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RESEARCH ARTICLE

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Evaluation of Nicotine Pharmacokinetics among Flavors in Electronic Nicotine Delivery Systems (ENDS): A Parallel, Randomized Study in Two ENDS across Four Flavors

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ABSTRACT

Introduction: The impact of e-liquid flavor on nicotine uptake is an important area of consideration regarding biological uptake of nicotine with conflicting data. This paper reports on Pharmaco Kinetics (PK) of plasma nicotine uptake and a subjective measure of Overall Product Liking (OPL) using four different e-liquid flavors in two commercially available cartridge-based Electronic Nicotine Delivery System (ENDS) systems, Vuse Vibe and Vuse Ciro.

Aims and methods: Two single-center, open-label, parallel cohort confinement studies were conducted in 2017. In total, 287 eligible adult cigarette smokers and dual users of ENDS were enrolled and randomized to Vuse Vibe (3% nicotine content by weight) in four flavors (Original (n=36), Mint (n=36), Tropical (n=36), or Nectar (n=36)), or to Vuse Ciro (1.5% nicotine content by weight) in four flavors (Original (n=35), Mint (n=36), Melon (n=39), or Tropical (n=33)). Subjects used their assigned products ad libitum during a 10-minute session after 12 hours of nicotine abstinence, and plasma nicotine PK and OPL were evaluated.

Results: Across each ENDS platform, baseline-adjusted geometric mean C_{max} values for the four evaluated flavors were generally similar. C_{max} values ranged from 4.60 to 6.84 ng/mL for Vuse Vibe and 4.35 to 5.88 ng/mL for Vuse Ciro among four flavor variants of each ENDS. While the study was not designed to compare nicotine uptake across products, nicotine uptake based on baseline adjusted C_{max} and $AUC_{nic\ 0\text{-}60}$ was generally higher in the Vuse Vibe group compared to the Vuse Ciro group, reflective of differences in nicotine concentration. OPL scores ranged from 6.1 to 7.3 for the Vuse Vibe group and 5.8 to 7.2 for the Vuse Ciro group.

Conclusion: Nicotine uptake for two different ENDS product platforms was similar across a range of assessed e-liquid flavors as evidenced by overlap of 95% confidence intervals in C_{max} and $AUC_{nic\ 0\text{-}60}$.

Implications: In these two studies on PK assessments of e-liquids containing 1.5 and 3.0% nicotine-salt in ENDS devices, we found similar (overlap of 95% confidence intervals) nicotine uptake profiles in subjects with different peak plasma concentrations between the two ENDS platforms that were mirrored by the difference in nicotine content

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Introduction

Cigarette smoking is the leading preventable cause of premature morbidity and mortality, with greater risk associated with longer and more intense smoking [1]. Products that do not combust tobacco plant material, such as ENDS or Tobacco Heating Products (THP) have been reported to have a lower risk of toxicant exposure for users as compared to Combustible Cigarettes (CC) [2-6]. ENDS generally consist of a battery, sensor, heating element or atomizer, and a reservoir (i.e., cartridge, pod or tank) for e-liquid, which typically is a mixture of propylene glycol, glycerol, nicotine (extracted from tobacco), and flavourings [7]. Drawing on the ENDS mouthpiece activates the heating element, which aerosolizes the e-liquid, yielding a vapour that is inhaled. The vapour composition largely reflects the composition of the e-liquid and has a far simpler chemical profile than cigarette smoke, dra-

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matically reducing the user's exposure to the most harmful combustion-related toxicants in cigarette smoke [5,8].

It has been suggested that ENDS could improve individual and public health by reducing exposure to toxicants and carcinogens among smokers who switch to ENDS [9-11]. Studies have demonstrated reductions in toxicant and carcinogen exposure for ENDS users compared to combustible cigarette smokers [4,12-14] and systematic reviews of ENDS studies concluded that ENDS use has fewer harmful effects than smoking, while recommending longitudinal studies to further assess the effects of ENDS use [14-18]. Despite the growing adoption of ENDS by adult smokers, limited data is available to assess the impact of e-liquid flavors on nicotine delivery. While some studies found that flavored e-liquids resulted in higher PK parameters and concluded that flavors influence nicotine exposure and absorption through pH effects and subjective effects [19,20] another study reported that e-liquid flavors did not consistently enhance the absorption of nicotine [21]. A study by Goldenson et al. reported no differences in nicotine PK across flavors, and Hong et al. showed that e-liquid flavor had no impact on nicotine uptake parameters of Vuse Solo [22,23]. In order to further assess the role of flavor in ENDS use, this evaluation characterized the nicotine PK and subjective OPL scores of two ENDS product platforms, Vuse Ciro and Vuse Vibe, each tested with four different e-liquid flavors.

