



AUTHORS: Elaine K. Round, Leanne C. Lee, Sheri A. Bowman, Kelly M. Harger, Tracy M. Hefner, Angela M. Slater, and Mitchell F. Stiles

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ASSESSMENT OF SERUM NICOTINE EXPOSURE FROM MODERN SMOKE-FREE TOBACCO PRODUCTS

OBJECTIVE

The primary objective of this study was to determine serum nicotine uptake over a three hour period following initiation of product use to clarify nicotine uptake results from use of modern smoke-free tobacco (MSFT) products observed in previous RJRT studies. Secondary objectives of this study were 1) to assess tobacco abstinence symptoms prior to and at designated intervals following initiation of MSFT product use, and 2) to assess carboxyhemoglobin levels prior to and for one hour following initiation of product use after overnight tobacco abstinence.

SUMMARY

Fifteen subjects completed a randomized, crossover, open-label study of Camel Orbs, Camel Strips, Camel Sticks, Camel Snus, and subjects' usual brand (UB) cigarettes. Subjects consumed a single unit of one product at each of five test visits after a 12-hour nicotine abstinence. Serum nicotine uptake and tobacco abstinence symptoms were assessed for three hours, and carboxyhemoglobin levels for one hour, following the start of product use.

Serum nicotine uptake, measured as the area under the concentration-versus-time curve for three hours (AUC_{0-180}), was highest for UB cigarette. Unadjusted nicotine uptake calculations following use of one snus pouch, ½ Stick, one Orb, and one Strip averaged 81%, 49%, 46%, and 25% of the UB value, respectively. After baseline correction, nicotine uptake averaged 78%, 28%, 28%, and 7% of UB, respectively. Smoking one UB cigarette resulted in the highest baseline-adjusted mean maximum concentration (C_{max}), 19.9 ng/mL, followed by one Camel Snus pouch (5.0 ng/mL), one Orb (2.3 ng/mL), ½ Stick (2.0 ng/mL), and one Strip (0.7 ng/mL).

Mean time to maximum concentration (T_{max}) was shortest for UB cigarette at 6.6 minutes, followed by one Camel Snus pouch (22.7 min), one Orb (35.3 min), one Strip (41.0 min), and ½ Stick (60.0 min). Average duration of use for a Strip was the shortest at 4.5 minutes, followed by UB cigarette (5.8 min), one Orb (12.2 min), and ½ Stick (18.8 min). Camel Snus was used for the longest period of time, an average of 20.2 minutes.

Tobacco abstinence symptoms were assessed by questionnaire responses once before and nine times after in-lab product administration. Ratings for urge to smoke decreased significantly after use of all products, but the suppression was greatest and remained statistically significant for the longest period of time after smoking UB. For the MSFT products, use of snus decreased mean urge to smoke ratings by the greatest magnitude and for the longest period of time, followed by ½ Stick, one Orb, and one Strip.

Statistically significant increases in carboxyhemoglobin level (% COHb) were seen only after smoking UB cigarette. Percent COHb either did not change with statistical significance or decreased from baseline levels after use of all MSFT products.

In this study, a direct measure of serum nicotine uptake could be determined from a single MSFT product because background nicotine levels were low following a 12-hour nicotine abstinence period. In contrast, three previous RJRT studies indirectly measured nicotine uptake due to high background levels of serum nicotine that resulted from a short abstinence period. The indirect nicotine uptake measurement was achieved by estimating and subtracting the remaining baseline nicotine at each time point over the study period before calculating AUC. Comparison of the previous results to current study results revealed an overestimation of serum nicotine uptake from one Strip and a portion of one Stick when the subtraction method performed in previous studies was used. That method relied on a serum nicotine half-life calculated from the initial, rapid serum nicotine decrease that occurs within 30 minutes of smoking. Nicotine uptake calculated in the RJRT Camel Snus study statistically matched the results from the current study. The correction applied to the Snus study results relied on a half-life calculated from the 40-90 minute time points, which occurred after the rapid serum nicotine decline within 30 minutes after the start of smoking. Both corrections resulted in greater variability than the direct measurement employed by the design of the current study. The design of the current study is recommended for future studies that evaluate nicotine uptake and tobacco abstinence symptoms after use of a smoke free product.

STATUS

The in-clinic phase of this study was conducted between September 23, 2009 and November 19, 2009. This study and report are complete.

KEYWORDS

Camel Snus; carbon monoxide; carboxyhemoglobin; COHb; dissolvable tobacco; expired CO; MPSS; modern smoke-free tobacco; Mood and Physical Symptoms Scale; MSFT; Orbs; serum cotinine; serum nicotine; SAU; snus after use; Sticks; Strips; tobacco abstinence; UB; uptake; usual brand; yield in use; YIU

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Authors:

EC Round 25 OCT 2011
 Elaine K. Round, Ph. D.
 Senior Staff Scientist
 Date

Leanne C. Lee 25-OCT-2011
 Leanne C. Lee, Ph. D.
 Senior Scientist
 Date

Sheri A. Bowman 25 Oct 2011
 Sheri A. Bowman
 Senior Scientist
 Date

Kelly M. Harger 25-Oct-2011
 Kelly M. Harger
 Senior Scientist
 Date

Tracy M. Hefner 25-Oct-2011
 Tracy M. Hefner
 Senior Technician
 Date

Angela M. Slater 25 Oct 2011
 Angela M. Slater
 Scientist IV
 Date

Mitchell F. Stiles 10/25/2011
 Mitchell F. Stiles, M. B. A.
 Senior Manager
 Date

Reviewed by:

Michael F. Borgerding 10/25/11
 Michael F. Borgerding, Ph. D.
 Senior Director, Clinical Studies
 Date

INTRODUCTION

The tobacco control community unanimously supports advising current smokers to quit smoking and never smokers not to start. Some public health officials support the use of smokeless tobacco products (STPs) for smokers who cannot or are unwilling to quit smoking ([Stratton et al., 2001](#)). STPs provide an alternative that eliminates exposure to certain combustion toxicants in cigarette smoke, such as carbon monoxide (CO). Additionally, some newer STPs contain lower levels of tobacco-specific nitrosamines (TSNAs) compared to cigarettes and more traditional STPs. In a 2007 study by Hatsukami et al., the dissolvable tobacco pellet Ariva® contained the lowest level of TSNAs of the tobacco products tested.

Some scientists have suggested that STPs must suppress smoking abstinence symptoms to be a successful alternative to cigarettes ([Cobb et al., 2009](#)). Without adequate suppression, smokers may not continue to use reduced toxicant products and consequently may resume exclusive or near-exclusive smoking. Smoking abstinence symptoms may include, but are not limited to, restlessness, irritability, anxiety, impaired concentration, depression, increased appetite, and urge to smoke ([Benowitz, 1996](#)). Several validated questionnaires exist to assess tobacco consumers' perceptions of these symptoms after a period of tobacco abstinence ([Hughes and Hatsukami, 1986](#); [Welsch et al., 1999](#); [Schiffman et al., 2000](#); [West and Hajek, 2004](#); [Etter, 2005](#)).

R. J. Reynolds Tobacco Company (RJRT) has developed several new modern smoke-free tobacco (MSFT) products, including Camel Dissolvables, which are currently sold in two lead consumer markets, and Camel Snus, currently in national distribution. Camel Dissolvables, which include Camel Orbs, Sticks, and Strips are tobacco products made primarily of milled tobacco that are designed to be completely consumed in the mouth without the need to spit. Camel Snus is a pouched, moist snuff product composed of pasteurized tobacco with low sodium and moisture contents. Similar to Camel Dissolvables, spitting is not required while using snus, allowing MSFT products to be used discreetly instead of smoking.

Previous RJRT studies examined the use of MSFT products by subjects throughout a three-week product transition from exclusive, *ad libitum* use of usual brand (UB) cigarettes to dual use of one MSFT product concurrent with a 75-100% reduction goal in cigarette consumption. Separate studies were conducted with each MSFT product. Those studies evaluated several aspects of the tobacco product transition, including product use, biomarkers of tobacco exposure in blood and urine, and subjective responses to sensory questionnaires. The studies involving Camel Strips and Camel Sticks included in-lab product use with the collection of timed blood samples just prior to and for 60 minutes following initiation of product use. The study in which subjects used Camel Snus extended the collection of blood samples to 90 minutes following the initiation of product use. In all three studies, nicotine concentrations were measured in serum from the blood samples to understand the timing and level of nicotine uptake from this new class of products. However, the tobacco abstinence period required of subjects was only 30 minutes, which resulted in high background serum nicotine levels.

Because of the significant incoming serum nicotine levels and the relatively small amount of nicotine uptake that occurred from one Strip or a portion of one Stick, results showed a steady decline in serum nicotine levels for 60 minutes following use of those products. Although the same 30-minute pre-visit tobacco abstinence was required in the Camel Snus study, serum nicotine levels increased slightly after

in-lab snus use, because nicotine uptake from snus was greater than uptake from a Strip or Stick. However, incoming nicotine levels still impacted the calculated level of serum nicotine uptake.

In an attempt to estimate the serum nicotine uptake from use of a single MSFT product, the amount of baseline nicotine that remained at each time point was estimated and subtracted before calculating nicotine uptake parameters. This was accomplished by first determining the nicotine half-life for each sample and using a derivation of the formula for exponential decay to estimate the amount of nicotine remaining at each time point. The calculated concentrations of remaining initial nicotine at each time point were subtracted from the observed concentrations, which resulted in baseline-adjusted concentrations that theoretically corresponded to the nicotine absorbed specifically from MSFT product use. These corrected concentrations did indicate a serum nicotine increase after use of each MSFT product; however, the validity of the half-life estimation on which the corrections were based was unknown.

The primary objective of the current study was to determine serum nicotine uptake over a three-hour period following initiation of product use to clarify the accuracy of the serum nicotine corrections performed on the data collected in the three previous RJRT studies. To remove the large background effect observed in previous studies, subjects were required to abstain from nicotine use for at least 12 hours before each of five test visits in the current study. During test visits, subjects were administered one of four MSFT products or one UB cigarette and provided blood samples just prior to and for three hours after the start of product use. Unadjusted and baseline-corrected results were compared to the subtraction modeling performed in previous studies to understand its utility to estimate the nicotine uptake from a single product when large background levels from previous product use are present. Secondary objectives of this study were to evaluate any changes in tobacco abstinence symptoms for three hours and in carboxyhemoglobin levels for one hour following MSFT or UB use.

METHODS

Subjects. The RJRT R&D Human Research Review Committee (HRRC) approved this study on August 30, 2009 after a review of the experimental protocol (HRRC proposal #0906). Bellomy Research Inc. of Winston-Salem recruited eligible smokers from the regional community. Interested recruits who passed telephone screening were scheduled for a Screening Visit. At the Screening Visit, subjects were given additional information about the study products and study requirements. Subjects provided written informed consent for study participation before any study procedures were performed.

Eligible subjects were required to be 21–55 years of age (inclusive) and reported smoking 10-30 cigarettes per day of a UB cigarette with Cambridge Filter Method (CFM) ‘tar’ levels of 8.0-14.0 mg/cigarette when machine-smoked according to the following regimen: 35 mL puffs, two seconds in duration; one puff per minute¹. Subjects were also required to be in generally good health with no active

¹ At the time this study was executed, this ‘tar’ range of cigarette was considered to be Full Flavor Low Tar (FFLT) and referred to as such during the study. The term FFLT has since been banned by the Family Smoking Prevention and Tobacco Control Act of 2009. Cambridge filter method (CFM) has been previously referred to as the FTC method (“FTC Rescinds Guidance from 1966 on Statements Concerning Tar and Nicotine Yields,” FTC, <http://www.ftc.gov/opa/2008/11/cigarettetesting.shtm>, accessed 2/26/09). Prior to its rescission in 2008 (*ibid.*), the method

oral lesions and no history of major uncontrolled health conditions. In addition, subjects were required to have an afternoon expired carbon monoxide (ECO) level of ≥ 15 ppm as an indication of smoke inhalation and hemoglobin measurements of ≥ 12.5 g/dl for blood collection requirements. Subjects who reported delaying a decision to quit smoking were not included in the study. A Medical Advisor determined eligibility of subjects and monitored adverse events throughout the study. Medical advisor services were provided by Clinical Trials of America, Inc., Winston-Salem, NC.

Subjects were required to have some prior experience using smoke-free tobacco products but were excluded if they were regular consumers. Of the 15 subjects enrolled in the study, 13 had participated in one previous RJRT study that involved short-term migration to dual use of Orbs, Strips, Sticks, or Snus. The remaining two subjects did not have experience with MSFT products, but did report previous smokeless tobacco use. No subjects reported current routine use of any smokeless tobacco product at the time of the Screening Visit.

Following the Screening Visit but before enrollment, 30 subjects completed study procedures in preparation for Test Visit 1 in order to enroll 15 subjects at Test Visit 1. Subjects recorded the number of cigarettes smoked each day the week prior to Test Visit 1 and stopped smoking at least 12 hours before they were to report to the testing facility for that test visit.

To be enrolled, subjects were initially required to have an ECO measurement of ≤ 10 ppm at check-in of Test Visit 1. However, with approval of the Medical Advisor and after additional review of internal data, four subjects were enrolled with ECO measurements > 10 ppm. One subject who reported a 12-hour smoking abstinence was enrolled with an ECO measurement of 13 ppm and three subjects who reported a 12-hour smoking abstinence were enrolled with an ECO measurement of 11 ppm. These subjects were counseled to stop smoking earlier in the day before subsequent test visits. Additional RJRT data suggested 12 ppm would be a reasonable cutoff to confirm a 12-hour smoking abstinence, and with approval of the Medical Advisor, the ECO criterion for completing subsequent test visits was raised to 12 ppm or less (Brown et al., in preparation). This change in criterion was reported to and accepted by the chairman of the HRRC.

Procedures. Subjects were instructed to stop smoking at least 12 hours before each test visit, scheduled at either 8:00 or 8:30 a.m. Completion of each test visit was dependent on the corresponding ECO measurement at check-in. If a subject successfully fulfilled the ECO requirement, the first of ten Mood and Physical Symptoms Scales (MPSS) was completed. Next, the IV catheter was placed, and timed blood draws started with the -2 minute sample collection. Immediately following the 0-minute sample collection, study product was administered and duration of product use was timed. Blood was collected and questionnaires were administered at designated times for three hours following the start of product use. (For details, see Methods sections *Timed Blood Collections and Sample Processing* and *Mood and Physical Symptoms Scale*.)

All subjects provided and smoked one UB cigarette at Test Visit 1. Placing UB first in the order of product testing allowed for MSFT product use (Test Visits 2, 3, 4, and 5) to occur in a smoke-free environment for all subjects, thereby reducing the confounding effects of environmental tobacco smoke

was prescribed by the FTC as the standardized method for reporting cigarette “tar” and nicotine values (Fed. Reg. 32 (147): 11178 (1967)).

on the “Urge to Smoke” rating of the MPSS. In addition, daily MSFT product use did not occur until after randomization.

At the conclusion of Test Visit 1, subjects were randomized to one of five different MSFT product presentation orders. They were given six units of one MSFT product for use at home during the upcoming six days, and used the same product during the next test visit. Subjects also recorded daily cigarette and MSFT consumption during the week on log sheets that were returned at the following test visit.

Once enrolled, if a subject’s ECO level was >12 ppm at check-in for any subsequent test visit, the subject did not complete test visit procedures that day and was given one opportunity to make up the test visit. If any subject registered >12 ppm at a second test visit, the subject was dismissed from the study.

Study Products. The products tested in this study included Camel Snus (Frost and Mellow), Camel Orbs (Fresh and Mellow), Camel Strips (Fresh), and Camel Sticks (Mellow). The dissolvable products were available in lead markets, and Camel Snus was in national distribution at the time the clinical phase of the study was conducted.

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MSFT Product Use. At the end of the Screening Visit, subjects were given a trial pack containing one unit of each MSFT product. If two varieties of a product were available, one unit of each variety was included in the trial pack. Subjects used the products during the week before the first test visit to provide familiarity with all test products.

At the end of Test Visits 1-4, subjects received a six-unit supply of the product to which they were randomized for use during their next test visit. Subjects also received instructions for use and were asked to use one unit per day according to instructions to become accustomed to each product prior to in-lab use. Subjects were instructed not to use any MSFT product the day before each test visit. During Test Visits 2-5, subjects used one unit of the MSFT product they tested throughout the previous week. In the case of Camel Snus and Camel Orbs, subjects were asked to choose one variety to take home with them and were given the same variety for in-lab use during the subsequent test visit. Time of in-lab use was measured for all products.

MSFT Product Use Instructions. Instructions for in-lab use were given for each product. Subjects were not permitted to eat or drink until the product completely dissolved or had been removed in the case of snus. Subjects were also asked not to spit during or after use of each product during the test visit.

Camel Orbs

Subjects were asked to use one Orb to completion by placing the Orb between their cheek and gum and occasionally moving to a different location in the mouth during use.

Camel Strips

Subjects were asked to use one Strip to completion by placing the Strip on the top of the tongue/roof of mouth or by folding and placing between the lip and gum.

Camel Sticks

Subjects were provided with a ½ Stick and were asked to use it to completion by placing the Stick portion between their cheek and gum and occasionally moving to a different location in the mouth during use.

Camel Snus

Subjects were asked to place one pouch between either upper or lower lip and gum and to leave in place for a minimum of 15 and a maximum of 30 minutes. Occasional movement of the pouch was suggested, but not required.

Timed Blood Collections and Sample Processing. Venous access was started and maintained at each visit by the insertion of an indwelling catheter into the antecubital region of the arm. The catheter remained in place for approximately 180 minutes. Heparin solution (approximately 0.1cc) was injected into the access port between blood draws to prevent clot formation. Prior to each blood collection, approximately 1.0 mL of blood was drawn and discarded to flush the heparin from the catheter port. Blood (~3 mL) was drawn into individual gold-topped serum separator tubes to obtain serum for nicotine and cotinine analyses at -2, 0, 3, 5, 7.5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 minutes with respect to the start of product use (time 0 was designated as the start of product use). Phlebotomy services were provided by Clinical Trials of America, Inc., Winston-Salem, NC. Blood samples were allowed to clot at room temperature for at least 30 minutes. Tubes containing clotted blood were centrifuged the same day at 3000 rpm for 20 minutes at ~8°C. Serum was aliquoted into cryovials (~750 µL each) and stored at approximately -70°C or below. Samples were shipped frozen to Celerion (Lincoln, NE) for cotinine and low-level nicotine measurements. Concentrations were determined in serum using high performance liquid chromatography with mass spectrophotometric detection.

At each visit, additional whole blood samples (~3 mL each) were drawn at -2, 30, and 60 minutes with respect to the start of product use for measurement of %COHb. Samples were drawn into tubes containing EDTA to prevent clotting. See *Carboxyhemoglobin (COHb) Saturation* for additional details.

Mood and Physical Symptoms Scale. The Mood and Physical Symptoms Scale (MPSS) is a seven-question instrument validated for the assessment of tobacco abstinence symptoms - see [Appendix 1](#) ([West et al., 2006](#)). The questionnaire asks subjects to rate six symptoms (depression, anxiety, irritability, restlessness, hunger, and poor concentration) on a scale of 1-5 and urge to smoke on a scale of 0-5. The questionnaire was administered once at the Screening Visit, and ten times during each test visit. Subjects completed the MPSS just prior to product use, and at 5, 15, 30, 45, 60, 90, 120, 150, and 180 minutes after the start of product use.

Expired Carbon Monoxide (ECO). Subjects provided breath samples for determination of expired carbon monoxide concentrations once at the Screening Visit and at check-in of each test visit. For proper sample measurement, subjects were asked to inhale deeply, hold their breath for 15 seconds, then exhale slowly and completely through a disposable cardboard mouth tube attached to a Bedfont Micro 4 Smokerlyzer unit. This instrument utilizes an electrochemical sensor to measure CO levels.

Carboxyhemoglobin (COHb) Saturation. Whole blood samples were collected in tubes containing EDTA and were measured for carboxyhemoglobin saturation (%COHb), defined as the percentage of total hemoglobin to which CO is bound. Samples were analyzed onsite by study staff, generally within 15 minutes of collection. Carboxyhemoglobin saturation was measured spectrophotometrically using Instrumentation Laboratories IL-682 CO-oximeters.

Yield-In-Use (YIU) Analysis. The used filter from the cigarette smoked at Test Visit 1 was collected from each subject to determine the maximum mouth-level exposure to nicotine. Butts were stored at -20°C until processing. An approximately 10-mm piece was cut from the mouth end of each butt and frozen at -70°C or below. Samples were shipped ambient to Labstat International (Kitchener, ON, Canada) for extraction with methanol and measurement of nicotine by gas chromatography (method described in [St. Charles et al., 2010](#)). Yield-in-use was determined by correlating the amount of nicotine

extracted and measured from the subject's filter tip to a calibration curve of Cambridge filter pad nicotine vs. filter tip nicotine over a range of machine smoking regimens for each subject's UB cigarette.

Snus-After-Use (SAU) Analysis. The snus pouch used during the relevant test visit was collected from each subject, placed in an amber glass jar, and frozen at -70°C or below. Samples were shipped frozen to Labstat International (Kitchener, ON, Canada) for extraction and measurement of remaining alkaloids. Analysis was performed on individual pouches. The same method was used for determining nicotine levels in used pouches that was used for determination in unused pouches. For details, see [Study Products](#).

Serum Nicotine Concentration Corrections and Endpoint Analyses - Current Study. (b) (4)

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Serum Nicotine Concentration Corrections and Endpoint Analyses - Previous Studies. (b) (4)

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RESULTS AND DISCUSSION

Subjects. A total of 40 subjects provided informed consent to participate in the study. Following the Screening Visit, 30 subjects were asked to complete all procedures through check-in of Test Visit 1. Of those, 15 subjects were notified of priority for enrollment dependent upon qualifying ECO levels. An additional 15 subjects were assigned alternate status in the event a subject with enrollment priority did not qualify. One alternate withdrew from the study before Test Visit 1.

