Characterization of Nicotine Exposure Profiles and Subjective Measures of e-Vapor Products in Adult Smokers Relative to Conventional Cigarettes

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Abstract

Introduction: NuMark LLC markets e-vapor products (EVPs) under the MarkTen® brand. Devices consist of a battery and cartridges containing propylene glycol, glycerol, flavors and tobacco derived nicotine. The purpose of these studies was to characterize nicotine pharmacokinetics (PK) and subjective measures with use of MarkTen® EVPs by adult cigarette smokers, relative to cigarette smoking.

Method: Two studies were conducted (n=30 in each) to test 8 differently flavored EVPs (2.4–2.5 % nicotine by weight, 4 per study) versus subject's own brand cigarettes (OBC). Generally healthy cigarette smokers (21–65 years of age, smoking 5–20 cigarettes per day, no use of EVP in past 30 days) were enrolled. Each subject used one of four EVPs or OBC over a 10-minute period, under controlled use conditions (10 puffs, 30 seconds between puffs) in the morning and ad libitum in the evening.

Results: Overall, the mean Cmax values ranged from 3.15–3.75 ng/mL and 5.13–6.82 ng/mL during controlled and ad libitum use condition of the 8 EVPs, respectively. These values were statistically significantly lower ($p<0.0001$) than observed with their OBC (13.72 and 14.25 ng/mL during controlled use, 12.92 and 13.25 ng/mL during ad libitum use, in the two studies, respectively). The mean maximum reduction in "urge to smoke" for the EVPs during controlled use (32.24–38.40, on a scale of 0–100) was statistically significantly lower than for OBC (51.00 and 47.28 in the two studies, respectively). The mean maximum rating of "pleasant" (42.83–60.38, on a scale of 0–100) was statistically significantly lower for each of the 8 EVPs versus OBC (80.87 and 74.34 in the two studies, respectively).

Conclusions: On average, the nicotine PK profiles for the EVPs are lower than the subject's OBC. Subjective measures were comparable across the 8 EVPs and lower than those of the subject's OBC, however, it remains to be seen whether these outcomes change after prolonged use. Although it was not the objective of the study, the data suggest different flavor variants of the MarkTen® EVPs, used under the study conditions, do not influence nicotine PK or subjective responses.

Objectives

1. To compare the nicotine PK profiles and nicotine delivery of four Nu Mark e-vapor products relative to subject's own brand cigarettes under controlled use and ad libitum use conditions; and
2. To compare the subjective effects of four Nu Mark e-vapor products relative to subject's own brand cigarettes under controlled use and ad libitum use conditions; and
3. To characterize product use behavior of four Nu Mark e-vapor products under ad libitum use conditions.

Introduction

The Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems Guidance for Industry: DRAFT GUIDANCE (https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM499352.pdf), Section VI.H.2.b.vi. Abuse liability, states:

> "Abuse liability evaluations, including pharmacokinetic evaluations, should consider the addictiveness and abuse and misuse potential of the new product and the exposure to nicotine during product use."

The two studies described in this poster were conducted in support of our assessment of the abuse liability of MarkTen® candidate products.

Test Products

Study A

Product A = MarkTen® Test Product, Flavor A, 2.4% NBW
Product B = MarkTen® Test Product, Flavor B, 2.4% NBW
Product C = MarkTen® Test Product, Flavor C, 2.5% NBW
Product D = MarkTen® Test Product, Flavor D, 2.5% NBW
Product E = Subject's Own Brand Cigarette (Reference Product)

Study B

Product A = MarkTen® Test Product, Flavor E, 2.5% NBW
Product B = MarkTen® Test Product, Flavor F, 2.5% NBW
Product C = MarkTen® Test Product, Flavor G, 2.5% NBW
Product D = MarkTen® Test Product, Flavor H, 2.5% NBW
Product E = Subject's Own Brand Cigarette (Reference Product)

References

Tobacco & Nicotine Withdrawal: Adapted from Hughes JR, Hatsukami D (1986). Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry. 43:289-294.

