A Randomized Controlled Six-way Crossover Study to Characterize the Nicotine Pharmacokinetics of a Novel Oral Nicotine Pouch Product

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Abstract

Aim: Adults who use moist smokeless tobacco products (MST) exclusively or in conjunction with cigarettes may benefit by switching to oral tobacco-derived nicotine (OTDN) products that are devoid of many harmful and potentially harmful constituents found in MST. Since nicotine is one of the primary drivers for switching, the objective of this study was to characterize the nicotine pharmacokinetics (PK) and pharmacodynamics (PD, subjective responses) of an OTDN pouch compared to MST products.

Methods: In this randomized, controlled, six-way crossover, confinement study among adults who use MST (n=54), we compared nicotine PK and PD of five nicotine pouches (Test) against a self-selected pinch of own brand MST (OBMST, Control). Participants were established MST users with no intentions of quitting in the next 6 months. The Test Products contained tobacco-derived nicotine, food-grade flavors, and humectants in a cellulose base, encased in a novel pouch material. Test products were Wintergreen (6, 9, and 12 mg nicotine), Mint (9 mg), and Tobacco (9 mg).

Results: C_{max} and $AUC_{0\text{-}180}$ were significantly lower for the 6 and all 9 mg pouches compared to OBMST. While the PK parameters were significantly higher for the 12 mg product overall, they were not significantly different among a subgroup of participants (~60%) using ≥ 3 g OBMST (representing current estimated population average). T_{max} values were similar across all products. Participants preferred OBMST over all Test products on every measure of subjective responses, including satisfaction, product pleasantness, urge to use, and craving OBMST. There were no serious adverse experiences (AEs) reported, and 16 mild and moderate Test product-related AEs, which were resolved.

Conclusions: Our findings suggest that the nicotine delivery from the Test products may be adequate for adults who use MST to switch. These findings support the harm reduction potential of the Test products.

Introduction

Background: Although moist smokeless tobacco (MST) use is not as prevalent as cigarette smoking, approximately 5.7 million United States adults (2.3%) reported they were currently using MST in a 2020 survey.[1] MST products contain harmful and potentially harmful constituents (HPHCs) of which some are classified as carcinogens by the FDA.[2] Therefore, innovative alternative products with low or non-quantifiable levels of HPHCs may present a potential to reduce harm among adult MST users or dual users who switch completely from MST products and combustible cigarettes to the test products.

Purpose: The purpose of this study was to develop scientific evidence to address the regulatory guidance set forth by the Food and Drug Administration (FDA) regarding assessment of abuse liability in support of premarket tobacco product applications (PMTAs).[3] This study characterized the nicotine PK profile and subjective measures of the five OTDN test pouch products relative to OBMST, to inform the abuse liability assessment.

Methods

Healthy adult MST users, age 22-65, were recruited for this in-clinic confinement study. Subjects were daily MST users for at least one year and used at least ½ can daily for the past 30 days. Published literature has reported a wide range of individual pinch masses, with an average range of 1.97 g to 2.99 g,[4-7] used for ~40-60 min. Therefore, recruitment stipulations included a minimum pinch mass of 2 g for all subjects, and 3 g for 50% of subjects. Safety labs for all subjects and pregnancy tests for female subjects were conducted at Screening, and a demonstration of each subject's ability to use their self-selected OBMST pinch for 45 minutes. Subjects were then sent home for at minimum 5-days of *ad libitum* test product use and returned to the clinic to 1) attest to their willingness to use all study products, 2) repeat pregnancy tests for female subjects, and 3) demonstrate their ability to use the test products for 45 min. On Day -1 subjects reported to the clinic, pregnancy tests were again repeated for female subjects, and subjects were randomized to one of six product use sequences. Each afternoon, Day -1 through Day 5, subjects completed a 2-hr *ad libitum* use session during which they could use up to two test product pouches or two self-selected pinches of OBMST non-simultaneously; the test product used during *ad libitum* use was the same that was to be used the following day during Controlled Use. Following overnight abstinence on Days 1 through 6 subjects were instructed to use that day's test product for a 45 min Controlled Use session. Blood was sampled at -5 min before test product use and again at 5/15/30/40/45/50/60/90/120/180 min after the start of product use. Four PD questionnaires were administered: the mCEQ was administered after *ad libitum* use, the Smokeless Urge and Craving questionnaire was administered at 5 min before and at 5/15/30/45/60/120/180 min after product use began, the Product Effects questionnaire was administered at 5/15/30/45/60/120/180 min after product use began, and the Use the Product Again questionnaire was administered after the 180 min blood draw. Post-hoc analyses were performed across all measures for subjects who used ≥ 3 g and < 3 g of OBMST.