Methods

Study design

Two randomized, open-label, parallel-cohort confinement studies (ClinicalTrials.gov identifiers: NCT03105804 and NCT03233997) were conducted between March 3 and December 1, 2017 at a single study site at DaVita Clinical Research, Lakewood, CO, USA. The study protocols were consistent, with the exception of the ENDS product assessed, and both were approved by the Chesapeake Institutional Review Board (Columbia, MD, USA). The study was conducted in accordance with the ethical standards in the Declaration of Helsinki, applicable sections of the United States Code of Federal Regulations (21 CFR 50, 54, and 56), and Good Clinical Practice guidelines [24].

Subjects

Subjects were recruited through Institutional Review Boards (IRB) approved advertising methods and from a site database. Key inclusion criteria were the following: subjects in general good health, aged 21-60 years, self-reported smoking of ≥ 10 cigarettes daily for past ≥ 6 months (exclusive smokers, or smokers with daily ENDS use or at least weekly ENDs use for ≥ 3 months prior to Screening), expired carbon monoxide >10 ppm, positive urine cotinine test, and use of contraception or surgically sterile if female. Key exclusion criteria were the following: uncontrolled acute/chronic medical conditions, presence of heart disease, underweight, history of cancer, using hormone-replacement therapy in post-menopausal females, a positive alcohol/drug screen, and tobacco company employment. An attempt was made to recruit a balance of genders and age groups, with the overall study population to include approximately 15%-20% African American subjects to match the reported demographic of US smokers [25,26].

ENDS products

ENDS product platforms assessed included Vuse Vibe and Vuse Ciro (RJ Reynolds Vapor Co. LLC, Winston-Salem, NC, USA), each with four flavors of e-liquid (Vuse Vibe: Original, Mint, Tropical, and Nectar; Vuse Ciro: Original, Mint, Melon, and Tropical) that were commercially available in the US market at the time of the study. Both ENDS products function by attaching a closed e-liquid tank or cartridge to a rechargeable power unit. The power unit is a 620 mAh (Vuse Vibe) or 380 mAh (Vuse Ciro) battery. Vuse Vibe cartridges hold 2 ml of e-liquid with 3% nicotine content by weight while Vuse Ciro cartridges hold 0.9 ml of 1.5% nicotine e-liquids. Labeling of all products was compliant with applicable regulatory requirements [27-29].

Randomization and product familiarization

Eligible subjects were invited to return to the study site for enrolment and randomization at 7 ± 2 days before the Study Day 1 visit. Enrolled subjects were randomized to study arms that would receive one of four flavor variants using computerized scheme for one of the two ENDS products.

Randomized subjects were provided with their assigned e-liquid flavor for 7 days of at-home product acclimation, followed by a check-in at the study site for an overnight (2-day) confinement and PK assessment. Subjects were allowed to use their own usual brand cigarettes ad libitum until the start of an overnight tobacco and nicotine product abstention period of at least 12 hours.

Assessments

Following the minimum 12-hour tobacco and nicotine abstinence period, subjects participated in a 60-min PK assessment period in which they used

their assigned ENDS flavor ad libitum for 10 minutes and blood samples were collected at –5, –0.5, 3, 5, 8, 10, 11, 12, 15, 20, 30, and 60 minutes (± 30 seconds) from the start of ENDS use for plasma nicotine assessment. Processed samples were transferred to Celerion Global Bioanalytical Services, Lincoln, NE, USA, for bioanalytical analysis. Overall product liking was rated at 13 minutes from the start of ENDS use. Responses were given as scores on a numeric scale of 0 to 10 where 0="strongly dislike" and 10="strongly like."

Safety was assessed by monitoring Adverse Events (AEs), physical examinations (including an oral examination), clinical laboratory tests, vital sign measurements and other safety assessments at various times during the study by the principal investigator and the medical monitor. Other safety assessments performed at screening included electrocardiography, urine cotinine screen, urine drug screen, an alcohol breathalyzer test, and urine and serum pregnancy tests.

Endpoints

The primary endpoint was maximum plasma nicotine concentration (C_{max}) and area under the curve for nicotine exposure over 60 minutes (AUC_{nic} 0–60). The secondary endpoints were time to maximum plasma nicotine concentration (T_{max}), nicotine exposure during first 15 minutes (AUC_{nic} 0–15), and Overall Product Liking (OPL) [23,24].

Statistical analysis

PK parameters were analyzed and reported using descriptive statistics for each ENDS across the four e-liquid flavor variants tested. The PK analyses included all subjects with evaluable PK data who also had usable baseline and 60-min post-use plasma samples. Subjects with baseline-adjusted nicotine concentration C_{max} values <1.0 µg/L during the 10-minute ad libitum IntraPeritoneal (IP) use period were considered "non-inhalers" and were excluded from the data and statistical analyses.

Individual nicotine concentrations were baseline-adjusted by estimating the pre-existing plasma nicotine concentration and assuming that nicotine elimination followed first-order pharmacokinetics, using the following formula: $C' = C_t — C_0\ (1/2)\ t/t_{1/2}$, where C'_t was the adjusted concentration at time t, C_t was the observed concentration at time t, C0 was the concentration at time 0, t was time in minutes, and $t_{1/2}$ was an average nicotine half-life of 120 minutes. Post-adjustment negative values were set to zero.

