Part Two: Pharmacokinetic Evaluation of E-Liquid Flavors of Vuse Solo Electronic Nicotine Delivery System, An Unblinded, Parallel, Randomized Study To Assess Nicotine Uptake In Smokers

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Abstract

This paper reports the findings of a randomized nicotine pharmacokinetic (PK) study of a closed electronic nicotine delivery system (ENDS). The study evaluated four flavor variants of Vuse Solo ENDS where subjects used their randomized investigational product (IP) for 10 minutes *ad libitum* and blood samples were collected for PK assessments that included maximum plasma nicotine concentration ($C_{\max}$) and area under the nicotine concentration-vs-time curve up to 60 minutes ($AUC_{\text{nic0-60}}$). Baseline-adjusted mean $C_{\max}$ ranged from 6.53 to 8.21 ng/mL, and mean $AUC_{\text{nic0-60}}$ ranged from 206.87 to 263.52 ng*min/mL for all ENDS IPs. Results for $C_{\max}$ and $AUC_{\text{nic0-60}}$ values were consistent among the ENDS IP flavor variants tested and results indicate that flavors did not affect nicotine uptake in human subjects.

Introduction

Cigarette smoking is a leading cause of preventable premature death, and significantly increases the risk of developing lung cancer, heart disease, chronic bronchitis, chronic obstructive pulmonary disease and other serious diseases and adverse health conditions¹. Whereas smoking conventional cigarettes requires combustion of tobacco, use of electronic nicotine delivery systems (ENDS) does not. ENDS were developed as potential reduced-harm alternative products for cigarette smokers. ENDS heat a nicotine-containing solution (e-liquid), which results in the generation of an aerosol containing fewer and lower levels of toxicants than are found in cigarette smoke^{2,3}, and reduced toxicant exposure to consumers who switch from cigarettes to ENDS⁴⁻⁹. Several public health authorities, such as Public Health England¹⁰, Royal College of Physicians¹¹, and National Academies of Sciences, Engineering, and Medicine¹², have recognized the potential public health benefit of current smokers switching to ENDS. A review by the National Academies of Sciences, Engineering and Medicine (NAS) concluded that “[t]he evidences about harm reduction suggests that across a range of studies and outcomes, e-cigarettes pose less risk to an individual than combustible cigarettes”¹².

This publication is the second part of a three-part series describing the clinical assessment of Vuse Solo. The clinical studies included in this publication series describe the nicotine pharmacokinetics (PK) of Vuse Solo across four e-liquid flavors; an assessment of the abuse liability of Vuse Solo as compared to CC and a nicotine replacement therapy product¹³; and a study to assess whether use of Vuse Solo results in a reduction in exposure to harmful and potentially harmful constituents (HPHCs) after smokers are switched to the product for five days¹⁴.

This report presents findings from a clinical study that assessed nicotine PK parameters of Vuse Solo during and following short-term, *ad libitum* use of one of four flavor variants of Vuse Solo products by smokers and dual smokers/ENDS users. The e-liquid flavors included Original (tobacco flavor), Mint, Tropical and Fusion. The study was executed following the parallel-group study design in which subjects

were randomized to a single product, and nicotine PK was evaluated during and after a 10 min *ad libitum* product use following a week of ambulatory product acclimation (at-home).

Results

Study Population

A total of 148 subjects were enrolled and randomized; All subjects were randomized to one of four Vuse Solo investigational products (IPs) and 122 (82.4%) subjects completed all scheduled PK assessments. A total of 26 subjects (17.6%) were randomized but terminated early from the study for reasons unrelated to study products. Of these 122 study completers, four subjects were excluded from the final PK analysis due to $C_{\max}$ less than 1.0 ng/mL, indicating the IP was used, but subjects did not use it appropriately during the product use period. Thus, 118 (96.7% of study completers) subjects completed the study with evaluable PK data. The number of subjects who completed the study (and the associate percentage of completers with evaluable PK data) in each IP group are as follows: Original (n=30, 93.3%), Mint (n=34, 100%), Tropical (n=29, 96.5%), and Fusion (n=29, 96.5%).

The demographic and baseline characteristics of subjects are summarized in **Supplementary Table S1**. Subjects were generally male (55.4%), white (56.8%), and predominantly non-Hispanic (74.3%). The mean age was 33.7 years. Subjects enrolled in the study included 135 smokers (91.2%) and 13 dual smokers and ENDS users (8.7%). Subjects reported a mean smoking duration of 18 years with a mean of 16 cigarettes per day.

