Assessment of Abuse Potential of a Moist Smokeless Tobacco Product Relative to Cigarette and Nicotine Gum Based on Nicotine Pharmacokinetics and Subjective Effect Measures

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Abstract

Abuse potentials of a compound are usually studied using pharmacokinetic approach and subjective measures. We used an open-label, randomized, two-stage, three-way crossover study with n=24 adult subjects who primarily smoke to evaluate nicotine pharmacokinetics (PK), subjective effects, and product use behavior of a test moist smokeless tobacco product (MST) relative to cigarettes (CIG), and nicotine polacrilex fresh mint chewing gum 4 mg (NG). During the first stage, subjects were randomly assigned to 3 sequences (4-hour ad libitum use with one product per day over 3 days). Questionnaires on Smoking Urges-Brief, Modified Cigarette Evaluation and Use the Product Again were administered before and/or at the end of 4-hour product use. Following a one-day wash-out after the first stage, the second stage began and subjects received one of the three products and used it under controlled conditions (i.e., using 2 g MST for 30 min; 10-puff smoking of a CIG; using one 4-mg NG for 30 min) with one product per day over 3 days. PK blood samples and responses (visual analogue scale, VAS) to Tobacco/Nicotine Withdrawal and Direct Effects of Product questionnaires were collected at pre-determined time points during each product use. During the 4-hour ad libitum use (Stage 1), a median of 2 quids of MST were used for ~39 min each; 7 CIG were smoked, and 4 NGs were used over ~27 min each. The proportion of subjects who indicated they would use the product again were 42%, 83%, and 63% for MST, CIG, and NG, respectively. During controlled use (Stage 2), plasma nicotine Cmax (geometric least squared mean, ng/mL) for MST (12.38) was slightly lower than CIG (14.10) but statistically significantly higher than NG (4.94). The maximum reduction from pre-use in "Urges to Smoke" VAS scores (least squared mean) for MST (38.51) was not statistically significantly different from either CIG (44.67) or NG (29.40). The maximum VAS scores in response to "Is the Product Pleasant Right Now" following the product use for MST (62.42) was statistically significantly lower than CIG (77.00) and statistically significantly higher than NG (59.00). We conclude that the abuse potential of the test MST product in the population studied is lower than CIGs and similar or higher than NG.

Background

Abuse potential of a new tobacco product is usually studied using pharmacokinetic and subjective effect measures. The purpose of this study is to develop scientific evidence to assess abuse potentials of a moist snuff tobacco (MST) product through nicotine plasma pharmacokinetic and subjective effects measurements in adult smokers who also use MST.

Objectives

- To characterize the nicotine PK profile of a test MST product relative to subject's own brand cigarettes and nicotine gum under controlled use conditions; and
- To evaluate the subjective effects of a test MST product relative to subject's own brand cigarettes and nicotine gum; and
- To characterize the product use behavior of a test MST product, subject's own brand cigarettes, and nicotine gum under ad libitum use conditions

Methods

Table 1. Study Products

A	A moist snuff tobacco product (test product)
B	Subjects own brand cigarettes (reference product)
C	Nicorette® Fresh Mint™ nicotine polacrilex gum, 4 mg (reference product)

Table 2. Study Population

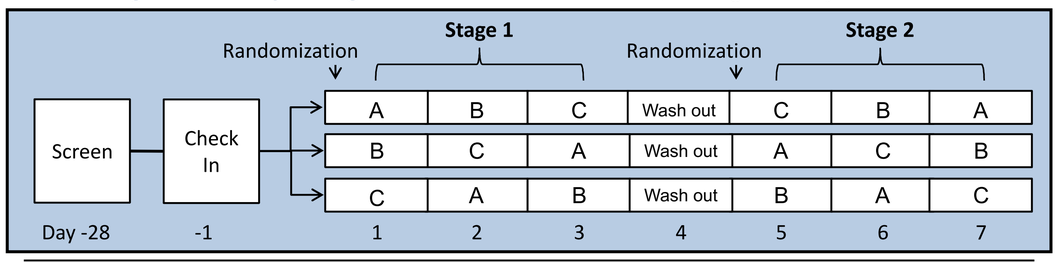
Healthy adult (age: 21 – 65 years) smokers who are also MST dippers

- Smoke ≥10 cigarette per day for at least one year
- Use "Natural", "Original", "Regular" MST at least 20 times in lifetime and on some days in the past 30 days

Number of Subject	24
Male	19
Female	5
Age (year)	39.6 (12.5)
Body Weight (kg)	96.6 (16.5)
Height (cm)	175.7 (6.6)
BMI (kg/m^2)	31.0 (5.1)
Tobacco Use History	
CPD/Smoke years	13.8 (3.8)/19.7 (10.8)
Cans per day/MST years	0.3 (0.3)/13.4 (11.8)
Quid per day/Minutes in mouth	2.2 (1.8)/33.7 (20.6)