The PK parameters (C_{max}, AUC_{nic} 0–15, AUC_{nic} 0–60, and T_{max}) were calculated with Phoenix® WinNonlin® (Version 6.3 or later; Certara USA Inc., Princeton, NJ, USA). No formal statistical comparisons either between ENDS or across e-liquid flavors were performed since the study wasn't designed and powered for such comparisons. All data analyses were performed with R version 3.0.2. (R Foundation for Statistical Computing, Vienna, Austria) or later and SAS® version 9.2.

Results

Demographics and product usage

A total of 389 subjects were screened for both studies, with 287 (144 for Vuse Vibe and 143 for Vuse Ciro) being enrolled and randomized. For Vuse Vibe, 36 were randomized to Original flavor, 36 Mint, 36 Tropical, and 36 Nectar. For Vuse Ciro, 35 were randomized to Original flavor, 36 Mint, 33 Tropical, and 39 Melon. A total of 247 subjects (86.0%) (126 for Vuse Vibe and 121 for Vuse Ciro) completed the studies and were included in the PK analysis. All subjects were included in the safety analysis.

For Vuse Vibe, the mean age of the subjects was 41 years (Table 1). Most subjects were male (61.1%) and Black or African American (59.0%), and approximately 9% were Hispanic or Latino. The subjects had a mean Body Mass Index (BMI) of 28.93 kg/m^2 (6.36). The subjects had smoked for a mean of 23.0 years and smoked a mean of 15 cigarettes per day.

For Vuse Ciro, the mean age of the subjects was 34 years (Table 1). The majority of subjects were male (60.1%) and White (57.3%). Approximately 19% were Hispanic or Latino. The subjects had a mean Body Mass Index (BMI) of 27.85 kg/m^2. The subjects had smoked for a mean of 16.26 years and smoked a mean of 17.09 cigarettes per day.

There were overlaps in demographic and baseline characteristics of subjects across ENDS groups, with the exception of race trends between the Vibe and Ciro groups (Table 1), indicating general consistency across the study populations. The average number of cigarettes smoked per day overall was 16. Most of the subjects were exclusive cigarette smokers, including 90% (130 out of 144 subjects) of subjects in the Vuse Vibe group and 94% (134 out of 143 subjects) of subjects in the Vuse Ciro group [30].

Table 1. Baseline characteristics.

	Vuse vibe				**Vuse ciro**			
Characteristic	**Original (N=36)**	**Mint (N=36)**	**Tropical (N=36)**	**Nectar (N=36)**	**Original (N=35)**	**Mint (N=36)**	**Tropical (N=33)**	**Melon (N=39)**
Age (years)								
Mean (SD)	43.8 (10.3)	39.8 (10.6)	39.3 (11.0)	39.7 (11.8)	35.2 (9.3)	31.3 (9.0)	34.6 (11.0)	34.0 (10.6)
Sex								
Male	26 (72.2%)	14 (38.9%)	23 (63.9%)	25 (69.4%)	22 (62.9%)	22 (61.1%)	17 (51.5%)	25 (64.1%)
Female	10 (27.8%)	22 (61.1%)	13 (36.1%)	11 (30.6%)	13 (37.1%)	14 (38.9%)	16 (48.5%)	14 (35.9%)
Race								
Black or African American	18 (50.0%)	21 (58.3%)	24 (66.7%)	22 (61.1%)	12 (34.3%)	10 (27.8%)	12 (36.4%)	13 (33.3%)
American Indian or Alaska Native	0	0	0	0	0	0	1 (3.0%)	3 (7.7%)
Asian	0	1 (2.8%)	1 (2.8%)	1 (2.8%)	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	1 (2.8%)	0	0	0	0
White	15 (41.7%)	12 (33.3%)	11 (30.6%)	12 (33.3%)	22 (62.9%)	23 (63.9%)	19 (57.6%)	18 (46.2%)
Multiple	3 (8.3%)	2 (5.6%)	0	0	1 (2.9%)	3 (8.3%)	1 (3.0%)	5 (12.8%)
Other	0	0	0	0	0	0	0	0
Ethnicity								
Hispanic or Latino	3 (8.3)	3 (8.3)	2 (5.6)	5 (13.9)	6 (17.1)	6 (16.7)	5 (15.2)	10 (25.6)
Not Hispanic or Latino	33 (91.7)	33 (91.7)	34 (94.4)	31 (86.1)	29 (82.9)	29 (80.6)	28 (84.8)	29 (74.4)
Smoking status								
Number of years smoked								
Mean (SD)	25.1 (11.0)	22.5 (11.5)	22.4 (11.8)	22.1 (12.2)	18.0 (10.7)	14.6 (8.1)	16.7 (11.6)	16.0 (10.1)
BMI (kg/m^2)								
Mean (SD)	29.0 (6.6)	28.6 (6.4)	28.7 (6.2)	28.5 (6.4)	28.7 (6.3)	28.3 (6.7)	27.2 (6.1)	28.3 (4.6)
Note: BMI: Body Mass Index; SD: Standard Deviation.								