Product use

ENDS product use, determined by volume of e-liquid used, was assessed over two IP use periods as a surrogate for product use and to evaluate how much e-liquid was used. The use periods included one-week ambulatory (at-home) trial period and four 10-minute use periods per PK assessment. The differences between initial and final cartridge weights were calculated for both periods and results are shown in Table 1.

Table 1
Vuse Solo e-liquid usage (grams) during the at-home trial and PK assessment periods

	Original	Mint	Tropical	Fusion
At-home trial period				
Number of subjects	35	39	38	36
Mean (SD)	0.2101 (0.2517)	0.1643 (0.1728)	0.2082 (0.2339)	0.2010 (0.2296)
Median (range)	0.1029 (0–0.8062)	0.1127 (0–0.7862)	0.0912 (0–0.7154)	0.1117 (0–0.7360)
Day 2 PK Assessment				
Number of subjects	30	34	29	29
Mean (SD)	0.0348 (0.0269)	0.0318 (0.0171)	0.0371 (0.0229)	0.0357 (0.0270)
Median (range)	0.0266 (0.0003-0.1120)	0.0293 (0.0097-0.0882)	0.0374 (0.0076-0.1052)	0.02980 (0.0002-0.1420)
Abbreviation: SD = standard deviation.				

Pharmacokinetic results

As illustrated in Figure 1, baseline-adjusted plasma nicotine concentrations increased rapidly within 15 minutes of use for each of the ENDS IPs evaluated. Mean plasma nicotine concentrations declined to less than 6 ng/mL for all IPs by 60 minutes. Baseline-adjusted nicotine PK parameters are summarized in Table 2. Nicotine uptake during the first 15 minutes following the start of product use ($AUC_{nic\ 0-15}$), C_{max} , $AUC_{nic\ 0-60}$ and the time to reach the maximum nicotine concentration (T_{max}) across the 60-minute sampling period were similar for all ENDS e-liquid flavor variants (Table 2).

Table 2
Plasma nicotine pharmacokinetic parameters across Vuse Solo variants

PK Parameters Assessed	Original (N=28)	Mint (N=34)	Tropical (N=28)	Fusion (N=28)
C_{max} (ng/mL) (95% CI)	6.91 (5.49–8.70)	6.53 (5.26–8.10)	8.21 (6.87–9.81)	6.67 (5.20–8.56)
AUC_{nic0-15} (ng*min/mL) (95% CI)	56.19 (42.85–73.69)	63.36 (50.64–79.27)	76.28 (63.38–91.81)	56.15 (43.81–71.97)
AUC_{nic0-60} (ng*min/mL) (95% CI)	223.79 (180.13–278.03)	215.37 (175.92–263.68)	263.52 (218.92–317.20)	206.87 (156.70–273.10)
T_{max}* (min) (range)	11.00 (5.0–60.0)	11.00 (3.0–30.0)	11.00 (3.0–30.4)	11.00 (3.0–30.0)
<p>PK Parameters presented in this table are baseline-adjusted geometric mean values except for T_{max}.</p> <p>*T_{max} reported as median value, followed by the range for minimum and maximum.</p> <p>Subjects with C_{max} <1.0 ng/mL were excluded from this analysis.</p> <p>Abbreviations: CI = confidence interval, C_{max} = maximum nicotine concentration, AUC_{nic0-15} = area under the curve for nicotine exposure over 15 minutes, AUC_{nic0-60} = area under the curve for nicotine exposure over 60 minutes, T_{max} = time to maximum nicotine concentration.</p>				

While this study was not designed to statistically compare flavors, two of the nicotine PK parameters, C_{max} and AUC_{nic0-60}, were qualitatively assessed across the ENDS flavor variants to evaluate nicotine uptake across the e-liquid flavors. Notched box plots of baseline-adjusted C_{max} and AUC_{nic0-60} are shown in Figures 2 and 3, respectively, to visually compare the distributions and point estimates in C_{max} or AUC_{nic0-60} across the flavors. Overall, the nicotine uptake parameters C_{max} and AUC_{nic0-60} were similar for all tested Vuse Solo flavors. No evidence of statistically significant difference in median C_{max} or AUC_{nic0-60} was found among the four flavor variants, as the notches in Figures 2 or 3 overlap with each other. This suggests that flavors do not appear to impact nicotine uptake in our study population.