Of the 29 remaining subjects, nine with priority status and six alternates were enrolled at Test Visit 1. All 15 subjects completed the study. Two of the 15 required a make-up visit due to high ECO levels at check-in of Test Visit 5.

Baseline Serum Nicotine and Cotinine Concentrations. Average baseline nicotine values for subjects in each of the five test visits are shown in Table 2. Baseline nicotine was averaged for each subject's -2 and 0 minute values. The values reported below are the group averages of the subject averages. The low baseline values indicate that the ECO cutoff all subjects were required to meet at check-in was effective as an indication of abstinence from smoking.

Table 2. Descriptive statistics of baseline nicotine concentrations (ng/mL) by product.

Study Product	n	Mean	St Dev	Minimum	Maximum
UB Cigarette	15	1.20	0.88	0.25	3.04
Orb	15	1.33	1.00	0.25	3.20
Stick (Half)	15	1.50	1.34	0.25	4.50
Strip	15	1.10	0.87	0.25	2.70
Snus (15 -30 minutes)	15	1.05	0.81	0.25	2.85

Cotinine concentrations before use of each product are listed in Table 3. The half-life of plasma cotinine is 770-1130 minutes or 12.8-18.8 hours (reviewed in [Hukkanen et al., 2005](#)). The concentrations observed for subjects in this study are as expected for smokers who have abstained from nicotine use for approximately 0.6-1.0 half-lives.

Table 3. Descriptive statistics of baseline cotinine concentrations (ng/mL) by product.

Study Product	n	Mean	St Dev	Minimum	Maximum
UB Cigarette	15	178	101	57	392
Orb	15	185	99	61	377
Stick (Half)	15	187	92	75	387
Strip	15	167	105	47	370
Snus (15 -30 minutes)	15	171	105	72	424

Serum Nicotine Uptake. Average serum nicotine concentration-vs.-time curves of observed results are shown in [Figure 1](#). Descriptive statistics for various nicotine endpoints are presented in [Table 4](#), including both observed and baseline-corrected values.

Results for UB cigarettes, Camel Snus, and Orbs were consistent with other RJRT and published studies of cigarettes, moist snuff, and Ariva® ([Kotlyar et al., 2007](#); [Blank et al., 2008](#); [Cobb et al. 2009](#); and reviewed in [Robinson 2008](#)). Serum nicotine uptake measured as the area under the concentration-versus-time curve for the 180-minute testing period (AUC_{0-180}) with observed values was greatest for UB cigarette, followed by Camel Snus, ½ Stick, one Orb, and one Strip, respectively. Results for maximum concentration (C_{max}) were similar: use of UB cigarette resulted in the highest C_{max} followed by Camel Snus, one Orb, ½ Stick, and one Strip, respectively. Relative ranking of baseline-adjusted AUC_{0-180} and C_{max} were the same as the relative rankings of products for observed C_{max} .

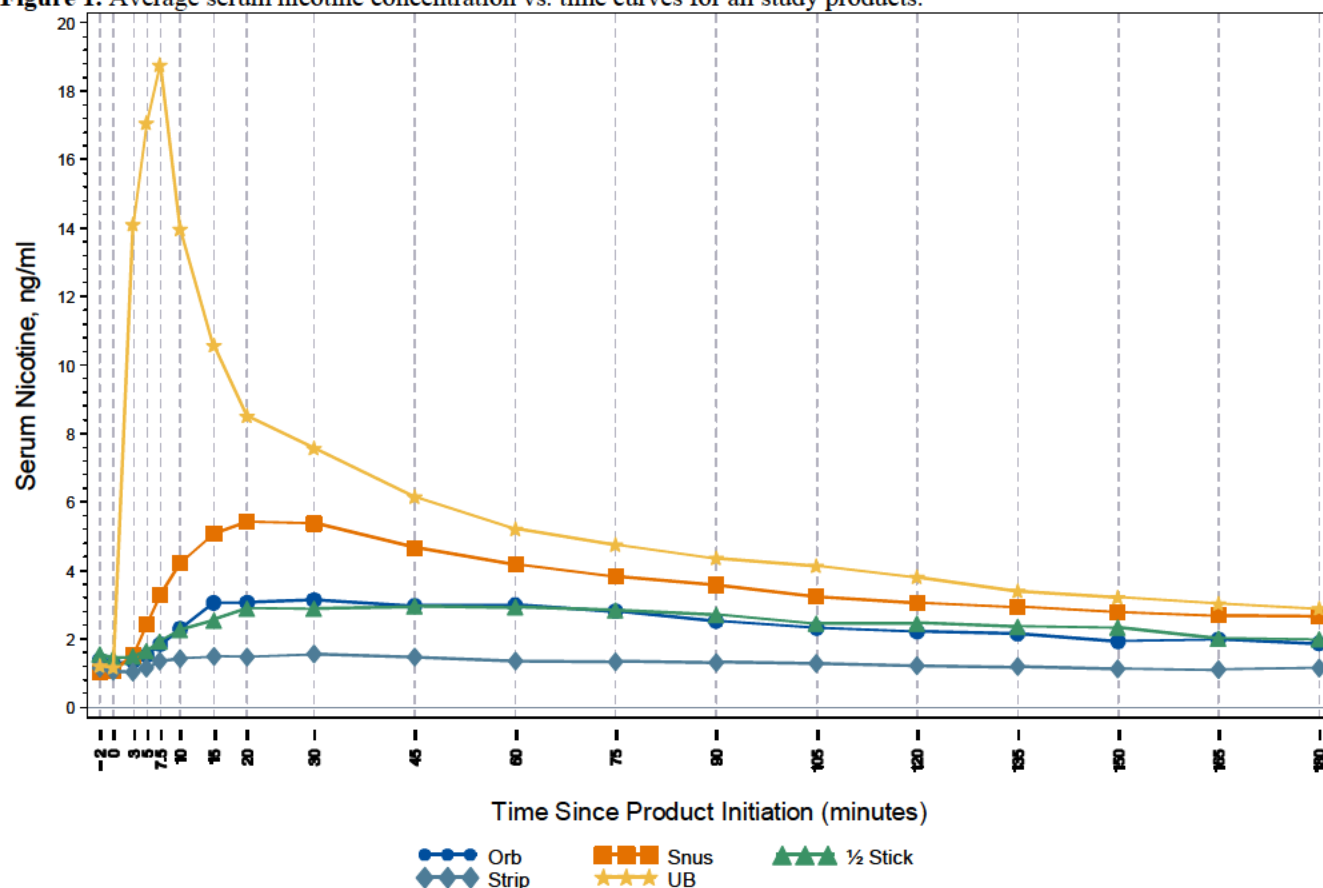
Time to maximum concentration (T_{max}) for UB cigarette occurred an average of 6.6 minutes following the start of smoking and an average of one minute after subjects finished smoking (calculated by subtracting mean duration of smoking/product use from mean T_{max}). The timing of T_{max} is consistent with other reports and is due to rapid uptake of nicotine in the lung (reviewed in Robinson 2008). Camel Snus was used an average of 20.2 minutes, and T_{max} occurred 22.7 minutes after the start of use; therefore, T_{max} occurred, on average, 2.5 minutes after completion. The timing of T_{max} in relation to pouch removal indicates that relatively rapid nicotine absorption occurred through the oral mucosa during snus use. Although absorption through the oral mucosa is relatively rapid, it is slower than absorption in the lung. This is indicated by the larger C_{max} following smoking and the similar AUC_{0-180} results of the two products: the baseline-adjusted AUC_{0-180} of Camel Snus is 78% of UB, while C_{max} is only 25% of UB (nicotine absorption is reviewed in [Hukkanen et al., 2005](#) and Robinson 2008).

In contrast to UB cigarette and snus, the T_{max} following use of the dissolvable products occurred an average of 13.1 minutes after completion of one Orb, 36.5 minutes after completion of one Strip, and 41.2 minutes after completion of ½ Stick. The larger difference between average duration of use and average T_{max} suggests that some amount of nicotine uptake resulting from dissolvable product use occurs through a slower route of absorption after swallowing. Absorption through the lung and oral mucosa, the primary routes of absorption for smoking and snus use respectively, occurs rapidly and allows nicotine to directly enter systemic circulation and avoid first-pass metabolism. In contrast, nicotine absorption after swallowing occurs poorly through the gastric membranes but is well absorbed in the small intestine. Nicotine absorbed after swallowing is initially routed through the liver, where first-pass metabolism converts some of the nicotine to its metabolites before entering systemic circulation (Reviewed in Hukkanen et al., 2005 and Robinson 2008). Descriptive statistics of duration of use are reported in [Table 5](#).

Although the shapes of the Orb and the ½ Stick are different, the nicotine content (mean of 1.13 mg for the two Orbs varieties and 1.14 mg for ½ Stick), the pH (mean of 7.8 for the two Orbs varieties and 7.9 for the ½ Stick), and the masses (0.227g for one Orb and 0.258g for ½ Stick) are similar. Likewise, the concentration-versus-time curve, AUC_{0-180} , and the C_{max} of the products are also similar. Although T_{max} occurs at different times after use of one Orb and ½ Stick, concentration-versus-time curves for both products are generally flat after approximately 20 minutes of use. The biggest difference observed between the two products is duration of use, which probably influenced the difference between the T_{max} for the two products but did not affect nicotine uptake overall.

Although the Strip contains approximately 40% of the amount of total alkaloids expressed as nicotine contained in an Orb or ½ Stick, the baseline-corrected AUC_{0-180} is 21-23% of those products. This suggests that a greater proportion of nicotine from the Strip may have been swallowed before absorption through the oral mucosa could occur. Nicotine absorbed through the stomach or small intestine would have undergone first-pass metabolism before entering systemic circulation; therefore, much of the nicotine would have been metabolized before detection in the serum collected from subjects could occur. The short mean duration of use for the Strip does not allow for the prolonged oral exposure that occurs during use of an Orb or ½ Stick. Figure 2 depicts the routes of nicotine uptake inferred from the nicotine uptake parameter results of the current study.

Figure 1. Average serum nicotine concentration vs. time curves for all study products.



n=14 for: Orbs at 10 and 15 min., Snus at 15 – 180 min., Strips at 20 min., and UB at 15 and 20 min.

n =15 for all other time points.

Table 4. Descriptive statistics of serum nicotine endpoints and duration of product use.