Data are shown as Mean (SD)

Figure 1. Study Design Randomized, controlled, 2-stage, 3-way crossover



Product Use							
4-hour ad libitum use	X	X	X				
Controlled use[a]					X	X	X
PK Blood Sampling[b]					X	X	X
Subjective Measures (Questionnaires)							
QSU-Brief[c]	X	X	X				
mCEQ[d]	X	X	X				
Use the Product Again[e]	X	X	X		X	X	X
Tobacco/Nicotine Withdrawal[f]					X	X	X
Direct Effect of Product[g]					X	X	X

a. A: using a 2 g MST quid for 30 min; B: smoking 1 cigarette with 10 puffs at 30-second inter-puff-intervals; C: using 1 piece of 4 mg nicotine gum for 30 min according to the product's instructions
b. Blood draw at 5 min prior to and 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 120, and 180 min following the start of product use
c. Questionnaire on Smoking Urge-Brief, administered prior to and at the end of the 4-hour session
d. Modified Cigarette Evaluation Questionnaire, administered at the end of the 4-hour session
e. Administered at the end of the 4-hour ad libitum use, and at 3 hours after the start of controlled product use
f. Administered prior to and at 5, 15, 30, and 60 min after the start of product use
g. Administered at 5, 15, 30, and 60 min after the start of product use

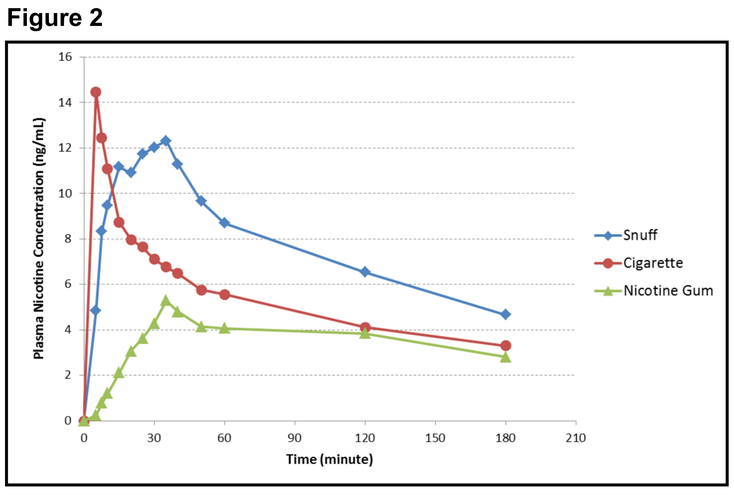
Primary Endpoints

- Maximum plasma nicotine concentration (C_{max}) measured following the product use.
- Maximum reduction in VAS score of "Urges to smoke" ($E_{max\text{-}urge}$) following the product use under controlled use conditions.
- Maximum VAS score of "Pleasant" ($E_{max\text{-}pleasant}$) following the product use under controlled use conditions.

Results

Group Mean Plasma Nicotine Concentrations (Baseline-Adjusted)

Figure 2



Plasma Nicotine PK Parameters

Table 3. Plasma Nicotine PK Parameters

	$C_{max\ (0\text{-}180)}$ (ng/mL)	$AUC_{(0\text{-}180)}$ (min•ng/mL)	$T_{max(0\text{-}180)}$ (min)
MST Snuff	12.38†	1306.11*†	28.58
Cigarette	14.10†	902.83†	8.188
Nicotine Gum	4.94	528.82	53.58

Data shown as geometric LS mean
* statistically significantly different from cigarette
† statistically significantly different from nicotine gum

Subjective Measures: Response Scores (median VAS scores)

Figure 3a. Urges to Smoke

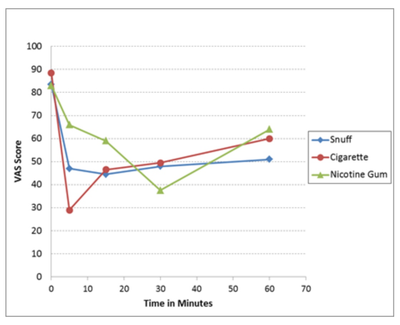
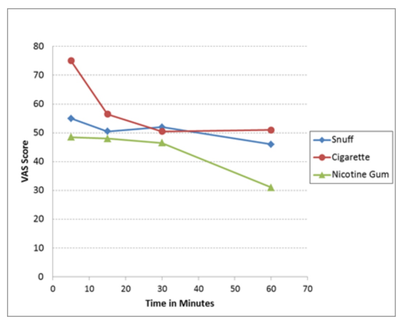


Figure 3b. Is the Product "Pleasant" Right Now



Subjective Measures: LS Mean of $E_{max\text{-}urge}$ and $E_{max\text{-}pleasant}$