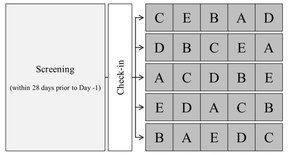
Direct Effects: Items were selected based on measures of product effects used in previous trials with e-vapor products and conventional cigarettes. Example: Hanson K, O'Connor R, Hatsukami D (2009). Measures for assessing subjective effects of potential reduced-exposure products. Cancer Epidemiology, Biomarkers & Prevention. 18:3209-3224.

Modified Cigarette Evaluation Questionnaire (mCEQ): Note: this questionnaire is generally adaptable to multiple nicotine and tobacco products as evidenced by other researcher adaptations to e-cigarettes and nicotine infusions. Examples: Rose JE, Salley A, Behm FM, Bates JE, Westman EC (2010). Reinforcing effects of nicotine and non-nicotine components of cigarettes smoke. Psychopharmacology. 210:1-12. St. Helen G, Havel C, Dempsey D, Jacob P, Benowitz NL (2016). Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes. Addiction. 111:535-544.

Use the Product Again: Adapted from Griffiths RR, Bigelow GE, Ator NA (2003). Principles of initial experimental drug abuse liability assessment in humans. Drug and Alcohol Dependence. 70:S41-S54.

Methods

Study Design



Study Day	-1	1	2	3	4	5
Randomization		X				
Product use	X[a]	X[b]	X[b]	X[b]	X[b]	X[b]
PK sampling		X	X	X	X	X
Questionnaires	X[c]	X[d]	X[d]	X[d]	X[d]	X[d]
Product Use Documentation		X[e]	X[e]	X[e]	X[e]	X[e]

a: Product trial—ad lib use of each product for 10 minutes
b: Two product use episodes per day, separated by 6 hours, with morning product use under controlled conditions (i.e., up to 10 inhalations taken at approximately 30 second intervals; 4 second puff duration, e-vapor products only) and afternoon product use under ad libitum use of one unit for 10 minutes).
c: Questionnaire training
d: Tobacco/Nicotine Withdrawal questionnaire administered at approximately 10 minutes prior to the start of each product use period. Both Tobacco/Nicotine Withdrawal and Direct Effects of Product questionnaires immediately following the scheduled PK blood draw at 5, 15, 30 and 60 minutes following the start of each product use episode. The appropriate mCEQ questionnaire will be administered immediately after each ad libitum product use episode. The Use the Product Again questionnaire administered immediately after and at 180 minutes following the start of each ad libitum product use episode.
e: Start and stop times, number of inhalations, duration of each inhalation, e-vapor cartridge weight change over each product use period

Subjects

These studies enrolled healthy adult male and female (no more than 60% of either gender) smokers 21–65 years of age, inclusive, who fulfilled the inclusion criteria and none of the exclusion criteria. Approximately 30 subjects were randomized on Day 1 to ensure that 25 subjects completed the study. All subjects were self-affirmed adult exclusive smokers of conventional cigarettes (consumption of 5–20 cigarettes per day) for at least 1 year and no other type of tobacco or nicotine containing product including e-vapor products in the past 30 days prior to Day 1. The subjects were not forced to use the tobacco/nicotine products at any time during the study.

Study A

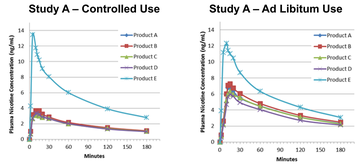
Trait	Category/Statistics	Overall
Sex	Female	12 (40%)
	Male	18 (60%)
Race	American Indian or Alaska Native	1 (3%)
	Asian	1 (3%)
	Black or African American	7 (23%)
	White	20 (67%)
	White, Black or African American	1 (3%)
Ethnicity	Not Hispanic or Latino	30 (100%)
	Hispanic or Latino	0 (0%)
Age (yrs)	Mean	38.5
	SD	12.22
Weight (lb)	Mean	179.35
	SD	31.508
Height (in)	Mean	67.0
	SD	3.50
Body Mass Index (kg/m^2)	Mean	28.211
	SD	5.2543