Product Liking Results:

Overall product liking (OPL) was assessed at the 13-minute timepoint during test sessions using an 11-point numeric rating scale (NRS) and results are presented in Table 3. Mean OPL scores (SD) ranged from 5.3 (2.5) for the Mint flavor to 7.5 (1.9) for the Tropical flavor, and were 6.4 (2.5) and 6.0 (2.5) for the Original and Fusion flavors, respectively. Median values reflect a similar trend with the Mint flavor with the lowest score of 5.5 and the Tropical with highest score of 8.0, and both the Original and Fusion flavors with same median score of 7.0.

Table 3
Summary of overall product liking scores

Summary statistics	Original (N=35)	Mint (N=39)	Tropical (N=38)	Fusion (N=36)
Number of subjects	30	34	29	29
OPL Mean (SD)	6.4 (2.5)	5.3 (2.5)	7.5 (1.9)	6.0 (2.5)
Median	7.0	5.5	8.0	7.0
Range: 0-10. Overall Product Liking (OPL) was measured on a numerical rating scale from 0 to 10, with 0 = strongly dislike and 10 = strongly like. Abbreviations: SD = standard deviation.				

Adverse events

Nine (6%) of 148 subjects experienced nine adverse events during the study. Gastroesophageal reflux (one subject) and oropharyngeal pain (one subject) were each considered by the principal investigator (PI) to be possibly related and related to IP, respectively. All other adverse events were judged by the PI not to be related to an IP. All adverse events were of mild intensity except for moderate ocular hyperemia in one subject, which led to subject withdrawal from the study by the PI. No serious adverse events were reported.

Discussion

We evaluated PK parameters of four flavor variants of e-liquids used in Vuse Solo ENDS with 4.8% (57 mg/mL) nicotine content by weight following an acute exposure in predominately ENDS naïve smokers. Our data showed that subjects achieved similar overall nicotine exposure ($AUC_{nic0-60}$), maximum plasma nicotine concentrations (C_{max}), and time to maximum concentrations (T_{max}) while using one of the four flavor variants of Vuse Solo ENDS. Evaluation of PK parameters, C_{max} and $AUC_{nic0-60}$, showed similar nicotine uptake distribution patterns across all flavors variants with overlap of the 95% confidence intervals (CIs) around the medians in both C_{max} and $AUC_{nic0-60}$ (illustrated as the notches in boxplots, Figures 2 and 3). In addition to the PK assessments, product liking (OPL) for each flavor was assessed at the 13-minute timepoint (Table 3).

As stated above, the results and distribution of baseline-adjusted C_{max} were similar across flavor variants. By comparison, baseline-adjusted maximum nicotine concentrations (C_{max}) of Vuse Solo flavor variants

in this study are higher (Table 2) than those previously reported by Stiles et. al. using Vuse Solo ENDS Original (tobacco) ¹⁵ and Vuse Solo ENDS Menthol ¹⁶; for reference, the 29 mg nicotine e-liquid used in the Stiles et. al. papers corresponds to roughly the same nicotine concentrations (57 mg/ml or 4.8%) as was used in the current study. It is important to note key differences among study designs of the abuse liability studies performed by the Stiles et. al. papers and the current study. The former studies utilized a crossover design (Williams design) and were conducted in an ambulatory setting. In contrast, our study utilized a parallel design in confinement. Both Stiles AL studies had approximately 7 days of at-home product acclimation as our study with instruction to use ENDS IP at least once but product use compliance was not assessed. In our study, subjects were told to use the ENDS IPs as often as they liked, and product use compliance was confirmed by weighing used cartridges at the end of the at-home trial period. Thus, differences in study design as well as level of familiarity with study products and general differences between study populations may account for variability among data reported. In a study to evaluate the abuse liability (AL) of ENDS in experienced ENDS users by Hajek and colleagues ¹⁷, Vuse Solo Original 4.8% was evaluated as one of the ENDS comparators and the results demonstrated that Vuse Solo Original 4.8% users achieved baseline-adjusted C_{max} of 13.6 ng/ml (9.7 SD), which is higher than what was found in the current study, but still lower than the C_{max} reported for cigarettes (17.9 ng/ml [16 SD]). In contrast, in an AL study of cigarette smokers conducted by Goldenson and colleagues ¹⁸, the authors reported that Vuse Solo Original 4.8% had a baseline-adjusted C_{max} of 6.8 ng/ml, which was similar to our study findings, and lower than cigarette C_{max} (15.4 ng/ml). Similarly, another AL study by Campbell et. al., with a similar subject population as the current study, reported a mean baseline-adjusted C_{max} for Vuse Solo Original 4.8% as 5.48 ng/mL ¹³. Additional results from other AL studies also suggest that experienced users of ENDS demonstrate higher nicotine uptake, compared to naïve ENDS users, but in general the C_{max} following acute exposure to ENDS was less than that observed with smoking a cigarette, regardless of the ENDS use experience ^{13,19-25}.