Home trial period

For the 7-day at-home product acclimation period, subjects were encouraged to use ENDS at least once a day while they continue to use their usual brand of cigarettes. The 7-day at-home product acclimation compliance was measured by obtaining the difference in tank/cartridge weights. E-liquid use ranged from 0.6168 to 0.9717 g for Vibe and 0.3946 to 0.5531 g for Ciro over the 7-day acclimation period (Supplementary information).

Pharmacokinetic results

The plasma nicotine concentrations over time plots using baseline adjusted arithmetic means in Figure 1a shows rapid increases in plasma nicotine concentrations over the first 10 minutes of using Vuse Vibe for all flavor variants, followed by a gradual decline thereafter. Baseline adjusted nicotine PK parameters for Vuse Vibe and its flavor variants are summarized in Table 2. For the first primary end point of this study, maximum nicotine concentrations (C_{max}), values ranged from 4.60 ng/mL to 6.84 ng/mL. For the second primary endpoint of this study, nicotine uptake over 60 minutes ($AUC_{nic\ 0\text{-}60}$), values ranged from 160.32 ng*min/ml to 236.11 ng*min/ml. For secondary endpoints, nicotine uptake during the first 15 minutes following the start of product use (AUC_{nic} 0-15) ranged from 42.01 ng*min/ml to 63.80 ng*min/ml, and the median time to reach the maximum nicotine concentration (T_{max}) was 11 minutes.

For Vuse Ciro, a similar trend was observed in baseline adjusted arithmetic means of plasma nicotine concentration over time plots shown in Figure 1b, with rapid increase in plasma nicotine concentrations during the first 10 minutes and gradual decline thereafter. The PK parameters for Vuse Ciro are summarized in Table 2. For the primary endpoints, C_{max} ranged from 4.35 ng/mL to 5.88 ng/mL and $AUC_{nic\ 0\text{-}60}$ ranged from 127.67 tab 54.79 ng*min/ml and the median T_{max} ranged from 10.5-11 minutes.

While both Vuse Vibe and Vuse Ciro studies were not

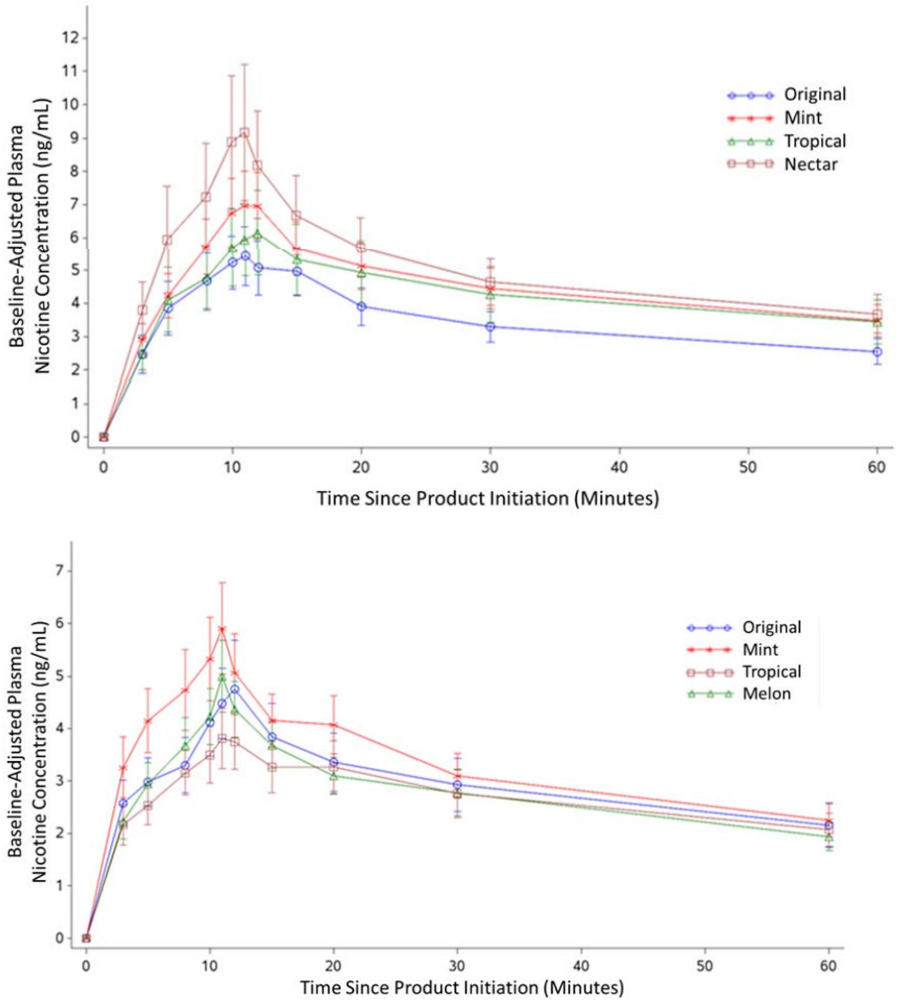

Figure 1. Mean plasma nicotine concentrations over time. (a): Vuse Vibe PK profile with standard error bars; (b): Vuse Ciro PK profile with standard error bars. **Note:** ( ): original; ( ): Mint; ( ): Tropical; ( ): Nectar.