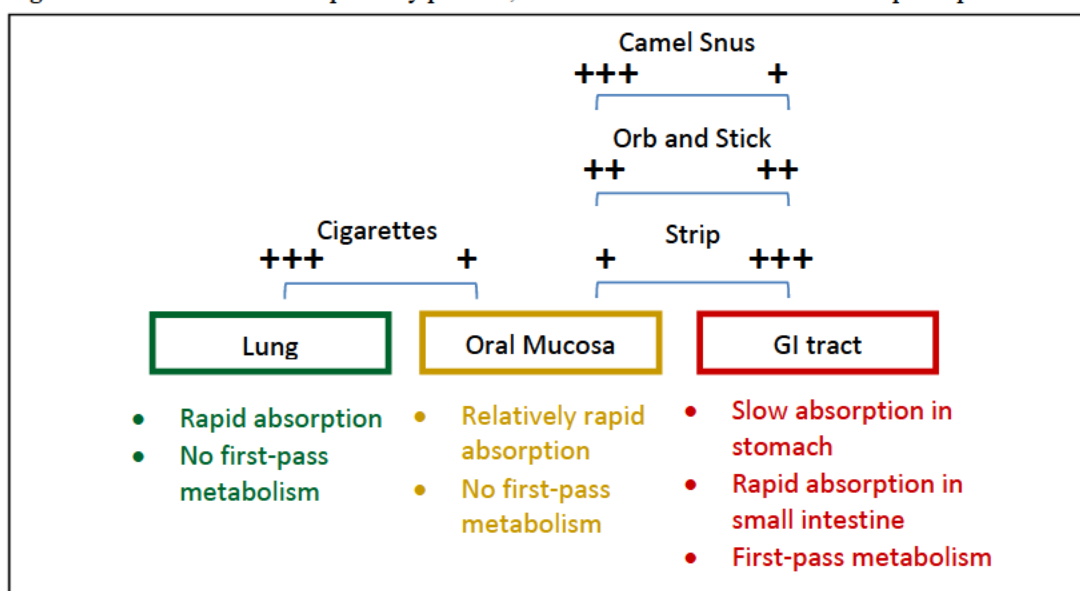
Study Product	n	AUC ₍₀₋₁₈₀₎		AUC ₍₀₋₁₈₀₎ baseline adjusted		C _{max}		C _{max, baseline} adjusted		T _{max}		Duration of use	
		(ng x min/ml)		(ng x min/ml)		(ng/ml)		(ng/ml)		(min)		(min)	
UB Cigarette	15	976	381	761	288	21.1	9.8	19.9	9.7	6.6	1.7	5.8	1.5
Orb	15	441	197	202	99	3.7	1.3	2.3	1.1	35.3	20.7	12.2	6.4
Stick (Half)	15	455	245	186	68	3.5	1.4	2.0	0.7	60.0	32.9	18.8	12.4
Strip	15	233	142	43	30	1.8	0.9	0.7	0.3	41.0	45.4	4.5	3.9
Snus (15 -30 minutes)	14*	651	194	486	187	6.2	1.7	5.0	1.9	22.7	8.8	21.1	6.0

* One subject experienced an adverse event while using Camel Snus and removed the product after 7.5 minutes. Data for that subject are not included in these determinations.

Table 5. Descriptive statistics of in-lab study product use times (minutes).

Study Product	n	Mean	St Dev	Min	Max
UB Cigarette	15	5.8	1.5	3.6	9.0
Orb	15	12.2	6.4	3.8	26.9
Stick (Half)	15	18.8	12.4	6.8	54.9
Strip	15	4.5	3.9	1.1	16.3
Snus (15 -30 minutes)	14*	21.1	6.0	15.1	30.1

* One subject experienced an adverse event while using Camel Snus and removed the product after 7.5 minutes. Data for that subject are not included in these determinations.

Figure 2. Routes of nicotine uptake by product, inferred from calculated nicotine uptake parameters.

Nicotine uptake resulting from use of each MSFT product was calculated as a percentage of the uptake resulting from smoking a UB cigarette. Results are summarized in Table 6.

Table 6. Descriptive statistics of MSFT AUC₀₋₁₈₀ as a percentage of UB AUC₀₋₁₈₀ for observed and adjusted values.

Study Product	n	Observed				Baseline adjusted			
		Mean	St Dev	Minimum	Maximum	Mean	St Dev	Minimum	Maximum
Orb	15	45.8%	14.4%	28.2%	86.5%	28.2%	12.8%	4.1%	50.8%
Stick (Half)	15	49.1%	25.4%	28.8%	114.1%	27.6%	15.6%	12.4%	75.0%
Strip	15	24.6%	13.0%	9.8%	57.4%	6.5%	5.4%	0.3%	16.3%
Snus (15 -30 minutes)	14*	80.7%	53.6%	34.9%	229.8%	77.8%	62.0%	32.0%	247.2%

* One subject experienced an adverse event while using Camel Snus and removed the product after 7.5 minutes. Data for that subject are not included in these determinations.

Mouth-Level Nicotine Exposure. Exposure to nicotine during use of Camel Snus and UB cigarette differed by subject due to the variability in product-use behavior. In contrast, consumption of the entire portion of the dissolvable product dispensed should result in a generally consistent nicotine exposure from those products, although route of uptake (oral mucosa vs. GI tract) may differ depending on placement in the mouth and how frequently the product is moved during use. A summary of the maximum mouth-level exposure for all products is reported in Table 7.

Table 7. Summary of average maximum mouth-level exposure to nicotine for all study products.

Study Product	Nicotine MLE
	Mean (mg)
UB Cigarette	1.59
Orb	1.13*
Stick (Half)	1.14*
Strip	0.44*
Snus (15 -30 minutes)	2.28

* Indicates total alkaloids expressed as nicotine. Actual nicotine MLE is expected to be 72%-83% of the total alkaloid value listed.

Maximum mouth-level exposure to nicotine from in-lab smoking and snus use were determined by yield-in-use and snus-after-use analysis, respectively. Results are presented in Tables 7 and 8.

Table 8. Yield-in-use and snus-after-use nicotine results for in-lab product use by subject and overall.

Subject	YIU information		SAU information		
	Brand	Nicotine (mg)	Camel Snus Variety	Nicotine extracted (mg)	Percent Extracted
1	Winston Lights Hard Pack (100s)	2.22	Mellow	2.53	31.0%
3	Camel Lights Hard Pack (KS)	1.54	Mellow	1.94	23.8%
5	Marlboro Lights Hard Pack (KS)	1.57	Mellow	4.19	51.3%
7	Marlboro Lights Hard Pack (KS)	1.02	Frost	0.02	0.3%
9	Salem Gold Hard Pack (KS)	1.65	Frost	0.02	0.3%
11	Doral Lights Menthol Hard Pack (100s)	2.23	Frost	0.88	13.2%
12	Marlboro Lights Hard Pack (KS)	1.66	Frost	1.55	23.3%
13	Kool Milds Menthol Hard Pack (KS)	1.72	Frost	3.2	48.1%
15	Camel Lights Hard Pack (KS)	2.00	Frost	1.66	24.9%
18	Camel Lights Hard Pack (KS)	1.10	Mellow	2.53	31.0%
19	Pall Mall Blue Hard Pack (KS)	1.49	Frost	2.57	38.7%
21	Marlboro Lights Hard Pack (72s)	0.74	Frost	5.19	78.1%
24	Marlboro Red Hard Pack (KS)	1.83	Frost	4.66	70.1%
26	Winston Lights Hard Pack (KS)	2.15	Mellow	2.59	31.8%
28	Camel Lights Hard Pack (KS)	0.91	Frost	0.68	10.3%
Average ± SD		1.59 ± 0.47		2.28 ± 1.57	31.7% ± 22.8%

The average amount of nicotine extracted from a single use of snus observed in this study, 2.28 mg per pouch, differs slightly from the average extraction amounts observed in two other RJRT studies. In the 2009 RJRT snus study, smokers were recruited to decrease smoking and use snus (Round et al., 2010). Subjects in that study extracted an average of 1.6 mg per pouch. Unlike the current study, subjects were not required to use snus for a specified period of time, and during test visits, used a single snus pouch for an average of 12.3 minutes (Round et al., 2010). In contrast, subjects in this study used snus an average of 20.2 minutes per pouch. These results suggest that duration of use contributes to the amount of nicotine extracted.

Natural adopters of Camel Snus were recruited for a separate study (Caraway and Chen, 2009). Analysis of used snus pouches collected in that study showed an average extraction of 2.8 mg of nicotine per pouch. Subjects included in that study reported using at least 15 pouches of Camel Snus per week for at least three months. Time of use per pouch was not reported.

The average mouth-level exposure to nicotine from a cigarette was 1.59 mg, less than that of snus, yet the AUC₀₋₁₈₀ from smoking was greater than from snus use. This may reflect differences in the rates of absorption in the lung compared to the oral mucosa and the rate of metabolism that occurs once absorbed by the two tissues (Robinson 2008).

Serum Nicotine Uptake Comparisons to Previous RJRT Studies. Previous studies assessed nicotine uptake from MSFT products during in-lab use after a minimum 30-minute tobacco abstinence. Under those conditions, nicotine was present from earlier tobacco use occurring the same day as the analysis period. Serum nicotine present at the start of the analysis period significantly confounded the

determination of nicotine uptake from the study product used during the test visit. Therefore, to determine the nicotine uptake solely from in-lab product use in those studies, it was necessary to estimate and subtract the levels of baseline serum nicotine expected to be cleared at each time point over the collection period. See [Methods](#) section for details of those calculations.

Uptake modeling estimations calculated for the previous Strips, Sticks, and Snus studies and baseline-adjusted uptake as measured in the current study for analysis periods equivalent to previous studies are presented in [Table 9](#). Comparisons indicate that the amount of nicotine uptake calculated in the previous Strips and Sticks studies was overestimated. This overestimation was likely due to the nicotine half-life determination made from the blood samples collected during the 30 minutes immediately following the initiation of smoking. This 30-minute period was the only period available for such a calculation in those studies. Even though care was taken to use only the time points after the average C_{\max} occurred, these time points still occurred during the rapid phase of serum nicotine decline that occurs immediately after a bolus of nicotine is absorbed. Therefore, the half-lives calculated - 33 minutes in the Strips study and 30 minutes in the Sticks study - were shorter than would be expected for the relevant elimination half-life of serum nicotine, which is approximately 120 minutes according to published sources (reviewed in Hukkanen et al., 2005; [Benowitz et al., 2006](#)).

Other factors that may have contributed to the overestimation of nicotine are 1) the small amount of nicotine uptake relative to the variability of the baseline serum nicotine concentrations, 2) the variability of individual serum nicotine half-lives, and 3) the variability of individual rates of nicotine uptake.

In contrast, the nicotine uptake calculated from results of the previous Camel Snus study is comparable to the nicotine uptake that occurred in the current study. This is likely because the half-life calculated from the previous study results was determined from data points that occurred after the initial rapid serum nicotine decline ended, and because nicotine uptake was greater after use of this product. In contrast to the previous Strips and Sticks studies, the nicotine half-life from the Snus study was calculated using data points 40-90 minutes after the start of smoking. The half-life of this later phase of clearance, 131 minutes, was likely more similar to the half-life of nicotine present in subjects who start a test visit after a minimal 30-minute tobacco abstinence period.

Corrections were also performed using the published plasma nicotine half-life of approximately 120 minutes in place of the half-lives calculated from subjects in previous studies (reviewed in [Hukkanen et al., 2005](#)). Results are reported in [Table 9](#). AUC calculations for those corrections were closer to current study results. Results for Sticks and Snus data were not statistically significantly different from current study results, but statistically significant differences were still seen between the Strips study and current study results. The large variability of the Strips study data combined with the small differences in serum nicotine concentrations before and after product use resulted in statistically significant differences in results between studies. The variability of the Sticks and Snus study data were also larger than the variability of current study data, but the greater nicotine uptake measured resulted in comparisons to current study data that were not statistically significantly different.

Table 9. AUC determinations for the current study, for Week 4 results of previous studies using correction techniques, and for Week 4 results of previous study with 120-minute serum nicotine half-life applied. p-values are for comparisons with current study results.

		Current study [#]			Previous study				Previous study with 120' half-life			
		n	mean	SD	n	mean	SD	p-value	n	mean	SD	p-value
Strips - AUC ₍₀₋₆₀₎	(ng x min/ml)	15	21.1	15.4	28	193.7	95.9	<0.0001	28	40.8	40.5	0.0272
Sticks - AUC ₍₀₋₆₀₎	(ng x min/ml)	15	70.1	31.4	27	315.6	199.2	<0.0001	27	75.9	94.1	0.7709
Snus - AUC ₍₀₋₉₀₎	(ng x min/ml)	14*	301.6	109.3	32	292.3	256.1	0.8646	32	306.6	264.5	0.9275

[#] AUC calculations for the current study are baseline-adjusted as described in Methods.

* One subject in the current study experienced an adverse event while using Camel Snus and removed the product after 7.5 minutes. Data for that subject are not included in these determinations.

Carboxyhemoglobin. Carboxyhemoglobin levels were measured just before product use and 30 and 60 minutes after the start of product use. Statistically significant increases in %COHb were observed following UB smoking, but not following any MSFT product use. Results indicate significant CO uptake during cigarette smoking only and support the hypothesis that no CO uptake occurs during use of any MSFT product. Results are reported in Table 10.

Table 10. Descriptive statistics of carboxyhemoglobin results for each product.

Study Product	-2 minutes			30 minutes			60 minutes		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
UB	15	2.3%	0.7	15	3.1%	0.7	15	2.9%	0.7
Orb	15	2.4%	0.7	15	2.5%	0.8	15	2.3%	0.6
1/2 Stick	15	2.5%	0.8	15	2.5%	0.7	15	2.4%	0.7
Strip	15	2.3%	0.7	15	2.1%	0.6	15	2.1%	0.6
Snus	15	2.2%	0.6	14	2.2%	0.5	13	2.0%	0.5

Numbers in red were statistically significantly higher ($p < 0.05$) than the product-matched -2 minute value.

Tobacco Abstinence Symptoms. Descriptive statistics were determined for MPSS ratings by time point and are reported in Tables 11-17. All MPSS items were rated on a scale of 1-5, with the exception of urge to smoke, which was rated on a scale of 0-5 (Appendix A). Mean ratings over time are presented graphically in Figure 3. To understand changes in rating of MPSS items after product use, differences between the pre-product use rating and rating at each subsequent time point were averaged for each product and presented as Δ in Tables 18-24. A positive Δ indicates a decrease in symptom relative to the pre-product use rating, whereas a negative Δ indicates an increase in symptom. Paired t -tests were used to assess changes in rating at each time point relative to pre-product rating.

MPSS Items 1-6.

Mean ratings for depression were low and did not significantly change over time for any product. Mean ratings for poor concentration were low and did not change significantly for any product aside from UB. Mean changes in poor concentration after smoking were small and due to a slightly increased mean pre-product use rating, similar to anxiety, irritability, and restlessness. Data for hunger ratings were

confounded by inconsistent snacking of subjects during test visits, but mean ratings were generally low and slightly increased over time for most products.

Pre-product use ratings of anxiety, irritability, restlessness, and urge to smoke were higher for UB cigarette than for the MSFT products. UB cigarette was the only study product not randomized. All subjects smoked UB at Test Visit 1, which was also the visit at which enrollment and randomization occurred. Due to these circumstances, the elevated pre-product ratings for UB may be unrelated to the specific product used that day, and may be attributable to subjects' uncertainty of enrollment at that particular test visit. Due to the layout of the facility, subjects had the ability to interact with each other prior to enrollment, which may have further increased their levels of anxiety, irritability, restlessness, and urge to smoke at that particular test visit.

Because of increased pre-product use ratings for these symptoms before smoking UB, the differences between pre-product and post-product use ratings for UB appear larger than those observed for the MSFT products when the average post-product rating is the same. This was true for anxiety, irritability, and restlessness. Mean ratings of those symptoms were similar for all products after product use, and mean changes reached statistical significance only after smoking UB. Mean ratings of anxiety and restlessness tended to increase after reaching their lowest values, which may be due to the necessity to remain seated for the duration of the 3.5 hour test visit.

Urge to Smoke.

Mean rating of urge to smoke statistically significantly decreased after use of all products. The decrease was greatest (maximum mean difference = 3.27) and remained statistically significant for the longest period of time (5-150 minutes) after smoking UB. The lowest mean rating for urge to smoke was 0.4, which occurred 15 minutes after the start of smoking.

Use of Camel Snus resulted in a maximum mean decrease in rating of 1.0. Mean decreases in rating were statistically significant from 5-60 minutes. The lowest mean rating for urge to smoke after snus use was 2.2, which occurred 30 minutes after the start of product use.

Use of a ½ Stick statistically significantly decreased urge to smoke from 5-30 minutes after the start of use, with a maximum mean decrease of 0.73. The lowest mean urge to smoke rating was 2.3, which occurred at 15 and 30 minutes after the start of use.

Use of one Orb statistically significantly decreased urge to smoke between 5-15 minutes after the start of use, with a maximum mean decrease of 0.53. The lowest mean urge to smoke rating was 2.5, which occurred at 15, 30, and 45 minutes after the start of use.

Use of one Strip statistically significantly decreased urge to smoke at 15 minutes after the start of smoking, with a mean decrease of 0.47. The mean urge to smoke rating at that time point was 2.6.

To summarize, smoking one UB cigarette decreased subjects' urge to smoke by the greatest magnitude and for the longest period of time. Of the MSFT products, Camel Snus decreased urge to smoke ratings by the greatest magnitude and for the longest period of time. Of the dissolvable products, ½ Stick and one Orb decreased urge to smoke to a similar degree. Use of one Strip resulted in the smallest decrease

in rating for the shortest period of time. [Figure 4](#) depicts the duration of statistically significant decreases in mean urge to smoke ratings for all products.

Smoking may alleviate the urge to smoke to a greater extent and for a longer duration for several reasons. Rapid serum nicotine uptake is an important factor; however, studies have shown that subjects who perform the physical rituals of smoking but absorb little to no nicotine also experience a statistically significant decrease in tobacco abstinence symptoms. In Cobb et al. (2009), smokers used one of several tobacco products after an overnight tobacco abstinence. Smoking a denicotinized cigarette statistically significantly decreased craving to smoke at nearly all time points for a 2 hour assessment period. These decreases were similar in pattern to smoking subjects' own brand cigarettes. The magnitude of decrease after smoking a denicotinized cigarette was greater and statistically significantly decreased for longer than after use of smokeless tobacco or Commit lozenge, but was not as great as after smoking subjects' own brand cigarette (Cobb et al, 2009). Smoking an electronic cigarette (e-cigarette) does not significantly increase plasma nicotine levels, but results in a decrease in craving to smoke of approximately 40-50% of subjects' own brand cigarettes after a 12-hour tobacco abstinence (Vansickel et al., 2010). Similar results were seen in longer-term studies that compared denicotinized cigarettes, cigarettes with nicotine, and no smoking for five days per condition. Urge to smoke was reported to be suppressed and did not significantly increase throughout the denicotinized cigarette or nicotine cigarette conditions (Buchhalter et al., 2005). Results from these studies indicate that smoking-related stimuli other than nicotine exposure are important factors in the suppression of urge to smoke.

Table 11. Descriptive statistics for urge to smoke at each time point. N=15 for each assessment.

Time Point	UB		Orb		½ Stick		Strip		Snus	
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Pre-10'	3.7	1.4	3.0	1.3	3.0	1.3	3.1	1.5	3.2	1.3
5'	0.6	0.8	2.7	1.3	2.5	1.2	2.7	1.6	2.5	1.6
15'	0.4	0.6	2.5	1.1	2.3	1.0	2.6	1.4	2.4	1.5
30'	0.7	0.6	2.5	1.3	2.3	1.1	2.7	1.3	2.2	1.4
45'	1.2	0.9	2.5	1.2	2.5	1.0	2.8	1.3	2.4	1.2
60'	1.5	0.9	2.7	1.1	2.6	1.0	2.9	1.1	2.7	1.1
90'	2.1	1.0	2.8	1.3	2.9	0.9	3.2	1.1	2.9	1.1
120'	2.4	1.1	3.1	1.2	3.0	1.0	3.3	1.2	3.1	1.1
150'	2.8	1.2	3.3	1.2	3.2	1.0	3.5	1.1	3.4	0.8
180'	3.0	1.4	3.8	1.0	3.7	1.1	3.8	0.9	3.5	0.9

Table 12. Descriptive statistics for anxious at each time point. N=15 for each assessment.

Time Point	UB		Orb		½ Stick		Strip		Snus	
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Pre-10'	2.7	1.5	1.7	0.7	1.5	1.1	1.7	0.5	1.9	1.1
5'	1.7	1.2	1.7	0.7	1.5	0.7	1.5	0.3	1.6	0.6
15'	1.4	0.5	1.5	0.6	1.4	0.6	1.5	0.3	1.4	0.5
30'	1.3	0.5	1.5	0.5	1.3	0.5	1.3	0.3	1.4	0.5
45'	1.4	0.5	1.5	0.6	1.4	0.5	1.5	0.3	1.5	0.6
60'	1.5	0.6	1.5	0.7	1.3	0.5	1.5	0.3	1.4	0.5
90'	1.6	0.7	1.7	0.7	1.4	0.7	1.6	0.3	1.6	0.6
120'	1.7	0.7	1.8	0.9	1.7	0.8	1.9	0.3	1.7	0.7
150'	1.9	0.9	1.9	1.0	1.7	0.8	1.9	0.3	2.0	1.0
180'	1.9	1.0	2.3	1.2	2.1	1.3	2.1	0.3	2.3	1.2

Table 13. Descriptive statistics for irritable at each time point. N=15 for each assessment.