As was the case with C_{max} , baseline-adjusted $AUC_{nic0-60}$ results and their distribution were also similar across Vuse Solo flavor variants. There are limitations in comparing the overall nicotine exposure, $AUC_{nic0-60}$, between the current study against published works due to the differences in AUC calculations performed across studies based on the duration of observation ¹⁵⁻¹⁷. Goldenson et al., in an AL study among cigarette smokers, reported a baseline-adjusted $AUC_{nic0-60}$ of 216 min*ng/ml for Vuse Solo Original 4.8%, which is similar to the $AUC_{nic0-60}$ for Vuse Solo Original in this study of 223.79 min*ng/ml ¹⁸. Taken together, the PK findings from this reported study are in agreement with previously published data using Vuse Solo ENDS ¹⁵⁻¹⁸.

In addition to PK assessments, subjects were also asked to rate OPL for the Vuse Solo flavor variants on an 11-point NRS. Subjects rated the Tropical flavor highest and rated the Mint flavor lowest with Original (tobacco) and Fusion flavors in-between (Table 3). These reported scores were consistent with published data. In two AL studies by Stiles et. al., subjects assessed product liking scores for two flavors (Vuse Original and Menthol) at multiple timepoints over six hours after start of ENDS use. In both studies by

Stiles et. al., maximum PL scores (E_{max}) for Vuse Solo Original and Menthol (36 mg/ml nicotine) were reported at 4.13 and 4.53, respectively ^{15,16}, compared to 6.4 and 5.3 for Vuse Solo Original and Mint 4.8% (57 mg/ml nicotine) reported in this study. Similarly, in the AL studies by Goldenson et. al., and Campbell et. al., where Vuse Solo Original 4.8% was used as an ENDS comparator, mean maximum product liking scores were between 4.5 and 5, and 5.56, respectively ^{13,18}.

Review of our data on e-liquid consumption measured by cartridge weight before and after PK test sessions in the context of OPL scores suggest some trends but failed to show a direct linear correlation. St. Helen and colleagues examined the impact of flavors (Strawberry vs. tobacco) on nicotine uptake and topography. The authors found no statistically significant differences in PK parameters and in puffing behavior and noted the need for further investigation ^{26,27}. Of note, these differences were seen in subjects who used fruity/sweet flavored e-liquids in their own ENDS products, suggesting potential subject bias towards flavors that resembled their usual flavors.

Similarly, in a topography study to assess the effect of flavor in regular smokers, Voos et al., concluded that the flavors used in their study delivered differential amounts of nicotine, potentially associated with product use topography, and differences in subjective effects are not solely a product of nicotine delivery, and recommended additional research ²⁸. In contrast, Cobb et. al., assessed subjective effects among young adult smokers using ENDS with three flavors (cream, tropical fruit and tobacco/menthol) at nicotine concentrations ranging from 0 to 36 mg/ml nicotine and concluded that e-liquid flavors did not appear to have significant impact on subjective effects ²⁹. Thus, the implications of overall product liking scores on both PK parameters and e-liquid consumption may require additional studies to further evaluate any potential relationship.

In our study, subjects were asked to familiarize themselves with ENDS products at home for one week prior to a PK test session, and the amount of e-liquid consumed was measured by differences in cartridges weights obtained before and after a week of at home use. We found that our subjects used approximately 10% of e-liquid by weight ranging from 0.16 (+/- 0.17) mg to 0.21 (+/- 0.25) mg across the four flavors (Table 1). These results were similar to e-liquid consumption observed on the first day of exclusive ENDS use in a biomarker of exposure study by Round and colleagues ⁸ and suggests that our ENDS naïve subjects were sufficiently acclimated to ENDS IPs during their at-home trial period prior to the PK test sessions.

