Part One: Abuse Liability of Vuse Solo Relative To Combustible Cigarettes And Nicotine Gum

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Abstract

Abuse liability (AL) of electronic nicotine delivery systems (ENDS) is relevant as the category increases in popularity as a potentially less-harmful alternative to cigarette smoking. AL assessments are important to the FDA in determining if a new product is appropriate for the protection of public health. This paper reports the results for Vuse Solo and high and low AL-comparators evaluated in an open-label, randomized crossover confinement AL study. The confinement design was adapted from previous ambulatory studies of Vuse Solo and included product familiarization sessions before each four-hour test session in which subjective measures, nicotine uptake, and physiological endpoints were assessed following a single 10-minute ad libitum product use session. Product liking, intent to use again, suppression of urge to smoke, and nicotine uptake were lower after use of Vuse Solo compared to cigarettes and higher after use of Vuse Solo compared to nicotine gum. No significant differences in blood pressure or heart rate were observed between the products pre- to post-product use. These data reinforce previous research showing that Vuse Solo has an AL profile lower than that of combustible cigarettes but higher than that of nicotine gum and may have sufficient AL for product adoption by current adult smokers.

Introduction

The abuse liability (AL) of a tobacco product has been defined as the likelihood that individuals will engage in persistent or problematic use and experience undesirable consequences as a result of use.[1] It is widely accepted that combustible cigarettes (CC) have the highest AL among tobacco- and nicotine-containing products and that other nicotine-containing products have varying levels of AL similar to or below that of CC.[2–4] One strategy for tobacco harm minimization is to ensure availability of less toxic but acceptably satisfying non-combusted alternatives; that is, products that can provide relief from cigarette craving and nicotine withdrawal effects with lower exposure to harmful or potentially harmful constituents.[5,6] Electronic nicotine delivery systems (ENDS) have been proposed as one such alternative.[7] An evaluation of the AL of ENDS compared to that of CC provides the FDA and the public health community with data to understand likelihood for long-term use of ENDS and subsequently their impact to both individual and population health.[8,9]

There are many physiological and psychological elements that contribute to a tobacco product's AL. These include nicotine uptake parameters, the ritual of using the product, perceived benefits, sensory aspects of the product, the balance between positive and negative subjective effects, and the ability to counteract feelings of withdrawal and craving.[1,10–13] Nicotine's reinforcing effects are linked to the speed and efficiency of nicotine uptake, such that products with slower or lower nicotine uptake are considered to be less reinforcing.[6,14] In addition, other attributes of tobacco product use contribute to the early experiences of craving relief, as demonstrated by studies with nicotine-free or low-nicotine products.[15] For example, nicotine-free e-liquids can perform on par with nicotine-containing products for endpoints related to cravings when there are cognitive expectations of craving relief and psychological reward.[13,16]

This is in contrast to other research which demonstrates that smokers can discriminate between products with and without nicotine and prefer products that contain nicotine.[17,18]

There is no single assessment that determines the relative AL of a tobacco product. Instead, tobacco product AL evaluation has been approached using a variety of methods. Clinical laboratory assessments have been used to assess the speed and extent of nicotine uptake after product use along with momentary evaluations of product liking, reduction in urge to smoke, and cigarette cravings.[19–24] Behavioral economic demand analysis has also been applied to evaluate relative product valuation of different categories where higher value is associated with higher AL.[25,26]

The Center for Tobacco Products within the FDA (CTP) considers AL evaluations integral to their determination of marketing authorization and has noted that liking and maximum effect are common primary outcome measures in 'standard' AL studies of pharmaceutical products.[9] For tobacco products, the FDA recommended that the AL assessment of a new tobacco product be considered relative to other tobacco products with known AL.[9] Combustible cigarettes are known to have a high AL and nicotine replacement therapy (NRT) are considered to have low AL and thus serve as useful comparator products to understand the relative abuse liability of a new product.[27] The FDA has not established an "acceptable" or "unacceptable" level of AL for new tobacco products, nor has it placed specific weight on different measures that factor into AL, such as nicotine pharmacokinetics (PK) and subjective effects. However, it is generally recognized that for potentially reduced risk tobacco products such as ENDS to be adopted by smokers as a replacement for CC, these products should have some level of AL for smokers to effectively displace use of their regular products.[5,28] Indeed, many smokers report the primary reasons for starting use of ENDS were to quit smoking and/or avoid relapse after quitting.[29–32] Recent evidence suggests that ENDS use can be more successful than NRT use in maintaining smoking cessation when combined with behavioral support.[33]

To accomplish long-term transition away from CC use, ENDS must be sufficiently satisfying and provide smokers with positive subjective experiences.[34,35] In 2012, the Institute of Medicine's Committee on Scientific Standards for Studies on Modified Risk Tobacco Products noted: "[t]here is a continuum of reinforcement value. