Characterization of Nicotine Pharmacokinetics from on!® Nicotine Pouches in Adult Smokers

Scott Rensch, Andrea Vansickel, Jeff Edmiston, Jingzhu Wang, Jianmin Liu, Mohamadi Sarkar
Altria Client Services LLC, Richmond, VA, USA

SRNT 26th Annual Meeting
March 11-14, 2020, New Orleans, LA, USA

http://sciences.altria.com

Altria

This scientific research is presented by Altria Client Services LLC (ALCS). ALCS affiliate companies are tobacco product manufacturers.

ABSTRACT

Significance: on!® nicotine pouches are oral tobacco-derived nicotine products available in multiple nicotine strengths and flavors.
Methods: A randomized seven-way crossover study with adult smokers was used to characterize the nicotine pharmacokinetics (PK) of 4mg on!® nicotine pouches using six flavor variants (Berry, Cinnamon, Citrus, Coffee, Original, and Wintergreen) relative to subject's own brand cigarettes. Prior to the in-clinic stay, qualified adult smokers were supplied one pack (20 pouches) of each of the six flavors for a three-day *ad libitum* product trial. During the clinic visit, n=42 adult smokers (17 female) were randomly assigned to one of seven product use sequences. Each product was used for four hours *ad libitum* the afternoon before PK assessments on a single product use (one pouch for 30 minutes or one cigarette smoked in five minutes).
Results: Plasma nicotine maximum concentration (C_{max}, Geometric Least Square Mean [LSM], ng/mL) for the on!® nicotine pouches ranged from approximately 9.1 to 11.5 and were statistically significantly lower than the cigarette (~16.3). The median time (minutes) to maximum plasma nicotine concentration ranged from approximately 30.1 to 34.9 for the on!® nicotine pouches compared to 7.5 for the cigarette. The area under the curve (AUC, LSM, ng*min/ml) for the on!® nicotine pouches ranged from approximately 860 to 1118 compared to 1008 for the cigarette.
Conclusion: We conclude that based on the nicotine PK parameters, under the study conditions, the 4mg on!® nicotine pouches may have lower abuse potential than cigarettes.

BACKGROUND & PURPOSE

BACKGROUND

There is overwhelming scientific evidence regarding a risk continuum in the range of tobacco products available currently in the market. According to this body of evidence, combustible tobacco products such as conventional cigarettes are the most risky and non-combustible tobacco products present relatively lower risks.[1] Many adult cigarette smokers and smokeless tobacco (ST) users (including dual users of cigarettes and ST products) are seeking alternatives to their current products.
The test products used in this study were pouch products containing tobacco-derived nicotine and flavors. These nicotine pouch products are currently marketed under the brand name of on!®. The on!® nicotine pouches are innovative oral tobacco products that do not contain cut, ground, powdered, or leaf tobacco – a point of differentiation compared to smokeless tobacco products currently commercially marketed in the US. The on!® nicotine pouches are intended for adult smokers and ST users (including dual users of cigarettes and ST 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).[2] The study was designed to investigate the reinforcing effects of oral tobacco-derived nicotine (TDN) pouch products currently marketed as on!® nicotine pouches, relative to adult subject's own brand combustible cigarettes, as well as to characterize product use behavior under *ad libitum* use conditions. The relative reinforcing effects of the on!® nicotine pouches may provide evidence to assess their abuse potential relative to subject's own brand combustible cigarettes amongst adult (21 - 65 years of age) smokers.

OBJECTIVES

- To compare the nicotine pharmacokinetic (PK) profiles and nicotine delivery of six flavors of 4mg on!® nicotine pouches relative to subject's own brand cigarettes under controlled use conditions.
- To compare the subjective effects of six flavors of 4mg on!® nicotine pouches relative to subject's own brand cigarettes under controlled use conditions.