designed to provide formal statistical comparisons among flavor variants, the results from two primary endpoints (C_{max} and $AUC_{nic\ 0\text{-}60}$) were used to generate notched box plots, where the notch (<=) represents 95% confidence intervals around the median values to see if there were any discernible differences among the values observed for C_{max} and AUC_{nic}0-60 ranges to qualitatively assess the data across the flavor variants of each ENDS platforms.

Notched box plots of the baseline-adjusted C_{max} and $AUC_{nic\ 0\text{-}60}$ for Vuse Vibe and Vuse Ciro are shown in Figures 2 and 3 respectively. For both ENDS platforms, across the flavor variants, the notched box plots of C_{max} and AUC_{nic}0-60 overlap, suggesting the median values for the two products are similar. In terms of product use on Study Day 2, during the 10-minute ad libitum use period, e-liquid use ranged from 0.0460 g to 0.0675 g in the Vibe group and from 0.0603 g to 0.0748 g in the Ciro group (Table 2).

Table 2. Baseline-adjusted plasma nicotine pharmacokinetic parameters across Vuse Vibe and Vuse Ciro flavor variants.

PK Parameters Assessed	**Original**	**Mint**	**Tropical**	**Nectar**
Vuse Vibe	(N=28)	(N=28)	(N=27)	(N=32)
C_{max} (ng/mL)	4.6	6.84	5.06	5.85
(95% CI)	(3.32-6.36)	(5.28-8.84)	(3.51-7.30)	(4.16-8.24)
AUC_{nic} 0-15 (ng*min/mL)	42.48	63.8	42.01	53.12
(95% CI)	(29.81-60.52)	(48.93-83.18)	(27.19-64.89)	(37.18-75.91)
AUC_{nic} 0–60 (ng*min/mL)	160.32	236.11	180.62	206.17
95% CI	115.32-222.90	182.67-305.19	123.09-265.02	149.18-284.91
T_{max}* (min) (range)	11.0 (2.8-30.0)	11.0 (7.6-30.0)	11.0 (3.0-70.2)	11.0 (3.0-30.0)

PK Parameters Assessed	**Original**	**Mint**	**Tropical**	**Nectar**
Vuse Ciro	(N=28)	(N=28)	(N=22)	(N=32)
C_{max} (ng/mL)	4.38	5.88	4.35	4.68
(95% CI)	(3.23-5.95)	(4.49-7.70)	(3.32-5.71)	(3.63-6.04)
AUC_{nic}0–15 (ng*min/mL)	37.92	54.79	38.28	39.24
95% CI	27.72-51.87	42.17-71.21	28.58-51.28	29.96-51.39
AUC_{nic} 0–60 (ng*min/mL)	138.11	184.67	143.95	134.63
95% CI	102.93-185.30	144.39-236.20	105.58-196.27	101.81-178.03

Note: PK Parameters presented in this table are baseline-adjusted geometric mean values except for T_{max}.* T_{max} reported as median value, followed by the range for minimum and maximum. Subjects with C_{max}<1.0 ng/mL were excluded from this analysis.

CI: Confidence Interval; C_{max}: Maximum nicotine concentration; AUC_{nic} 0–15: area under the curve for nicotine exposure over 15 minutes; AUC_{nic} 0–60: Area under the curve for nicotine exposure over 60 minutes; T_{max}: Time to maximum nicotine concentration.

Overall product liking results

The OPL questionnaire was completed by 247 subjects: 126 in the Vuse Vibe group, and 121 in the Vuse Ciro group. The mean score of OPL were similar across the flavor variants tested for each ENDS group. The OPL ranges for Vuse Vibe were 6.1 to 7.3, and 5.8 to 8.0 for Vuse Ciro.

Adverse events

8 of 144 subjects (5.6%) in the Vibe group reported eight Adverse Events (AEs). The most frequent AE was presyncope, which was reported by 2 subjects (1.4%). All AEs were deemed not related or unlikely to be related to an IntraPeritoneal (IP). In the Ciro group, 13 of 143 subjects (9.1%) reported 14 AEs. The most frequently reported AE was dizziness by 5 subjects (3.5%). One AE of headache was judged to be related to the Ciro mint flavor variant, and one report of dizziness and one of productive cough were considered possibly related to the melon flavor variant. All other AEs were either not related or unlikely related to an IP. All AEs in both studies were of mild to moderate intensity, and there were no serious AEs in either group.