Time Point	UB		Orb		½ Stick		Strip		Snus	
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Pre-10'	2.1	1.4	1.4	0.6	1.5	0.7	1.6	1.1	1.3	0.8
5'	1.4	0.9	1.5	0.7	1.3	0.5	1.5	0.8	1.3	0.5
15'	1.2	0.4	1.4	0.5	1.1	0.4	1.3	0.5	1.3	0.5
30'	1.1	0.3	1.1	0.4	1.1	0.4	1.3	0.5	1.3	0.6
45'	1.1	0.3	1.2	0.4	1.1	0.4	1.3	0.5	1.2	0.4
60'	1.1	0.4	1.3	0.6	1.1	0.4	1.4	0.6	1.2	0.4
90'	1.3	0.6	1.3	0.6	1.1	0.3	1.3	0.5	1.3	0.6
120'	1.5	0.7	1.3	0.6	1.2	0.4	1.4	0.6	1.5	0.6
150'	1.5	0.9	1.3	0.6	1.3	0.6	1.4	0.6	1.5	0.7
180'	1.3	0.5	1.4	0.6	1.3	0.6	1.5	0.7	1.5	0.6

Table 14. Descriptive statistics for restless at each time point. N=15 for each assessment.

Time Point	UB		Orb		½ Stick		Strip		Snus	
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Pre-10'	2.2	1.4	1.5	0.9	1.7	1.0	1.7	1.1	1.5	0.8
5'	1.4	0.7	1.5	0.7	1.3	0.5	1.5	0.8	1.4	0.7
15'	1.3	0.5	1.4	0.7	1.3	0.5	1.5	0.6	1.3	0.6
30'	1.4	0.7	1.3	0.5	1.3	0.5	1.4	0.6	1.3	0.5
45'	1.4	0.6	1.5	0.6	1.3	0.5	1.5	0.8	1.5	0.6
60'	1.5	0.6	1.7	0.9	1.3	0.5	1.7	1.0	1.7	0.8
90'	1.8	0.9	1.9	0.9	1.7	0.7	1.8	1.0	1.6	0.7
120'	2.1	1.1	1.9	0.8	1.7	0.7	2.0	0.7	1.8	0.9
150'	2.1	1.0	1.9	0.9	2.0	0.9	2.0	2.0	2.1	1.0
180'	2.1	1.0	2.1	1.0	2.0	1.2	2.1	2.0	2.3	1.2

Table 15. Descriptive statistics for depressed at each time point. N=15 for each assessment.

Time Point	UB		Orb		½ Stick		Strip		Snus	
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Pre-10'	1.1	0.5	1.1	0.3	1.0	0.0	1.1	0.5	1.1	0.3
5'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.1	0.3
15'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.1	0.3
30'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.0	0.0
45'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.1	0.3
60'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.0	0.0
90'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.0	0.0
120'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.0	0.0
150'	1.0	0.0	1.1	0.3	1.0	0.0	1.1	0.3	1.0	0.0
180'	1.0	0.0	1.0	0.0	1.0	0.0	1.1	0.3	1.0	0.0

Table 16. Descriptive statistics for poor concentration at each time point. N=15 for each assessment.

Time Point	UB		Orb		½ Stick		Strip		Snus	
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Pre-10'	1.7	1.0	1.5	0.7	1.3	0.7	1.3	0.8	1.5	0.7
5'	1.3	0.6	1.2	0.4	1.3	0.6	1.3	0.6	1.2	0.4
15'	1.1	0.4	1.1	0.4	1.3	0.6	1.2	0.6	1.3	0.5
30'	1.1	0.4	1.1	0.4	1.2	0.4	1.3	0.6	1.2	0.4
45'	1.1	0.4	1.1	0.4	1.2	0.4	1.2	0.4	1.2	0.4
60'	1.1	0.4	1.2	0.4	1.1	0.4	1.1	0.5	1.2	0.4
90'	1.2	0.4	1.3	0.5	1.3	0.5	1.1	0.3	1.2	0.4
120'	1.2	0.6	1.3	0.5	1.2	0.4	1.3	0.6	1.1	0.4
150'	1.3	0.6	1.3	0.5	1.1	0.4	1.1	0.3	1.2	0.4
180'	1.3	0.6	1.3	0.5	1.3	0.6	1.2	0.6	1.1	0.4

Table 17. Descriptive statistics for hungry at each time point. N=15 for each assessment.

Time Point	UB		Orb		½ Stick		Strip		Snus	
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Pre-10'	1.4	0.9	1.3	0.8	1.4	0.8	1.0	0.0	1.1	0.4
5'	1.2	0.4	1.3	0.8	1.3	0.6	1.0	0.0	1.1	0.4
15'	1.3	0.6	1.3	0.8	1.3	0.6	1.0	0.0	1.1	0.4
30'	1.2	0.6	1.1	0.3	1.2	0.6	1.0	0.0	1.1	0.4
45'	1.2	0.6	1.1	0.3	1.1	0.4	1.0	0.0	1.0	0.0
60'	1.3	0.6	1.1	0.3	1.2	0.4	1.0	0.0	1.0	0.0
90'	1.5	0.6	1.2	0.6	1.1	0.4	1.1	0.3	1.1	0.3
120'	1.7	0.8	1.3	0.6	1.2	0.6	1.1	0.3	1.1	0.4
150'	1.9	1.0	1.3	0.7	1.2	0.4	1.1	0.4	1.2	0.6
180'	2.1	1.2	1.3	0.8	1.5	0.8	1.1	0.3	1.4	0.6

Table 18. Mean differences between pre-product rating and rating at each time point for urge to smoke. N=15 for each assessment.

Time Point	UB			Orb			½ Stick			Strip			Snus		
	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value
5'	3.07	0.34	0.0000	0.33	0.13	0.0192	0.47	0.17	0.0135	0.40	0.24	0.1109	0.67	0.19	0.0031
15'	3.27	0.36	0.0000	0.53	0.22	0.0266	0.73	0.25	0.0104	0.47	0.19	0.0290	0.80	0.20	0.0013
30'	2.93	0.33	0.0000	0.53	0.29	0.0878	0.67	0.23	0.0124	0.33	0.23	0.1733	1.00	0.22	0.0004
45'	2.47	0.38	0.0000	0.47	0.31	0.1502	0.47	0.24	0.0684	0.27	0.25	0.3008	0.80	0.20	0.0013
60'	2.20	0.33	0.0000	0.33	0.25	0.2071	0.40	0.25	0.1383	0.13	0.22	0.5457	0.53	0.24	0.0406
90'	1.60	0.32	0.0002	0.20	0.34	0.5667	0.07	0.02	0.7744	-0.13	0.24	0.5816	0.33	0.25	0.2071
120'	1.27	0.30	0.0009	-0.13	0.32	0.6848	0.00	0.26	1.0000	-0.20	0.20	0.3343	0.13	0.26	0.6102
150'	0.87	0.36	0.0318	-0.33	0.30	0.2905	-0.20	0.24	0.4243	-0.47	0.22	0.0479	-0.20	0.22	0.3840
180'	0.67	0.36	0.0859	-0.80	0.30	0.0172	-0.67	0.29	0.0359	-0.73	0.21	0.0032	-0.33	0.29	0.2654

Table 19. Mean differences between pre-product rating and rating at each time point for anxious. N=15 for each assessment.

Time Point	UB			Orb			½ Stick			Strip			Snus		
	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value
5'	1.00	0.38	0.0192	0.00	0.14	1.0000	0.07	0.70	0.5816	0.13	0.17	0.4332	0.27	0.60	0.1643
15'	1.33	0.33	0.0013	0.13	0.17	0.4332	0.13	0.60	0.4332	0.20	0.17	0.2711	0.47	0.50	0.0479
30'	1.40	0.34	0.0009	0.20	0.11	0.0824	0.20	0.50	0.3343	0.33	0.21	0.1362	0.47	0.50	0.0290
45'	1.33	0.32	0.0009	0.20	0.14	0.1887	0.13	0.50	0.5457	0.13	0.22	0.5457	0.40	0.60	0.0541
60'	1.27	0.34	0.0025	0.20	0.17	0.2711	0.20	0.50	0.3840	0.13	0.22	0.5457	0.47	0.50	0.0479
90'	1.13	0.36	0.0075	0.00	0.14	1.0000	0.13	0.70	0.5816	0.07	0.21	0.7513	0.27	0.60	0.2620
120'	1.07	0.34	0.0079	-0.13	0.17	0.4332	-0.13	0.80	0.6337	-0.20	0.17	0.2711	0.13	0.70	0.6102
150'	0.87	0.31	0.0134	-0.27	0.21	0.2170	-0.20	0.80	0.4577	-0.20	0.20	0.3343	-0.13	1.00	0.6337
180'	0.87	0.31	0.0134	-0.60	0.29	0.0572	-0.53	1.30	0.1782	-0.40	0.34	0.2526	-0.47	1.20	0.2038

Table 20. Mean differences between pre-product rating and rating at each time point for irritable. N=15 for each assessment.

Time Point	UB			Orb			½ Stick			Strip			Snus		
	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value
5'	0.67	0.37	0.0961	-0.13	0.14	0.4332	0.13	0.17	0.4332	0.13	0.13	0.3343	0.00	0.20	1.0000
15'	0.87	0.32	0.0175	0.00	0.12	1.0000	0.33	0.19	0.0961	0.33	0.19	0.0961	0.00	0.22	1.0000
30'	1.00	0.35	0.0131	0.27	0.19	0.1038	0.33	0.19	0.0961	0.27	0.21	0.2170	0.07	0.28	0.8178
45'	1.00	0.35	0.0131	0.20	0.20	0.1887	0.33	0.19	0.0961	0.33	0.19	0.0961	0.13	0.26	0.6102
60'	0.93	0.34	0.0170	0.07	0.28	0.7192	0.33	0.19	0.0961	0.20	0.17	0.2711	0.13	0.26	0.6102
90'	0.73	0.28	0.0217	0.07	0.29	0.7192	0.40	0.21	0.0824	0.27	0.21	0.2170	0.07	0.27	0.8062
120'	0.60	0.27	0.0450	0.07	0.27	0.7192	0.27	0.21	0.2170	0.20	0.17	0.2711	-0.13	0.29	0.6534
150'	0.60	0.25	0.0335	0.07	0.31	0.7192	0.20	0.24	0.4243	0.20	0.17	0.2711	-0.13	0.31	0.6702
180'	0.73	0.28	0.0217	0.00	0.27	1.0000	0.13	0.24	0.5816	0.07	0.28	0.8178	-0.13	0.29	0.6534

Table 21. Mean differences between pre-product rating and rating at each time point for restless. N=15 for each assessment.