Results

Average self-selected pinch masses for OMBST were as follows: Overall population (n=54)- 4.00 g, ≥ 3 g subgroup (n=32)- 5.06 g, < 3 g subgroup (n=22)- 2.46 g.

Nicotine PK results for the overall study population revealed a C_{max} and AUC that were statistically significantly higher for OBMST than four of the five test products; C_{max} and AUC were significantly higher for the 12 mg Wintergreen test product than OBMST. The post-hoc analyses revealed that for subjects whose self-selected OBMST pinch was ≥ 3 g, C_{max} and AUC for the 12 mg Wintergreen test product and OBMST were not statistically significantly different. Flavors do not appear to impact nicotine pharmacokinetics.

Subjective responses were similar across test products for the overall population and the ≥ 3 g and < 3 g subgroups. Subjects reported that while all test products relieve urges to use MST and craving MST, their OBMST product was most effective at relieving craving and urges to use. While most subjects across the overall population and the ≥ 3 g and < 3 g subgroups reported a willingness to use the test products again, generally, the highest ratings to use again were for subjects' OBMST.

18% of subjects reported an adverse experience (AE) (32 total). AEs most reported were headache, dizziness, and hiccups, and only one AE was moderate (syncope). The number of product related AEs per test product were as follows: 3 (6 mg Wintergreen), 7 (9 mg Wintergreen), 2 (12 mg Wintergreen), 3 (9 mg Mint), 1 (9 mg Tobacco) and 5 (OBMST). There does not appear to be a dose-response relationship with any reported AEs.

Conclusions

The heterogeneity of MST use behaviors suggests that consumers may require a variety of potentially reduced harm products to suit different use behaviors. Our findings indicate that while the 12 mg Wintergreen test product delivers more nicotine than OBMST for the Overall Population and the < 3 g subgroup, C_{max} and AUC were comparable for subjects who use more than 3 g of OBMST per pinch.

Results of the subjective responses indicate that the OTDN test products were able to relieve urges to use and craving, were pleasant and satisfying, and were products that subjects would use again. However, on almost every subjective measure the responses were greatest for OBMST.

Our study is limited by the specific population recruited, whose larger pinch mass use patterns may not necessarily reflect the overall population of adult MST users. Additionally, while literature suggests that use duration is ~45-60 min, the controlled use conditions of 45 min may either under- or overestimate nicotine delivery for adult users with a shorter or longer use duration.

Our data informs the abuse liability assessment of these test nicotine pouches. Given the wide range of MST use behaviors our findings suggest that a range of products with different nicotine levels and flavors presents a viable substitute for subjects' OBMST, thereby presenting a harm reduction opportunity for adults who use MST products.

References

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Study Design, Subjects

Figure 1: Study flow: randomized, controlled, 6-way crossover, single-blind study design.

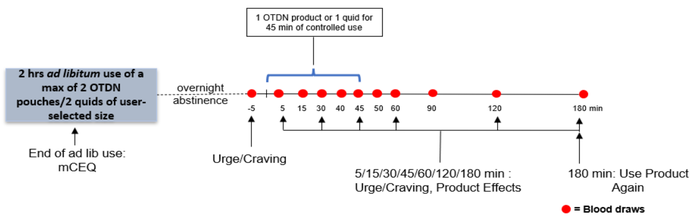

Table 1: Qualifying Products -OBMST*

Copenhagen®
• Snuff Fine Cut
• Original Long Cut
• Mint Long Cut
• Wintergreen Long Cut
Skoal®
• Mint Long Cut
• Straight Long Cut
• Wintergreen Long Cut
Grizzly®
• Mint Long Cut
• Natural Long Cut
• Wintergreen Long Cut

Table 2: Subject Demographics

Subjects	
Male	98%
Female	2%
AIAN	5%
Black	7%
White	86%
Mixed	2%
Hispanic or Latino	5%
Not Hispanic or Latino	95%
Age	35.2 (10.9, median 32.5)
BMI	29.9 (4.8)
Cans of MST per Day	0.9 (0.34)
Years Dipped	12.1 (11.23; median 10, range 1-50)

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Questionnaires

Smokeless Urge and Craving Questionnaire

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line. 1. Urges to use smokeless, 2) craving smokeless.

Not at All — Extremely (100 mm)

Use the Product Again Questionnaire

Please respond to the following statement based on your experience with the product you used today.

If given the opportunity, I would want to use this product again.

Definitely Would Not — Don't Care — Definitely Would (-50 to 50, 100 mm)

Product Effects Questionnaire

Not at All — Extremely (100 mm)

1. Is the product "Pleasant" right now?
2. Is the product "Satisfying" right now?
3. Is the product making you feel "Head Rush" right now?
4. Is the product making you feel "Stimulated" right now?
5. Is the product making you feel "Active, Alert, or Energetic" right now?
6. Is the product making you feel "Shaky or Jittery" right now?
7. Is the product making you feel "Nauseated, Queasy or Sick" right now?

Modified Cigarette Evaluation Questionnaire (mCEQ)

Please mark the number that best represents how using the product made you feel (1-not at all, 2-very little, 3-a little, 4-moderately, 5-a lot, 6-quite a lot, 7-extremely).

1. Was using the product satisfying?
2. Did the product taste good?
3. Did you enjoy the sensation in your mouth?
4. Did using the product calm you down?
5. Did using the product make you feel more awake?
6. Did using the product make you feel less irritable?
7. Did using the product help you concentrate?
8. Did using the product reduce your hunger for food?
9. Did using the product make you feel dizzy?
10. Did using the product make you nauseous?
11. Did using the product immediately relieve your craving for your usual brand smokeless product?
12. Did you enjoy using the product?

Pharmacokinetics and Subjective Responses

Figure 2

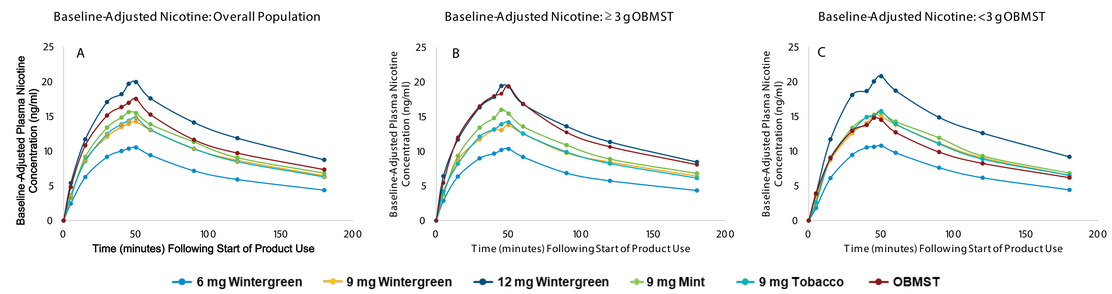

Figure 2 (left): Baseline-adjusted plasma nicotine concentrations. A) Overall Population - C_{max} and AUC were statistically significantly higher for the 12 mg Wintergreen test product than OBMST ($p=0.0005$, $p<0.0001$, respectively). All other test products were statistically lower than OBMST. B) ≥ 3 g Subgroup - C_{max} and AUC for 12 mg Wintergreen and OBMST were not statistically different ($p=0.4878$, $p=0.2959$, respectively), but all other test products were statistically lower than OBMST. C) < 3 g Subgroup - C_{max} and AUC were statistically significantly higher for 12 mg Wintergreen ($p<0.0001$ for both) than OBMST, the 6 mg Wintergreen product was statistically significantly lower than OBMST ($p<0.0001$ for both), and the 9 mg test products were not statistically different from OBMST.

Figure 3

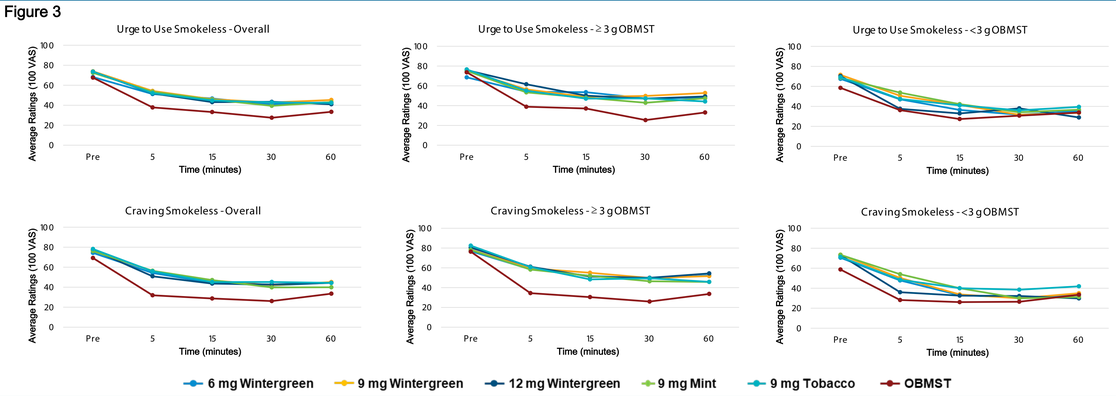

Figure 3 (left): Results of the Smokeless Urge and Craving Questionnaire indicate a similar time course of responses across all study products, and similar responses were observed among the five OTDN test products regardless of nicotine level or flavor. OBMST products provided the greatest reduction in urge and craving. Findings were similar between the overall population and the ≥ 3 and < 3 g subgroups. Relief from urge and craving tended to be greatest around 30 min.