METHODS

STUDY PRODUCTS

Six Flavors of the on!® nicotine Pouches at the 4mg Nicotine Level and Subjects Provided Their Own Brand Combustible Cigarettes

Table 1. Study Product & Product Characterization

Product ID	Product Name	Flavor	Target Nicotine Per Pouch	Est. Nicotine Per Pouch
A	on!®	Original	4mg	3.47
B	on!®	Wintergreen	4mg	3.59
C	on!®	Cinnamon	4mg	3.80
D	on!®	Citrus	4mg	3.82
E	on!®	Berry	4mg	3.80
F	on!®	Coffee	4mg	3.30
G	Cigarette	-	-	-

STUDY DESIGN

Study Title: A Randomized, Controlled, Crossover Clinical study to Characterize the Nicotine Pharmacokinetics and Subjective Effects of Six on!® Nicotine Pouch Products Relative to Combustible Cigarettes in Adult Smokers.

Key Inclusion/Exclusion Criteria:

Inclusion Criteria
- Voluntary consent
- Healthy adult males & females 21 to 65 years of age
- Self-affirmed adult exclusive smokers of combustible manufactured cigarettes (at least 10 per day, for at least 12 months)
- Positive urine cotinine (≥500 ng/mL at screening)

Exclusion Criteria
- Use of any TDN pouch products within the 30 days prior to screening
- Attempted to quit smoking in the 3 months prior to Day -1
- Self-reported puffers (draw smoke into mouth but don't inhale)
- Planning to quit smoking or postponement of quitting smoking

Figure 1. Study Design

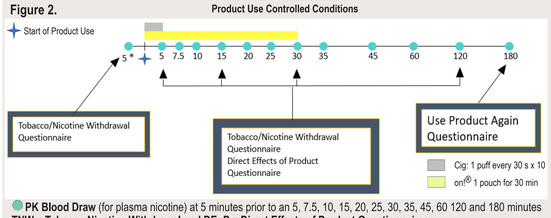
Product Randomization Sequences

	Screen	Product Trial					Check-in	
	A	B	G	C	F	D	E	
	B	C	A	D	G	E	F	
	C	D	B	E	A	F	G	
	D	E	C	F	B	G	A	
	E	F	D	G	C	A	B	
	F	G	E	A	D	B	C	
	G	A	F	B	E	C	D	
Study Day	-28	-6	-2	-1	1	2	3	4	5	6	7
Randomization				X							
Ad Libitum Product Use		X	X	X	X	X	X	X	X	X	X
Controlled Product Use					X	X	X	X	X	X	X
PK Sampling [a]					X	X	X	X	X	X	X
Questionnaires				X	X	X	X	X	X	X	X
Product Use Documentation		X[b]	X	X	X	X	X	X	X	X	X

[a] PK blood draw at approximately 5 minutes prior to and 5, 7.5, 10, 15, 20, 25, 30, 35, 45, 60, 120 and 180 minutes following start of each product use
[b] Subjects were required to complete a diary during the at home product trial to track use of on!® product

PRODUCT USE, QUESTIONNAIRE & PK BLOOD DRAW

Figure 2. Product Use Controlled Conditions



PK Blood Draw (for plasma nicotine) at 5 minutes prior to an 5, 7.5, 10, 15, 20, 25, 30, 35, 45, 60 120 and 180 minutes
TNW = Tobacco Nicotine Withdrawal and DEoP = Direct Effects of Product Questionnaires
(Scoring: 0 = Not at All, 100 = Extremely):
[a] – 5 minutes prior to start of product use [b] – after the scheduled blood draw at 5, 15, 30 & 60 minutes
Use Product Again Questionnaire (Scoring 0 = Definitely Would Not, 50 = Don't Care, 100 = Definitely Would):
– 2 minutes after 180 min blood draw
*is presented as time point 0 in the results

RESULTS

STUDY POPULATION

Table 2. Study Population Characteristics

Number of Subjects	42
Male	25 (60%)
Female	17 (40%)
Age (yrs)	41.5 (SD 10.66)
Weight (kg)	82.90 (SD 18.96)
Height (cm)	172.3 (SD 10.86)
BMI (kg/m^2)	27.7 (SD 5.12)
CPD	16.5 (SD 5.06)

GROUP MEAN PLASMA NICOTINE CONCENTRATIONS (BASELINE ADJUSTED) OVER TIME

Figure 3.

