Characterization of Nicotine Pharmacokinetics and Subjective Effects from a Novel Oral Tobacco Product in Adult Smokers

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Abstract

VERVE® Chews (VC) is a chewable, non-dissolvable tobacco-derived nicotine (~1.5 mg/piece) novel oral tobacco product available in blue mint (VBM) and green mint (VGM) flavors. A randomized four-way crossover study with n=28 adult smokers (AS) was used to characterize the nicotine pharmacokinetics and subjective effects of VBM and VGM relative to cigarettes (CIG) and nicotine polacrilex fresh mint chewing gum (NG). Prior to the visit to the clinic, AS (n=30) were supplied 24 pieces of VBM and VGM for 5-day ad libitum product trial. Subjects recorded number of VBM, VGM or CIG used per day. During the clinic visit, n=28 AS were randomly assigned to one of 4 sequences (one piece of VGM or VGM for 30 minutes, smoked one CIG of their own brand, or chewed a 2-mg NG for 30 minutes) on separate days. Responses to Tobacco/Nicotine Withdrawal, Direct Effect of Product, Use the Product Again questionnaires were recorded on a visual analogue scale. During the product trial period, subjects used on an average ~2 pieces/day of VC and reduced their cigarette consumption by ~3 CIG relative to self-reported smoking history. Plasma nicotine Cmax (Geometric Least Square Mean [LSM], ng/mL) for VBM (2.73) and VGM (2.90) were statistically significantly lower than CIG (12.11) and higher than NG (2.04). The maximum reduction in "Urges to Smoke" Visual Analog Scale (VAS) scores (LSMean) for VBM (20.67) and VGM (24.90) were statistically significantly lower than CIG (40.41) and similar to NG (26.44). Similar results were observed for the maximum VAS scores of "Is the Product Pleasant Right Now". We conclude that under the study conditions nicotine Cmax and subjective responses from VBM and VGM are lower than CIG and are similar (Cmax) or slightly higher (subjective responses) as compared to NG. No apparent pharmacokinetic and subjective differences between the flavor variants were observed between VBM and VGM.

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 like conventional cigarettes are the most risky and non-combustible tobacco products present relatively lower risks. The two chewable tobacco-derived nicotine products tested in this study are currently available in the marketplace under the brand VERVE® Chews as innovative product alternatives to current tobacco product consumers.

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 potential in support of premarket tobacco product applications (PMTAs). The study was designed to investigate the reinforcing effects of non-combustible tobacco derived nicotine oral products currently marketed as VERVE® Chews, relative to adult subject's own brand cigarettes and nicotine replacement therapy (NRT) gum amongst adult cigarette smokers (21 and above years of age).

Objectives

1. To compare the nicotine PK profiles and nicotine delivery of two non-dissolvable tobacco-derived nicotine chewable products relative to Subject's Own Brand Cigarettes and Nicotine gum under controlled use conditions
2. To compare the subjective measures of two non-dissolvable tobacco-derived nicotine chewable products relative to Subject's Own Brand Cigarettes and Nicotine gum under controlled use conditions
3. To characterize product use behavior of two non-dissolvable, tobacco-derived nicotine chewable products under ad libitum use conditions

Study Products

- VERVE® Chews are chewable tobacco-derived nicotine products available in two flavors, Blue Mint and Green Mint, with approximately 1.5 mg of tobacco-derived nicotine per piece.

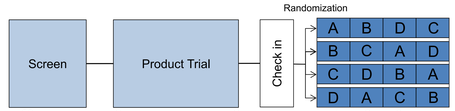
Table 1. Study Products

Product ID	Product Name	Flavor	Nicotine	Purpose
A	VERVE® Chews	Blue Mint	~1.5mg/piece	Test
B	VERVE® Chews	Green Mint	~1.5mg/piece	Test
C	Subjects' own cigarettes	-	Varies based on cigarette type	Reference
D	Nicorette® Fresh Mint™ nicotine polacrilex gum	Fresh Mint	2 mg	Reference

Methods

Study Design

Figure 1.

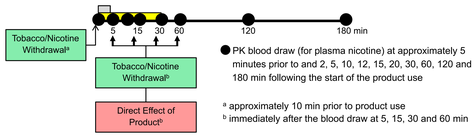


Randomization				X			
Product Use		X[a]		X[b]	X[b]	X[b]	X[b]
PK sampling				X	X	X	X
Questionnaires			X[c]	X[d,e]	X[d,e]	X[d,e]	X[d,e]
Amount of product use		X[f]					

a: Product trial - ad lib use of the test product (Verve® only) for 7 days
b: One product under controlled use condition (cigarette: 10 puffs/every 30 s; Test product/Nicotine gum: 30 min in mouth)
c: Modified Cigarette Evaluation questionnaire (mCEQ)
d: Use the Product Again questionnaire - at end of the product use
e: Tobacco/Nicotine Withdrawal and Product Effect questionnaire - at pre-determined time-points
f: Number of product used and duration in mouth

Product Use, Questionnaire & PK Blood Draw

Figure 2.