Figure 4

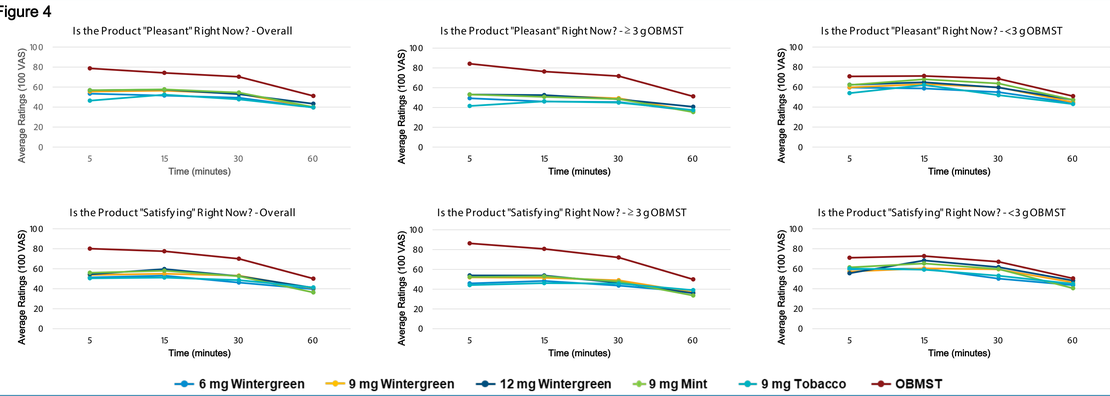

Figure 4 (left): Results of the Product Effects Questionnaire indicate a similar time course of responses across all study products, and similar responses were observed among the five OTDN test products regardless of nicotine level or flavor. Responses were highest for OBMST vs. study products and were similar between the overall population and the ≥ 3 and < 3 g subgroups. Responses tended to be highest at 5 min, the earliest timepoint after the start of product use, and decreased gradually over time.

Figure 5 (below): Results of the Modified Cigarette Evaluation Questionnaire indicate similar responses across the five factors. Responses were highest for OBMST vs. study products, were similar across the nicotine levels and flavors tested, and were similar between the overall population and the ≥ 3 and < 3 g subgroups.

Figure 5

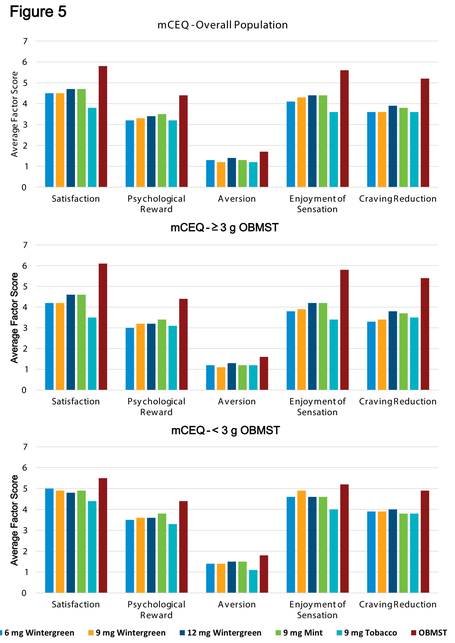

Table 3: Use the Product Again

Subjects	6 mg Wintergreen	9 mg Wintergreen	12 mg Wintergreen	9 mg Mint	9 mg Tobacco	OBMST
Overall Population						
-50 to < 0	30.9%	29.6%	23.1%	28.3%	41.8%	14.8%
0	3.6%	5.6%	7.7%	1.9%	3.6%	3.7%
> 0 to 50	65.5%	64.8%	69.2%	69.8%	54.5%	81.5%
≥ 3 g Subgroup						
-50 to < 0	33.3%	30.3%	23.3%	32.3%	50.0%	12.5%
0	3.0%	3.0%	13.3%	3.2%	5.9%	0.0%
> 0 to 50	63.6%	66.7%	63.3%	64.5%	44.1%	87.5%
< 3 g Subgroup						
-50 to < 0	27.3%	28.6%	22.7%	22.7%	28.6%	18.2%
0	4.5%	9.5%	0.0%	0.0%	0.0%	9.1%
> 0 to 50	68.2%	61.9%	77.3%	77.3%	71.4%	72.7%

Table 3 (above): Results of the Use the Product Again Questionnaire show most subjects expressed a positive willingness to use the test products again. Almost uniformly, the highest percentage of subjects expressing a willingness to use the product again was reported following use of their OBMST. A very small percentage of subjects were ambivalent about using any of the products again, across nicotine levels, flavors, and population/subgroup.

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