Our study had several strengths. First, we included a large sample size to reduce variability compared to previous ENDS nicotine PK studies ^{23,30-34}. In addition, our subjects were required to acclimate to ENDS for seven days to become familiar with ENDS products prior to confinement and PK test sessions. Subjects were also required to abstain from tobacco products for 12 hours prior to PK test sessions to ensure their blood nicotine concentrations were close to baseline prior to the start of product use. Furthermore, we collected blood samples at intervals that allowed characterization of nicotine PK following *ad libitum* ENDS exposure and the nicotine concentrations of blood samples were baseline-adjusted to ensure more accurate results.

Despite these strengths, the study had several limitations. Although we allowed participation of dual users, more than 98% of our subjects were exclusive cigarette smokers. As the prevalence of dual and poly use of multiple types of tobacco and nicotine products, such as ENDS or other non-combustible nicotine products, continues to increase, inclusion of a greater proportion of dual users of CC and ENDS in future studies may be useful to make study findings more applicable to current nicotine and tobacco users. Future studies may also benefit from cross-over designs to evaluate nicotine PK with multiple flavor variants to reduce inter-user variability. Lastly, for this study, subjects were allowed a 10-minute *ad libitum* use of the ENDS^{15,16,24,28,33,34}. We chose the duration of 10-minutes of ENDS use to align with an estimated duration to smoke a single CC. However, this study design element may be modified in the future studies to align more closely with historical data on the time it takes to smoke a single CC, as well as current data trends around ENDS topography. Moreover, other considerations might include current reports on the time for subjects to smoke a single CC^{18,35,36} or recent study designs which leverage a shorter ENDS use period^{17,22,29,31,32,37-42}.

In conclusion, the primary endpoints of this study, C_{max} and $AUC_{nic0-60}$, were similar across all four flavors as evidenced by the overlap of 95% confidence intervals, suggesting that flavors are not significant factors in nicotine exposure in an acute exposure setting. The results of this study will add to the growing body of literature regarding the effects of flavors on nicotine delivery and uptake.

Methods

This study was a single-center study (ClinicalTrials.gov identifier: NCT03234010, 31/07/ 2017) designed to evaluate plasma nicotine uptake and overall product liking with use of four flavor variants of the Vuse Solo ENDS (Vuse Solo Original, Mint, Tropical and Fusion) in tobacco consumers who were exclusive smokers or dual users of cigarettes and ENDS. The study was completed at a single clinical research site (DaVita Clinical Research, Lakewood, CO) and was reviewed and approved by Chesapeake Institutional Review Board (Columbia, MD).

The target number of subjects to be randomized was 35 subjects per IP group (140 subjects in total) to allow for approximately a 15% attrition rate (5 subjects per IP group) with a goal of completing 30 subjects per IP group. Attempts were made to recruit 15-20% African-Americans within each IP group in an effort to balance the study sample for the reported percentage of U.S. smokers who are African American¹. During a screening visit, eligibility criteria were assessed to ensure that potential subjects met all criteria for inclusion and none of the exclusion criteria. Eligible subjects included male and female smokers, aged 21–60 years who self-reported smoking 10 or more cigarettes per day for at least the previous 6 months, or dual users who self-reported smoking 10 or more cigarettes per day for at least the previous 6 months, and using a nicotine-containing cig-a-like or tank-style ENDS at least weekly for at least the previous 3 months. Brief periods of abstinence longer than 30 days before screening were allowed at the discretion of the PI. Smoking history was confirmed at screening and reassessed on Study Day 1 with an expired carbon monoxide (ECO) assessment, and only subjects with ECO levels

greater than 10 ppm were eligible to participate in the study. Informed consent was obtained from all subjects before any study procedures were performed.

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, and ICH E6 Good Clinical Practice guidelines.

Study Design

The study was designed as a randomized, open-label, parallel-cohort study to assess nicotine uptake in human subjects following ENDS use. The study examined plasma nicotine PK parameters in Vuse Solo ENDS with four flavor variants: Original, Mint, Tropical and Fusion.

Each Vuse Solo cartridge consisted of a sealed unit containing 0.5 mL of e-liquid comprising 4.8% nicotine by weight [58 mg/mL], propylene glycol, glycerin, flavorings, and water. The products were powered by a rechargeable power unit and included a heating element, microchips, and a sensor. Aerosol generation is activated by detection of a pressure differential within the ENDS product during puffing.