Time Point	UB			Orb			½ Stick			Strip			Snus		
	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value
5'	0.80	0.38	0.0541	0.00	0.14	1.0000	0.33	0.16	0.0552	0.27	0.12	0.0406	0.07	0.15	0.6702
15'	0.93	0.33	0.0135	0.07	0.12	0.5816	0.40	0.16	0.0281	0.27	0.15	0.1038	0.13	0.17	0.4332
30'	0.80	0.33	0.0281	0.13	0.19	0.4985	0.40	0.16	0.0281	0.33	0.21	0.1362	0.20	0.22	0.3840
45'	0.80	0.33	0.0281	0.00	0.20	1.0000	0.40	0.16	0.0281	0.20	0.17	0.2711	0.00	0.20	1.0000
60'	0.73	0.30	0.0285	-0.27	0.28	0.3636	0.33	0.19	0.0961	0.00	0.17	1.0000	-0.20	0.30	0.5103
90'	0.40	0.32	0.2328	-0.40	0.29	0.1887	0.00	0.24	1.0000	-0.07	0.15	0.6702	-0.13	0.24	0.5816
120'	0.07	0.28	0.8178	-0.40	0.27	0.1643	0.00	0.31	1.0000	-0.27	0.15	0.1038	-0.33	0.27	0.2377
150'	0.07	0.28	0.8178	-0.47	0.31	0.1502	-0.33	0.19	0.0961	-0.27	0.15	0.1038	-0.67	0.33	0.0653
180'	0.13	0.32	0.6848	-0.60	0.27	0.0450	-0.33	0.30	0.2905	-0.40	0.25	0.1383	-0.87	0.40	0.0484

Table 22. Mean differences between pre-product rating and rating at each time point for depressed. N=15 for each assessment.

Time Point	UB			Orb			½ Stick			Strip			Snus		
	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value
5'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.00	0.00	.
15'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.00	0.00	.
30'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.07	0.07	0.3343
45'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.00	0.00	.
60'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.07	0.07	0.3343
90'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.07	0.07	0.3343
120'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.07	0.07	0.3343
150'	0.1	0.13	0.3343	0.00	0.00	.	0.00	0.00	.	0.07	0.07	0.3343	0.07	0.07	0.3343
180'	0.1	0.13	0.3343	0.07	0.07	0.3343	0.00	0.00	.	0.07	0.07	0.3343	0.07	0.07	0.3343

Table 23. Mean differences between pre-product rating and rating at each time point for poor concentration. N=15 for each assessment.

Time Point	UB			Orb			½ Stick			Strip			Snus		
	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value
5'	0.40	0.16	0.0281	0.27	0.12	0.0406	0.07	0.12	0.5816	0.07	0.07	0.3343	0.27	0.15	0.1038
15'	0.60	0.25	0.0335	0.33	0.16	0.0552	0.07	0.12	0.5816	0.13	0.13	0.3343	0.20	0.17	0.2711
30'	0.60	0.25	0.0335	0.33	0.16	0.0552	0.13	0.13	0.3343	0.07	0.12	0.5816	0.27	0.18	0.1643
45'	0.60	0.25	0.0335	0.33	0.16	0.0552	0.13	0.13	0.3343	0.13	0.17	0.4332	0.27	0.15	0.1038
60'	0.60	0.25	0.0335	0.27	0.15	0.1038	0.20	0.17	0.2711	0.20	0.11	0.0824	0.27	0.15	0.1038
90'	0.53	0.24	0.0406	0.20	0.17	0.2711	0.07	0.15	0.6702	0.27	0.15	0.1038	0.27	0.15	0.1038
120'	0.53	0.27	0.0717	0.13	0.19	0.4985	0.13	0.13	0.3343	0.07	0.12	0.5816	0.33	0.16	0.0552
150'	0.47	0.27	0.1103	0.13	0.19	0.4985	0.02	0.17	0.2711	0.27	0.21	0.2170	0.27	0.15	0.1038
180'	0.47	0.27	0.1103	0.20	0.17	0.2711	0.07	0.18	0.7192	0.13	0.09	0.1643	0.33	0.16	0.0552

Table 24. Mean differences between pre-product rating and rating at each time point for hungry. N=15 for each assessment.

Time Point	UB			Orb			$\frac{1}{2}$ Stick			Strip			Snus		
	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value	Δ	SE	p-value
5'	0.20	0.14	0.1887	0.00	0.00	.	0.13	0.09	0.1643	0.00	0.00	.	0.00	0.00	.
15'	0.13	0.09	0.1643	0.00	0.00	.	0.13	0.09	0.1643	0.00	0.00	.	0.00	0.00	.
30'	0.20	0.17	0.2711	0.27	0.21	0.2170	0.20	0.11	0.0824	0.00	0.00	.	0.00	0.00	.
45'	0.20	0.17	0.2711	0.27	0.15	0.1038	0.27	0.15	0.1038	0.00	0.00	.	0.13	0.09	0.1643
60'	0.13	0.19	0.4985	0.27	0.15	0.1038	0.20	0.17	0.2711	0.00	0.00	.	0.13	0.09	0.1643
90'	-0.07	0.23	0.7744	0.13	0.22	0.5457	0.27	0.15	0.1038	-0.07	0.07	0.3343	0.07	0.07	0.3343
120'	-0.33	0.25	0.2071	0.07	0.23	0.7744	0.20	0.24	0.4243	-0.07	0.07	0.3343	0.00	0.10	1.0000
150'	-0.53	0.27	0.0717	0.00	0.20	1.0000	0.20	0.17	0.2711	-0.13	0.09	0.1643	-0.07	0.18	0.7192
180'	-0.67	0.30	0.0453	0.07	0.32	0.8358	-0.07	0.28	0.8178	-0.07	0.07	0.3343	-0.27	0.15	0.1038

Figure 3. MPSS average symptom rating vs. time. Error bars indicate 95% confidence intervals.

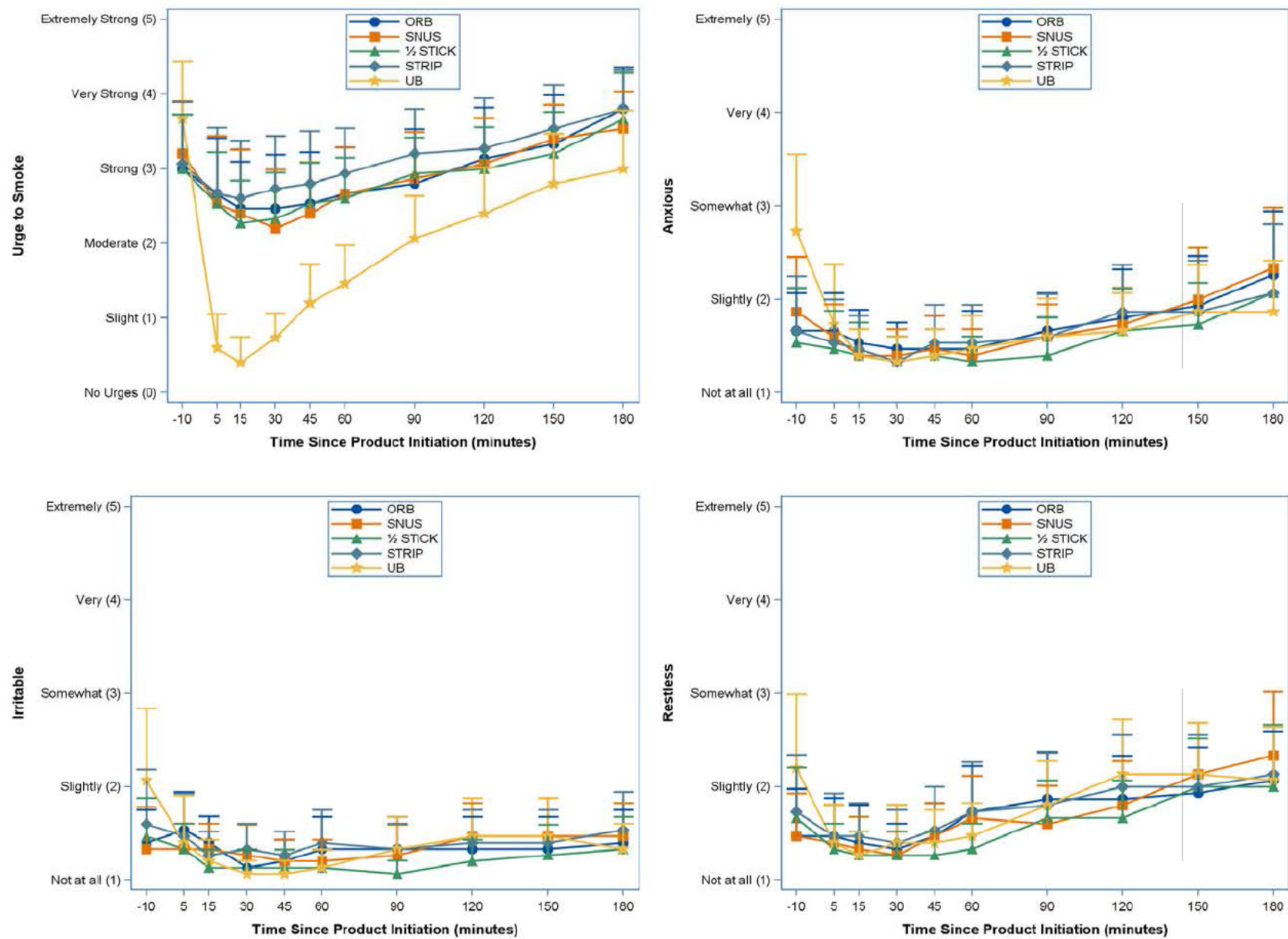


Figure 3. (cont'd) MPSS average symptom rating vs. time. Error bars indicate 95% confidence intervals.