Table 4. LS Mean of $E_{max\text{-}urge}$ and $E_{max\text{-}pleasant}$

	$E_{max\text{-}urge}$	$E_{max\text{-}pleasant}$
MST Snuff	38.51	62.42*
Cigarette	44.67†	77.00†
Nicotine Gum	29.40*	59.00*

$E_{max\text{-}urge}$ = Maximum reduction of VAS scores from pre-use in response to the question "Urges to smoke"
$E_{max\text{-}pleasant}$ = Maximum VAS score recorded in response to the question "Is the product "pleasant " right now"
* statistically significantly different from cigarette
† statistically significantly different from nicotine gum

Subjective Measures: Tobacco/Nicotine Withdrawal (E_{max})

Tobacco/Nicotine Withdrawal Questionnaire[1]

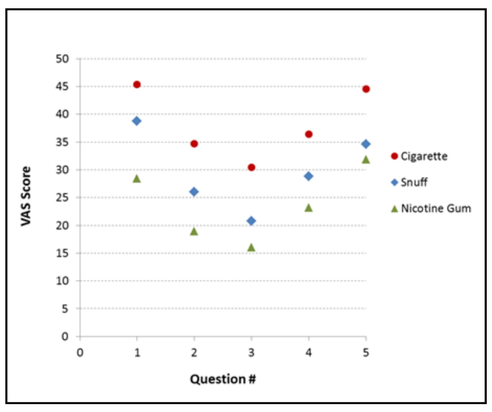
These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

Not at All ——— 100 mm ——— Extremely

1. Urges to smoke
2. Anxious
3. Difficulty Concentrating
4. Impatient
5. Craving a Cigarette

[1]Adapted from: *Hughes JR, Hatsukami D (1986) Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry. 43:289-294.*

Figure 4. Maximum Reduction in Response Scores to Tobacco/Nicotine Withdrawal Questionnaire



Subjective Measures: Direct Effect of Product (E_{max})

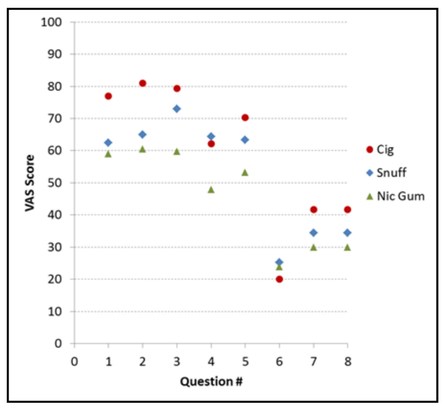
Direct Effects of Product[2]

Not at All ——— 100 mm ——— Extremely

1. Is the product "Pleasant" right now
2. Is the product "Satisfying" right now
3. Is the product making you feel "Calm" right now
4. Is the product helping you "Concentrate" right now
5. Is the product making you feel more "Awake" right now
6. Is the product making you feel "Sick" right now?
7. Is the product reducing your "Hunger" for food right now?
8. Would you like "More" of the product right now?

[2]Items were selected based on measures of product effects used in previous trial (*Hanson, O'Connor, Hatsukami, 2009*) with e-vapor products and conventional cigarettes.

Figure 5. Maximum Response Scores to Direct Effects of Product Questionnaire



Product Use

Table 5. Product Use (ad libitum 4 h)

Study Product	Trait	Statistics
MST Snuff	Number of Quids Used	2.3 ± 1.27 (1, 5)
	Use Time per Quid (min)	37.18 ± 24.154 (2.0, 110.0)
	Quid Size per Quid (mg)	2461.19 ± 2355.551 (55.0, 10703.0)
Cigarette	Number of Cigarettes Smoked	7.0 ± 2.29 (4, 11)
	Smoke Time per Cigarette (min)	12.60 ± 5.367 (5.9, 22.3)
Nicotine Gum	Number of Gums Used	3.9 ± 2.79 (1, 11)
	Use Time per Gum (min)	29.49 ± 20.617 (8.0, 109.5)

Data shown as mean ± SD (range)

Summary

- Nicotine PK profile (C_{max}) for the Test MST product was similar to cigarette, but higher than the nicotine polacrilex gum.
- The subjective effects ($E_{max\text{-}urges}$ and $E_{max\text{-}pleasant}$) were lower for the Test MST product as compared to cigarettes and higher as compared to nicotine polacrilex gum, with only statistically significant difference observed for $E_{max\text{-}pleasant}$
- The use behavior under ad libitum conditions for the Test MST product was generally lower than cigarettes and nicotine polacrilex gum.

Conclusion

- Based on the pharmacokinetic profile (lower C_{max}, longer T_{max}) and subjective effects (lower maximum responses) measured in our study, the abuse potential of the Test MST Product appears to be lower than that of cigarette smoking.
- Based on the pharmacokinetic profile (higher C_{max}, shorter T_{max}) and subjective effects (higher/similar maximum responses) measured in our study, the abuse potential of the Test MST Product appears to be greater than, or similar to, that of nicotine polacrilex gum.