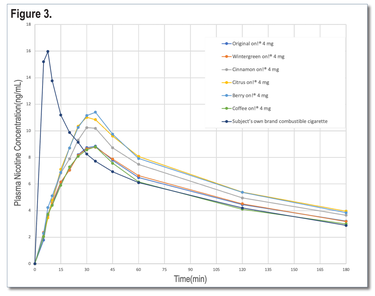


Table 3. Plasma Nicotine PK Parameters

on!® 4mg Nicotine Pouch/Cig	C_{max}[a] (ng/mL)	95% CI	AUC[a] (ng*min/mL)	95% CI	T_{max}[b] (min)
Original	9.31	8.37-10.36	931.4	840.41-1032.26	31.50
Wintergreen	9.53	8.57-10.60	935.9	844.42-1037.19	31.87
Cinnamon	10.94	9.83-12.17	1051	948.37-1164.86	31.57
Citrus	11.49	10.33-12.78	1118	1008.89-1239.20	32.88
Berry	11.23	10.10-12.48	1092	986.27-1210.05	33.20
Coffee	9.07	8.16-10.08	860	776.41-952.58	31.70
Cigarette	16.32	14.68-18.14	1008	910.22-1116.75	7.93

a-C_{max} and AUC values are Geometric LS Mean values, 95% CI, p-value <.0001.
b-T_{max} values are arithmetic Mean.

TOBACCO/NICOTINE WITHDRAWAL QUESTIONNAIRE (MEAN VAS SCORES)

Figure 4.

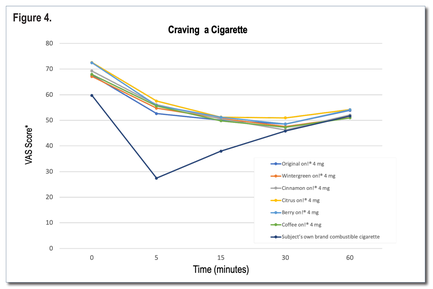


Figure 5.

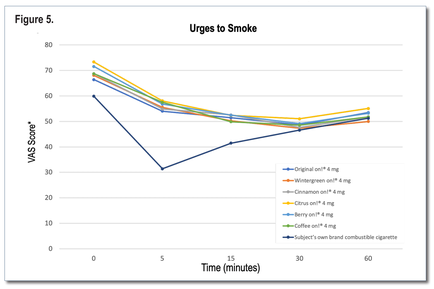


Table 4. Maximum Change from Baseline: Urge to Smoke, Craving a Cigarette

Study Product	Urge to Smoke (LS Mean*)	Craving Cigarette (LS Mean*)
Original on!® 4mg	22.48	25.25
Wintergreen on!® 4mg	25.10	25.96
Cinnamon on!® 4mg	26.76	26.99
Citrus on!® 4mg	27.07	27.29
Berry on!® 4mg	29.37	30.51
Coffee on!® 4mg	24.21	25.53
Cigarette	31.88	35.38

*LS means: Max change from baseline; least square means from statistical model

DIRECT EFFECT OF PRODUCT

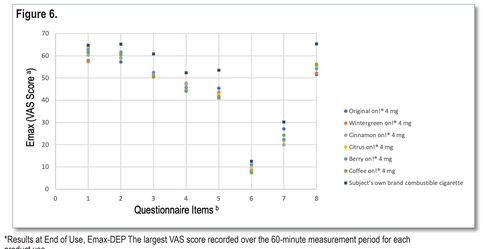
VAS Direct Effects of Tobacco Questions (Items were selected based on measures of product effects used in previous trials with conventional cigarettes and other tobacco products)

Note: Each question will be paired with a VAS. The VAS anchored with "Not at All" on the left and "Extremely" on the right. Subjects place a vertical line at the place along the VAS based on how he/she feels in the moment.