Subjects were given a 1-week at-home trial period to become familiar with the assigned Vuse IPs. Subjects were randomized to specific ENDS flavors and were provided two cartridges with instructions for use. Product use compliance was checked by weighing ENDS cartridges three times before and after use to a sensitivity of 1×10^{-4} grams before and after the at-home trial period.

On Study Day 1, subjects arrived at the study site and began their check-in procedures prior to confinement. Subjects returned ENDS IP e-liquid cartridges from the at-home trial period to the site. Eligibility criteria were reconfirmed, and those who successfully completed all check-in procedures were confined to the study site for approximately 24 hours. Subjects were allowed to use their assigned IP *ad libitum* until the start of a mandatory 12-hour abstinence from tobacco and nicotine products.

On the morning of Study Day 2, each subject was given their assigned ENDS IP for use during the PK assessment. Subjects were then allowed to use the assigned ENDS IP *ad libitum* for 10 minutes (± 10 seconds). Start and stop times were documented. ENDS IP cartridges were weighed three times before and after use to a sensitivity of 1×10^{-4} grams.

During the PK assessment, blood samples were collected and processed to plasma for nicotine measurements at the following time points relative to the start of IP use: -5, -0.5, 3, 5, 8, 10, 11, 12, 15, 20, 30, and 60 minutes. The -0.5 min sample was used as the preferred baseline sample. All samples were collected, processed, and transferred to Celerion Global Bioanalytical Services (Lincoln, NE) for nicotine quantitation using a validated liquid chromatography tandem mass spectrometry method.

In addition to blood sample collection, subjects were required to provide an OPL score at 13 minutes after start of IP use on a numeric scale of 0 to 10, with 0 corresponding to “strongly dislike,” 5 corresponding to

“neither like nor dislike”, and 10 corresponding to “strongly like.” Each subject was assessed for adverse events and vital signs, and a symptom-driven physical examination was performed, if necessary, prior to discharge from the study to ensure subject’s safety. Upon the PI’s review of subjects’ status, if there were no new adverse events or physical examination findings to warrant further follow up, subjects were discharged from the study.

Statistical Analysis

The primary PK parameters ($C_{\max}$, $AUC_{\text{nic0-60}}$) were summarized using descriptive statistics by IP group without inter-group comparisons. Standard summary statistics for quantitative and qualitative variables were calculated.

The pharmacokinetic (PK) analyses were performed by Nuventra Pharma Sciences, Inc. located in Durham, NC. PK parameters were derived from the baseline-adjusted plasma nicotine concentrations-time data by noncompartmental methods using Phoenix® WinNonlin® (Version 6.3; Certara USA Inc., Princeton, NJ).

AUCs were calculated using the linear trapezoidal rule. $C_{\max}$ and $T_{\max}$ were obtained directly from the baseline-adjusted plasma nicotine concentration-time data. Observed concentrations below the lower limit of quantification (LLOQ; 0.200 ng/mL) were set at half the LLOQ for data summarization and analysis. Baseline adjustment was done by estimating and subtracting pre-existing nicotine levels from observed levels, and all PK parameters were calculated from the adjusted concentrations. The amount of pre-existing nicotine was estimated by using a model that assumed that nicotine elimination followed first-order kinetics^{43,44} and a nicotine half-life of 120 minutes^{23,35,45}. Each individual PK profile was examined for completeness and suitability for inclusion in the analysis. Subjects with $C_{\max}$ values less than 1.0 ng/mL were considered to be not inhaling aerosol during the 10-minute period of *ad libitum* IP use; therefore, sensitivity analyses excluding those subjects were performed.

Declarations

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Author Contributions

Study concept and design: K.S.H; P.D., B.A.J., E.R., P.N.

Acquisition of data: E.S.

Drafting of the manuscript: K.S.H.

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: T.J.

All authors have read and approved the final manuscript.

Competing Interests Statement

All authors are full-time or former employees of RAI Services Company. RAI Services Company is a wholly owned subsidiary of Reynolds American Inc., which is a wholly owned subsidiary of British American Tobacco plc.

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Figures

Figure 1

Baseline-Adjusted Plot of Arithmetic Mean Plasma Nicotine Concentrations (0-60 minutes) for Four Flavor Variants of Vuse Solo

Figure 2

Notched Box Plot of Baseline-Adjusted C_{max} for Four Flavor Variants of Vuse Solo

Figure 3

Notched Box Plot of Baseline-Adjusted AUCNic0-60 for Four Flavor Variants of Vuse Solo

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