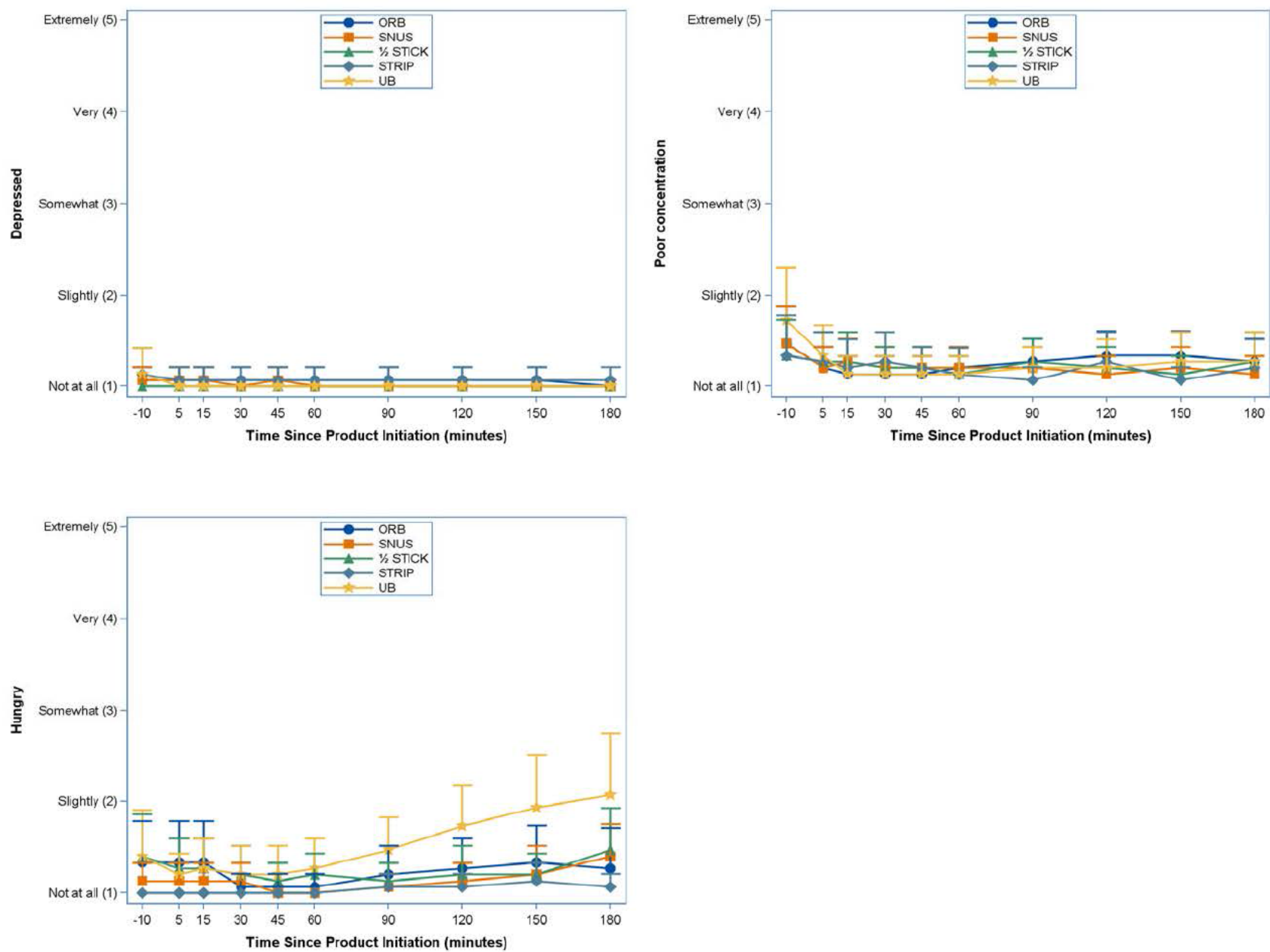
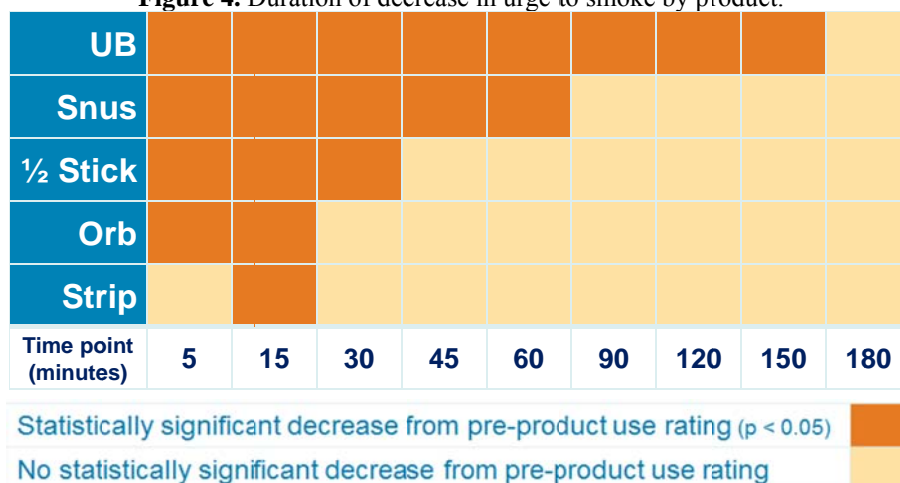


Figure 4. Duration of decrease in urge to smoke by product.

Comparison to Nicotine Uptake and Tobacco Abstinence Symptom Results in Published Studies. Two published studies have examined nicotine uptake from use of either dissolvable tobacco products or from U.S. snus products. Kotlyar et al. (2007) recruited Copenhagen smokeless tobacco users to attend five test sessions. Each session started after a minimum 12-hour tobacco abstinence. Subjects used one of five products in a randomized order: Copenhagen moist snuff (2 g), an Ariva® lozenge, a Stonewall® lozenge, a Revel snus pouch, and 4 mg Commit lozenge. According to Star Scientific, one Ariva® lozenge contains approximately 1.5 mg of nicotine, and one Stonewall® lozenge contains approximately 4 mg of nicotine. In Cobb et al. (2010), smokers were recruited to complete seven test sessions, each after an overnight tobacco abstinence. Subjects in that study used Ariva®, Marlboro Snus, Camel Snus, 2 mg Commit lozenge, usual brand cigarette, Quest (low nicotine) cigarette, and sham smoking (puffing an unlit cigarette) in a randomized order.

Results from the current study show levels of nicotine uptake from Camel Snus use comparable with those reported by Cobb et al. (2010). Although the pouch sizes of the Camel Snus used in the two studies differed (400 mg pouches in the Cobb study and 600 mg pouches in the current study), results from internal RJRT studies support the findings that uptake from the different pouch sizes is similar among subjects who are not natural adopters of the product. Smoking subjects who were switched to dual use with 400 mg Camel Snus pouches in the Quality of Life study extracted, on average, 1.8 mg of nicotine per pouch (Caraway and Lee, 2010). Smoking subjects who were switched to dual use with 600 mg Camel Snus pouches in the RJRT Camel Snus study extracted, on average 1.6 mg of nicotine per pouch (Round et al., 2010).

The mass and nicotine content of one Orb are slightly less than one Ariva®. Accordingly, results from the current study compared to the Kotlyar study indicate that nicotine uptake from one Orb may be slightly less than from one Ariva®; however, similarities in uptake were observed. The C_{max} and the AUC_{0-90} reported by Kotlyar et al. after consumption of one Ariva are 2.7 ng/mL and 192 ng·min/mL, respectively. Baseline adjusted C_{max} and AUC_{0-90} after consumption of one Orb in the current study are 2.3 ng/mL and 129 ng·min/mL, respectively. Although exact values are not reported by Cobb et al. (2010), a figure showing nicotine uptake suggests a similar C_{max} was measured after Ariva® use in that study. These results, together with the physical product similarities, suggest that the buccal absorption of tobacco constituents by daily smokeless tobacco users may be similar to buccal absorption in smokers.

Both Kotlyar et al. (2007) and Cobb et al. (2010) also assessed tobacco use urges. The craving score assessed in the Kotlyar study is not directly comparable to the one for smokers in the current study because subjects in the former study were regular users of smokeless tobacco. An inclusion criterion of that study required subjects to have used Copenhagen smokeless tobacco daily for at least one year prior to enrollment.

Although urge to smoke was assessed using different instruments in the current study and the Cobb study, similar trends were observed for subject responses. Urge to smoke was mildly suppressed when subjects in either study used any of the smokeless tobacco products and was strongly suppressed only when the subjects smoked their UB/Own cigarettes. It is unclear whether the lack of smoking ritual or the reduced nicotine uptake compared to cigarette smoking was the primary driver of this result.

Adverse Events. Nine of 15 subjects reported experiencing at least one adverse event (AE) during the course of the study that was judged by the Medical Advisor to be possibly, probably, or definitely related to study product use. Of these, five subjects reported experiencing more than one AE. Reported AEs were associated with Orb, Stick, and Camel Snus use. AEs are listed according to product association and are shown in Table 25. MPSS items were not recorded as AEs unless subjects reported an item when asked if they had experienced any change in health since their last study visit. No reports of this type occurred. AE symptoms were generally mild and resolved within 45 minutes. One incidence of nausea occurred for up to four hours.

Table 25. Adverse events reported by product association and total number of subjects.

Adverse Event	Product associated with AE					Total number of subjects reporting
	UB	Orb	Strip	Stick	Snus	
Throat Irritation	0	0	0	0	1	1
Nausea	0	1	0	1	2	3
Mouth Burn/Irritation	0	1	0	1	2	2
Bumps in mouth	0	0	0	1	0	1
Hiccups	0	1	0	0	1	2
Heartburn	0	0	0	1	1	2
Vomiting	0	0	0	0	1	1
Total	0	3	0	4	8	9

CONCLUSION

Fifteen smokers completed a randomized, crossover, open-label study of Camel Orbs, Camel Strips, Camel Sticks, Camel Snus, and subjects' usual brand (UB) cigarettes. Subjects consumed a single unit of one product at each of five test visits after a 12-hour nicotine abstinence.

Smoking one UB cigarette resulted in the largest AUC₀₋₁₈₀ of any product examined. Unadjusted nicotine uptake calculations following use of one snus pouch, ½ Stick, one Orb, and one Strip averaged 81%, 49%, 46%, and 25% of the UB value, respectively. After baseline correction, nicotine uptake averaged 78%, 28%, 28%, and 7% of UB, respectively. Smoking one UB cigarette resulted in the

highest baseline-adjusted mean maximum concentration (C_{\max}), 19.9 ng/mL, followed by one Camel Snus pouch (5.0 ng/mL), one Orb (2.3 ng/mL), ½ Stick (2.0 ng/mL), and one Strip (0.7 ng/mL).

Mean time to maximum concentration (T_{\max}) was shortest for UB cigarette at 6.6 minutes, followed by one Camel Snus pouch (22.7 min), one Orb (35.3 min), one Strip (41.0 min), and ½ Stick (60.0 min). Average duration of use for a Strip was the shortest at 4.5 minutes, followed by UB cigarette (5.8 min), one Orb (12.2 min), and ½ Stick (18.8 min). Camel Snus was used for the longest period of time, an average of 20.2 minutes.

Nicotine uptake in this study was compared to uptake estimates determined from nicotine data collected after a shorter nicotine abstinence in previous studies. Uptake estimates from previous studies were determined using nicotine concentrations that were modified by subtracting the estimated baseline nicotine remaining at each time point. Comparisons showed that although AUC determined from modified nicotine concentrations can be useful, the most accurate results with the smallest variability were observed with the current study design. Therefore, this study design is recommended for future studies that evaluate nicotine uptake after use of a smoke-free tobacco product. The longer nicotine abstinence also allows for concurrent assessment of urge to smoke ratings, which may relate to whether a smoker would consider use of a MSFT product in place of cigarettes.

Finally, unadjusted and baseline-adjusted values for nicotine parameters were reported in this study. Although incoming nicotine concentrations are greatly reduced following a 12-hour nicotine abstinence, a small residual amount remains that can significantly affect AUC values when determined for a three-hour period. Therefore, for future studies, it is recommended to report only baseline-adjusted values.

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APPENDIX 1

Mood and Physical Symptoms Scale

Please show for each of the items below how you currently feel.
(Circle one number for each item.)

	Not at all	Slightly	Somewhat	Very	Extremely
1. Depressed	1	2	3	4	5
2. Anxious	1	2	3	4	5
3. Irritable	1	2	3	4	5
4. Restless	1	2	3	4	5
5. Hungry	1	2	3	4	5
6. Poor concentration	1	2	3	4	5

7. How strong is your current urge to smoke? (Circle one number.)

No urges	Slight	Moderate	Strong	Very strong	Extremely strong
0	1	2	3	4	5

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Source: West R and Hajek P. 2004. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. Psychopharmacology 177:195-199.