Discussion

We conducted two clinical studies to evaluate the nicotine PK of two ENDS platforms, Vuse Vibe (3% nicotine) and Vuse Ciro (1.5% nicotine), each tested with four flavor variants, in ENDS naïve smokers (>90%) or smokers/ENDS dual users. The four flavor variants tested for Vuse Vibe were Original, Mint, Nectar and Tropical. We assessed the maximum plasma nicotine concentrations (C_{max}) and overall nicotine exposure over 60 minutes ($AUC_{nic\ 0\text{-}60}$) following 10 minutes of ad libitum ENDS use. Our data showed that subjects achieved similar maximum plasma nicotine levels and overall nicotine exposure after using the Vuse Vibe flavor variants. In addition, a review of plasma nicotine profiles (plasma nicotine concentration versus time) among flavor variants showed that they were similar in profile and consistent with first-order kinetics of nicotine in humans. This suggests that additional ingredients for flavors did not seem to affect the PK behaviors of nicotine in our subjects. Furthermore, in a notched box plot analysis, both values showed similar nicotine distribution patterns across all flavors with overlap of 95% Confidence Intervals (CIs) around the median values (Figure 2).

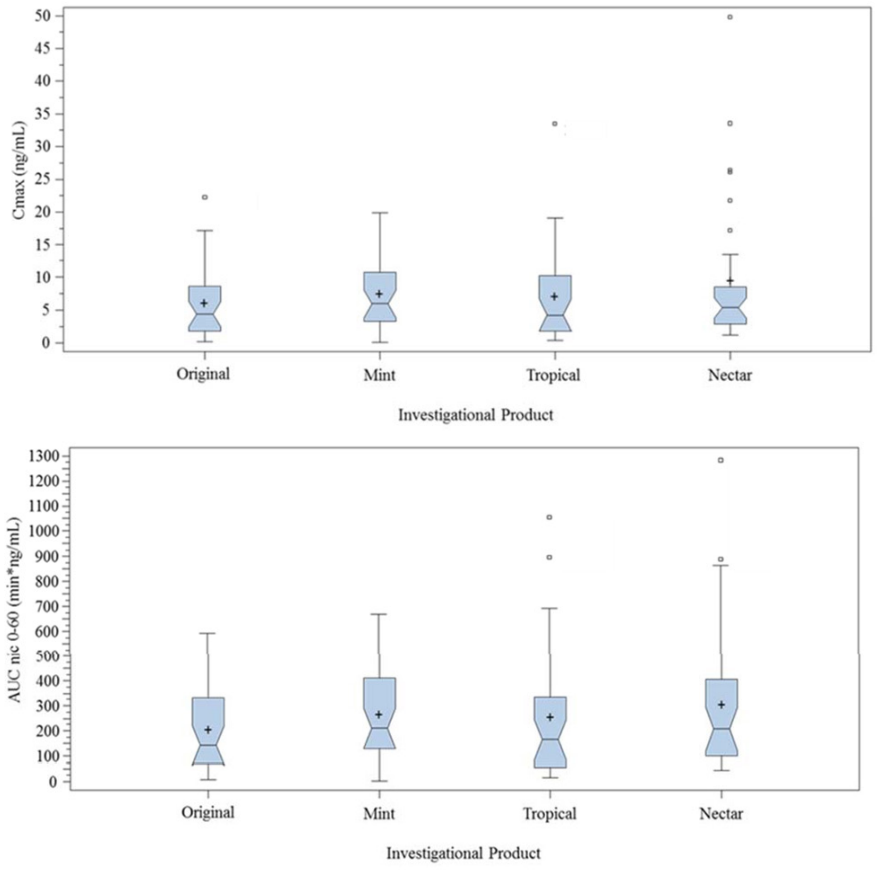

Figure 2. Notched box plots for Vuse Vibe (a): Vuse Vibe C_{max}; (b): Vuse Vibe $AUC_{nic\ 0\text{-}60}$.

We observed similar patterns in both C_{max} and $AUC_{nic\ 0\text{-}60}$ among four flavor variants of Vuse Ciro. In addition, notch box plot analysis also demonstrated that both values had similar nicotine distribution patterns across all flavor variants with overlap of 95% Confidence Intervals (CIs) around the median values (Figure 3). While both C_{max} and $AUC_{nic\ 0\text{-}60}$ were similar among flavor variants of each ENDS, there were differences between ENDS platforms that reflect the differences in nicotine strengths as Vuse Vibe showed slightly higher values than Vuse Ciro. Lastly, for both ENDS platforms and all their flavor variants, the median T_{max} values were 11 minutes and this was in line with the ad libitum use duration given the first-order pharmacokinetics of nicotine.

In addition to PK parameters, we also assessed investigational product use during PK sessions and Overall Product Liking (OPL) at the end of 60 minutes. The review of device mass loss during test sessions for the two ENDS platforms and their flavor variants supports our conclusion that within each ENDS platform, flavor does not appear to have a significant impact on e-liquid use as Standard Deviations (SDs) overlap, suggesting no differences in amount used among flavors (Table 3). When subjects were asked to rate the OPL during test sessions after ENDS use, Nectar and Tropical flavors in both the Vuse Vibe and Ciro groups had marginally higher mean scores. However, overall, the scores were similar to each other among flavor variants within each ENDS platform as indicated by the flavors receiving the highest OPL scores being consistent across ENDS platforms (Table 4) [23,24].

