; 49 AEs in 20 subjects were considered treatment related. AEs were consistent with what has been observed with the use of NRT products,[14] most commonly dyspepsia, headache, throat irritation, and nausea. All but 1 AE were mild in intensity. Three subjects discontinued the study because of AEs. One SAE (appendicitis) occurred after receiving the 4-mg mint-flavored mini lozenge and resulted in study discontinuation; the event was not considered treatment related. Two other participants discontinued the study because of AEs. One had several mild AEs of dyspepsia, euphoria, and swollen lymph nodes that were considered treatment related, and 1 subject had mild chills and body aches that were not considered treatment related. No pregnancies or deaths occurred during this study.

Discussion

NRT is an effective first-line treatment to aid in smoking cessation. Unfortunately, only a small subset of smokers uses these products. The lack of NRT recommendations received from health care professionals and patient factors such as perceptions of NRT ineffectiveness or poor tolerability negatively impact the fight against smoking and its related comorbidities. As a result, many new NRT options have been introduced through the years, enabling patients to personalize their smoking cessation treatment.

The current study demonstrated the bioequivalence between a newly formulated cherry-flavored mini lozenge with a currently marketed mint-flavored mini lozenge at both the 2- and 4-mg doses. Bioequivalence was based on the rate (C_{max}) and extent (AUC_{0-t})

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

AE Preferred Term	2-mg Cherry (n = 47)	2-mg Mint (n = 46)	4-mg Cherry (n = 45)	4-mg Mint (n = 47)
Number of subjects with at least 1 AE (%)	10 (21.3)	11 (23.9)	13 (28.9)	15 (31.9)
Dyspepsia	2 (4.3)	0	3 (6.7)	4 (8.5)
Nausea	1 (2.1)	1 (2.2)	1 (2.2)	4 (8.5)
Headache	1 (2.1)	2 (4.3)	4 (8.9)	1 (2.1)
Dizziness	0	3 (6.5)	1 (2.2)	1 (2.1)
Throat irritation	2 (4.3)	2 (4.3)	3 (6.7)	1 (2.1)
Hiccups	0	1 (2.2)	1 (2.2)	4 (8.5)
Fatigue	0	2 (4.3)	0	0
Euphoric mood	1 (2.1)	1 (2.2)	1 (2.2)	2 (4.3)

AE, adverse event.

of nicotine absorption and supported by findings from the secondary PK parameters. It is unclear why the between-treatment ratios were lower for the 2-mg lozenge comparisons than for the 4-mg lozenge comparisons. Mean dissolution times for mini cherry lozenges were similar to those of mini mint lozenges for both the 2- and 4-mg formulations. Dissolution times for 2- and 4-mg lozenges were similar.

Importantly, both the cherry-flavored mini lozenge and the mint-flavored mini lozenge demonstrated similar tolerability profiles at each of the doses tested. The reported AEs were consistent with those observed in past studies of nicotine lozenges and nicotine gum,[9,15,16] and all except 1 were mild. A single SAE of appendicitis was not considered related to treatment.

Limitations of this study include its crossover design, which could possibly lead to carryover effects from one session to the other. However, a 48-hour washout period between sessions was provided to avoid this possibility. Given the enrollment of smokers who were generally healthy, the results observed here may not be generalizable to individuals with moderate to severe comorbid illness or those taking concomitant medications. Last, the study design precluded assessment of treatment efficacy for either the test or reference nicotine lozenge formulations. However, providing additional options to the range of NRT products currently available, including those with different flavors, is a strategy that may increase the use of these products among smokers who desire to quit and may increase adherence, thus improving the likelihood of success. As such, this newly developed cherry-flavored mini nicotine lozenge provides another NRT option that is bioequivalent to the currently available mint-flavored mini nicotine lozenge.

Funding

This study was sponsored by GlaxoSmithKline Consumer Healthcare, Parsippany, New Jersey. Medical writing assistance was provided by Peloton Advantage, LLC, Parsippany, New Jersey, and was funded by GlaxoSmithKline Consumer Healthcare.

Declaration of Conflicting Interests

At the time that the study was conducted, Scott C. Rasmussen was an employee of Celerion, Lincoln, Nebraska, which was contracted by GlaxoSmithKline Consumer Healthcare to aid in the conduct of this study, and William D. Becker (now an independent consultant) was an employee of GlaxoSmithKline Consumer Healthcare, Warren, New Jersey. Gilbert M. Shanga is an employee of GlaxoSmithKline Consumer Healthcare, Warren, New Jersey.

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 July 19, 2017.
3. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57–71.
4. Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol*. 2009;(192):29–60.
5. Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev*. 2005;57(1):79–115.
6. Tutka P, Mosiewicz J, Wielosz M. Pharmacokinetics and metabolism of nicotine. *Pharmacol Rep*. 2005;57(2):143–153.

7. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: 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; 2014.
8. Tobacco and smoking. 2016. http://www.gallup.com/poll/1717/tobacco-smoking.aspx. Accessed July 19, 2017.
9. 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.
10. Shahab L, Brose LS, West R. Novel delivery systems for nicotine replacement therapy as an aid to smoking cessation and for harm reduction: rationale, and evidence for advantages over existing systems. *CNS Drugs*. 2013;27(12):1007–1019.
11. Frazier LM, Molgaard CA, Fredrickson DD, Early JL, Schukman JS, Dismuke SE. Barriers to smoking cessation initiatives for Medicaid clients in managed care. *Subst Use Misuse*. 2001;36(13):1875–1899.
12. Etter JF, Perneger TV. Attitudes toward nicotine replacement therapy in smokers and ex-smokers in the general public. *Clin Pharmacol Ther*. 2001;69(3):175–183.
13. Hammond D, McDonald PW, Fong GT, Borland R. Do smokers know how to quit? Knowledge and perceived effectiveness of cessation assistance as predictors of cessation behaviour. *Addiction*. 2004;99(8):1042–1048.
14. Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med*. 2002;162(11):1267–1276.
15. Shahab L, McEwen A, West R. Acceptability and effectiveness for withdrawal symptom relief of a novel oral nicotine delivery device: a randomised crossover trial. *Psychopharmacology (Berl)*. 2011;216(2):187–196.
16. Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tob Res*. 2003;5(5):635–644.