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?

Figure 6.



*Results at End of Use, Emax-DEP The largest VAS score recorded over the 60-minute measurement period for each product use.
a VAS Score: 0 (Not at All), 100 (Extremely)
b Questionnaire Items: 1 = Pleasant, 2 = Satisfying, 3 = Feel Calm, 4 = Help Concentrate, 5 = Awake, 6 = Sick, 7 = Hungry, 8 = Would like more

Figure 7.

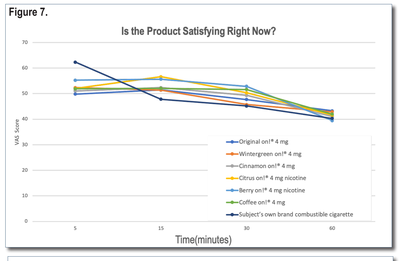
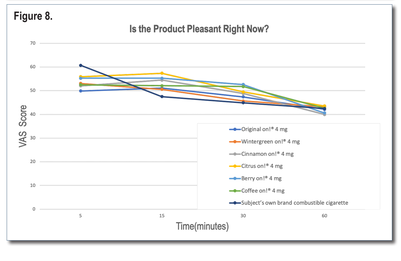
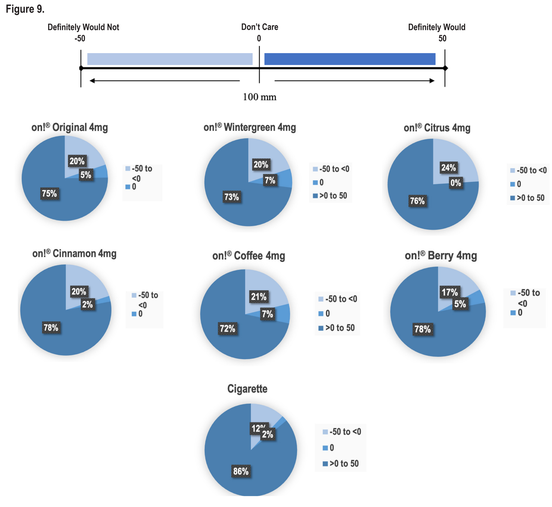


Figure 8.



USE PRODUCT AGAIN QUESTIONNAIRE

Figure 9.



CONCLUSIONS

- The rate (Cmax and Tmax) and extent (AUC) of nicotine for all 4mg on!® nicotine pouches are significantly lower than that for the cigarette.
- Self-reported outcome measures (Responses to the Tobacco and Nicotine Withdrawal, Direct Effect of Product and Use the Product Again Questions) are lower for all the on!® nicotine pouches than for cigarettes.
- The totality of this evidence suggests that the 4mg on!® nicotine pouches have lower abuse potential than cigarettes, regardless of flavor.

STRENGTHS AND LIMITATIONS

Strengths:
- Randomized design allows for assessment of test and reference product under same conditions
- Subjective measures based on questionnaires frequently referenced in literature
- Relatively large sample size compared to similar abuse liability studies

Limitations:
- Controlled use conditions may not reflect how products are actually used however subject were given a minimum of 3 days at home use and a 4-hr ad libitum use prior to PK assessments
- In-clinic setting for self-reported measures, however all assessments were done relative to a control done under the same conditions

REFERENCES

1. Hatsukami DK, Joseph AM, Lesage M, et al. Developing the Science Base for Reducing Tobacco Harm. Nicotine Tob Res 2007; Suppl 4:S537-53.
2. U.S. Department of Health and Human Services. Applications for Premarket Review of New Tobacco Products. 2011 September. http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM273425.pdf. Last accessed September 9, 2016.