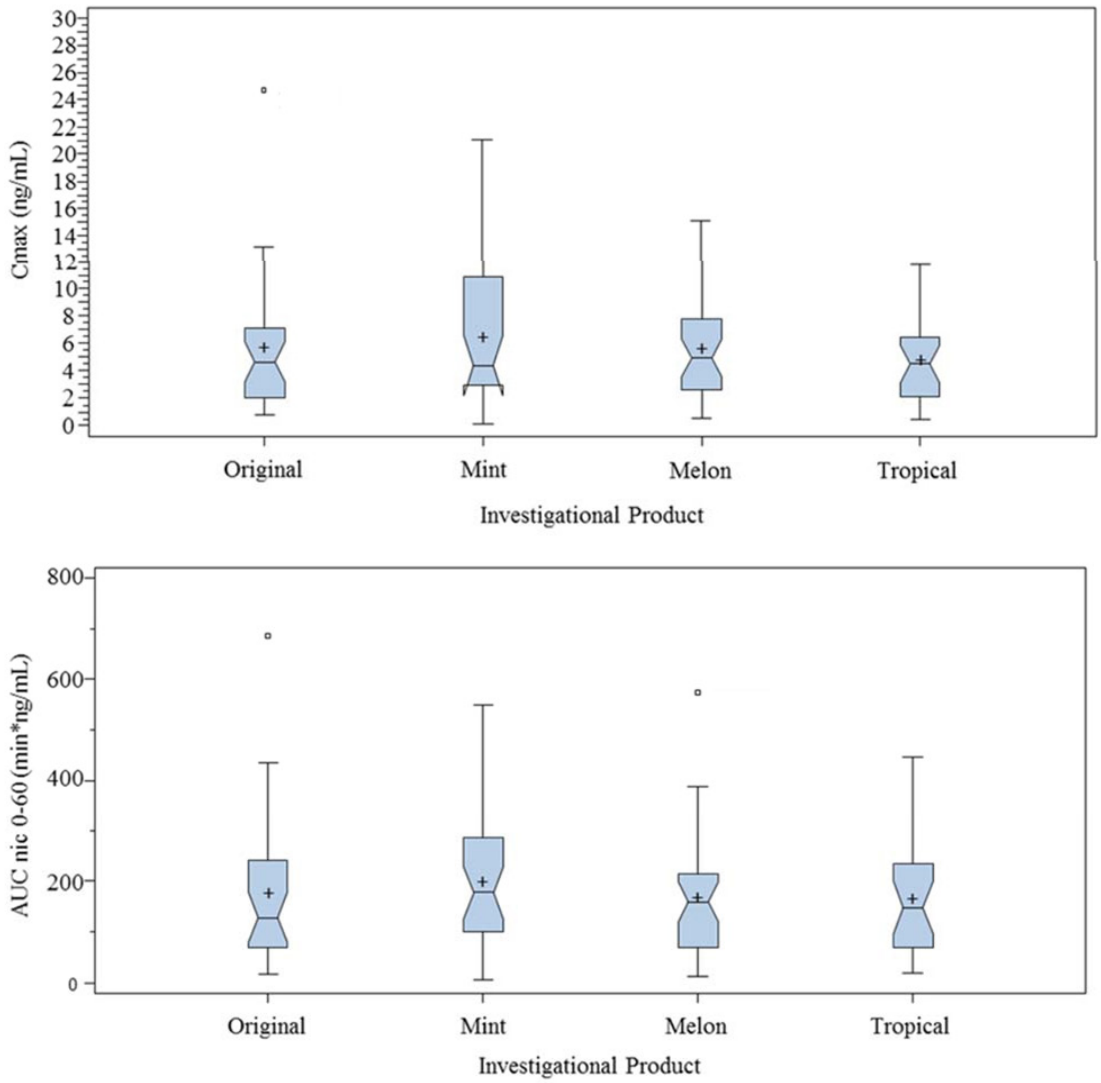

Figure 3. Notched box plots for Vuse Ciro (a): Vuse Ciro C_{max}; (b): Vuse Ciro $AUC_{nic\ 0\text{-}60}$.

Table 3. Cartridge weights after 10 minute of product use during test session.

Vuse vibe cartridge weight (g)				
Statistics	Original	Mint	Tropical	Nectar
n	31	32	31	32
Mean ± SD	0.046 ± 0.032	0.055 ± 0.033	0.068 ± 0.054	0.064 ± 0.036
Vuse vibe cartridge weight (g)				
n	30	32	25	34
Mean ± SD	0.060 ± 0.046	0.075 ± 0.051	0.065 ± 0.048	0.067 ± 0.041

Table 4. Summary of overall product liking score.