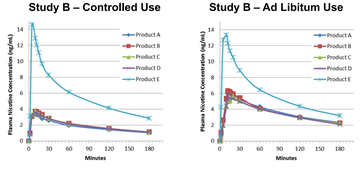
Study B

Trait	Category/Statistics	Overall
Sex	Female	16 (53%)
	Male	14 (47%)
Race	American Indian or Alaska Native	1 (3%)
	Black or African American	9 (30%)
	White	20 (67%)
Ethnicity	Hispanic or Latino	1 (3%)
	Not Hispanic or Latino	29 (97%)
Age (yrs)	Mean	36.3
	SD	10.99
Weight (lb)	Mean	180.36
	SD	28.385
Height (in)	Mean	66.8
	SD	3.49
Body Mass Index (kg/m^2)	Mean	28.524
	SD	4.1053

Results

PK





All data shown are arithmetic means.

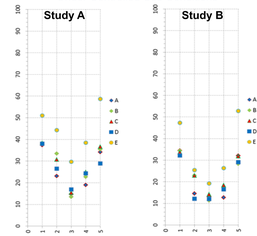
Puff Count and Duration

Ad Libitum Use

Test Product	N	Mean Puff Number	Mean Puff Duration (sec)
Study A – Ad Libitum Use Conditions			
A	29	27.8	2.58
B	29	28.0	2.70
C	30	28.3	2.65
D	29	26.7	2.51
E	30	12.5	1.94
Study B – Ad Libitum Use Conditions			
A	30	26.9	2.68
B	29	27.1	2.58
C	30	26.3	2.69
D	29	25.7	2.70
E	29	12.7	2.23

Tobacco / Nicotine Withdrawal

Under Controlled Use Conditions

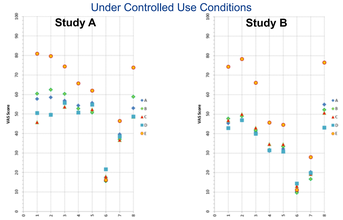


Values of Emax: maximum change from baseline for the indicated attribute

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

Direct Effects of Product Use

Under Controlled Use Conditions

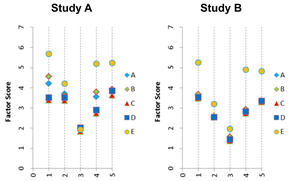


Values of Emax: maximum VAS value for the indicated attribute

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?

Modified Cigarette Evaluation Questionnaire

Under Ad Libitum Use Conditions



Scores: based on 7-point rating scale for attributes loading onto the indicated factor
When using EVP, references to "smoking" were changed to "vaping"

Factors
1. Smoking Satisfaction
2. Psychological Reward
3. Aversion
4. Enjoyment of Sensation
5. Craving Reduction

Summary

- The C_{max} under controlled use conditions for the 8 MarkTen® e-vapor products was statistically significantly lower than the C_{max} for subjects' own brand cigarettes
  - The C_{max} for the 8 MarkTen® e-vapor products under ad libitum use conditions was approximately double the C_{max} for these products under controlled use conditions
- The $E_{max\text{-}urge}$ under controlled use conditions for the 8 MarkTen® e-vapor products was statistically significantly lower than the $E_{max\text{-}urge}$ for subjects' own brand cigarettes (results under ad libitum use conditions were comparable)
- The $E_{max\text{-}pleasant}$ under controlled use conditions for the 8 MarkTen® e-vapor products was statistically significantly lower than the $E_{max\text{-}pleasant}$ for subjects' own brand cigarettes (results under ad libitum use conditions were comparable)
- Although the study was not sufficiently powered for differences between the 8 MarkTen® e-vapor products, the 8 MarkTen® e-vapor varieties appeared to have similar nicotine delivery and subjective effect profiles
  - Any observed differences may be due to differences in subjects' preference (see mCEQ results)