[a] approximately 10 min prior to product use
[b] immediately after the blood draw at 5, 15, 30 and 60 min

Study Population

- Healthy adult (21 years and above) smokers smoking 10 – 20 cigarettes per day (CPD) for ≥12 months

Table 2. Study Population Characteristics

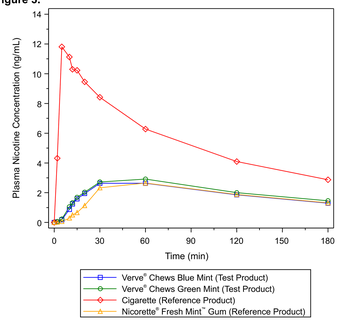
Number of Subject	28
Male	18
Female	10
Age	42.3 (13.3)
Weight (lb)	179 (33)
Height (in)	67 (3)
BMI (kg/m^2)	27.8 (4.1)
CPD	16.8 (3.6)

Data shown as mean (SD)

Results

Group Mean Nicotine Concentrations (Baseline-Adjusted)

Figure 3.



Plasma Nicotine PK Parameters

Table 3. Plasma Nicotine PK Parameters

	$C_{max\ (0\text{-}180)}$[a] (ng/mL)	$AUC_{(0\text{-}180)}$[a] (min*ng/mL)	$T_{max(0\text{-}180)}$[b] (min)
VERVE® Chews Blue Mint	2.73*†	327.11*†	45.46
VERVE® Chews Green Mint	2.90*†	348.98*†	47.16
Cigarette	12.11	946.29	11.35
Nicotine Gum	2.04	246.30	54.32

* statistically significantly different from cigarette
† statistically significantly different from nicotine gum
a: geometric LS mean; b: arithmetic mean

Subjective Measures Response Scores (median VAS scores)

Figure 4a. Urges to Smoke

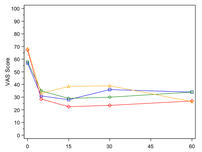
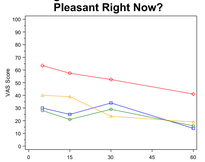


Figure 4b. Is the Product Pleasant Right Now?



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

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

	$E_{max\text{-}urge}$	$E_{max\text{-}pleasant}$
VERVE® Chews Blue Mint	20.67*	42.13*
VERVE® Chews Green Mint	24.90*	37.68*
Cigarette	40.41	74.06
Nicotine Gum	26.44	44.70

* statistically significantly different from cigarette
a. $E_{max\text{-}urge}$ = maximum reduction of VAS score from pre-use in responses to the question "Urge to Smoke"
b. $E_{max\text{-}pleasant}$ = largest VAS score recorded in responses to the question "Is the product "Pleasant" right now"

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

Tobacco/Nicotine Withdrawal Questionnaire[1]

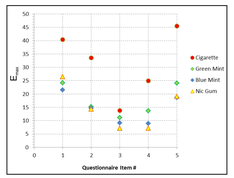
These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

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 5. Maximum Reduction in Response Scores to Tobacco/Nicotine Withdrawal Questonnaire



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

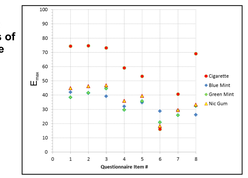
Direct Effects of Product[2]

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 6. Maximum Response Scores to Direct Effects of Product Questonnaire



Summary

- The plasma nicotine C_{max} and AUC were 2.73, 2.90 (ng/mL) and 327.11, 348.98 (min•ng/mL) for VERVE® Chews Blue Mint and VERVE® Chews Green Mint, respectively, which were statistically significantly ($p < 0.05$) lower than cigarette (12.11 ng/mL and 946.29 min•ng/mL) but comparable with nicotine gum (2.04 ng/mL and 246.30 min•ng/mL).
- The subjective measures for Urges to Smoke ($E_{max\text{-}urge}$) and for Direct Effect of Product ($E_{max\text{-}pleasant}$) were 20.67, 24.90 and 42.13, 37.68 for VERVE® Chews Blue Mint, VERVE® Chews Green Mint, respectively, which were statistically significantly ($p < 0.05$) lower than cigarette (40.41 and 74.06) but comparable with nicotine gum (26.44 and 44.70).

Conclusions

- No differences were apparent in the PK parameters and subjective responses between the two flavor variants of the VERVE® Chews, Blue Mint and Green Mint.
- The VERVE® Chews exhibits relatively lower abuse potential than cigarettes, but similar to that observed with nicotine gum.

No conflict of interest