Vuse vibe cartridge weight (g)				
Statistics	Original	Mint	Tropical	Nectar
n	31	32	31	32
Mean ± SD	6.1 ± 2.87	6.5 ± 2.49	6.9 ± 2.24	7.3 ± 2.29
Vuse vibe cartridge weight (g)				
n	30	32	25	34
Mean ± SD	6.0 ± 2.74	5.8 ± 2.25	7.2 ± 1.93	5.8 ± 2.52
Note: N: Number of non-missing observations; SD: Standard Deviation; overall product liking is measured on a numerical rating scale from 0 to 10, with 0: strongly dislike and 10: strongly like.				

The literature around impact of flavors on nicotine absorption and exposure is limited with varying inferences around the study data, with some studies suggesting flavors have minimal to no impact and other studies suggesting that flavors may increase nicotine absorption and exposure [25-30]. In a study designed to evaluate the influence of e-liquid flavors and nicotine concentrations on subjective measure of abuse liability in young adult smokers, Cobb et al. [14]. concluded that in addition to suppressing the urge to smoke in current smokers, ENDS flavors did not appear to significantly enhance or mask the subjective effects of Overall Product Liking; and furthermore, found that acceptability ratings were not related consistently to ENDS flavor or nicotine concentrations [21]. In an abuse liability study by Goldenson et al. which evaluated four flavor variants of JUUL System (JS) ends (Mint, Mango, Virginia Tobacco and Crème) with the same nicotine concentration, it was found that while certain flavors were more satisfying than others, nicotine PK did not differ among the flavor variants [22]. While these two latest studies support our findings, discordant findings have also been reported.

A series of two studies published by Helen et al. examined the impact of flavor on vaping topography and nicotine uptake [19,20]. In those studies, the authors concluded that vaping behavior changes with flavor and that flavors influence nicotine uptake. In addition, flavors were associated with nicotine exposure through user preference, and the authors suggest that flavors may have affected nicotine uptake *via* pH effects. However, there are some key differences to note. In those studies, the products were the subjects' usual brand of e-liquids in refillable cartridge/tank devices with user-adjustable power units. In contrast, ENDS used in our study did not allow modification of e-liquids or power settings, thus exhibiting better experimental control of independent variables [31-36]. Furthermore, our study had a larger sample size than the St. Helen studies. In a study with eight subjects, Voos et al. evaluated the effects of e-liquid flavors on nicotine uptake and topography in an ambulatory setting and concluded that flavors yielded different patterns of nicotine delivery but conceded that the differences are due to variation in puffing duration [26]. In contrast, our study did not find differences in nicotine delivery across flavor variants among each ENDS platform, but more importantly, we did not see evidence of differences in the amount of e-liquids consumed during the test sessions among flavors within each ENDS platform [37-40]. Recent publications suggest that sufficient product appeal or product liking, as well

as delivery of sufficiently high amount of nicotine per use, appear to be important in facilitating either reducing the number of cigarettes used, or complete switching to take full advantage of reduced toxicants found in ENDS and therefore leading to tobacco harm reduction [14,16-18]. Thus, additional research is needed to determine the implication of Overall Product Liking scores on both PK parameters and e-liquid consumption [41,42].

In addition to the contrast with some published studies on effect of flavor on nicotine delivery from ENDS noted above, the work presented here also had the advantages of a robust sample size, 7 days of at-home ENDS acclimation prior to test sessions, confinement with 12 hours of tobacco and nicotine product abstention prior to test sessions, 10-minute ad libitum use during test sessions, assessment of e-liquid consumption during test sessions, and the use of same ENDS platforms (Vuse Vibe and Vuse Ciro) [43]. We chose the 10 minute ENDS duration to align with an estimated duration to smoke a single CC. The ENDS use period of 10 minutes for these studies also aligns with the product use period used for published studies which assessed the abuse liability of other Vuse ENDS products that included a nicotine PK assessment [17,19,26]. Data from a recent study by Ebajemito et al. as well as data from an unpublished internal study indicate that there is higher nicotine uptake in subjects during ad libitum puffing compared to using a controlled puffing regimen over a given ENDS use duration [39]. Future study designs may consider reported data trends around ENDS topography, current trends on time for subjects to smoke a single CC, and recent published ENDS use periods for nicotine PK assessments [21,29,31]. As the prevalence of dual and poly tobacco product use increases, inclusion of a greater proportion of dual users in future studies will be useful to make study findings more applicable to the broader population of users. Future studies will also benefit from crossover designs to evaluate nicotine PK with multiple flavor variants to reduce inter-user variability [44].

Conclusion

Results of our study employing adult smokers showed similar PK parameters across flavors for each ENDS assessed. Difference in nicotine uptake between the two ENDS platforms assessed appear to reflect differences in nicotine strength (% nicotine). While certain flavors were favored in terms of OPL, Overall Product Liking rating did not directly correlate to the PK parameters or the amount of e-liquid consumed.

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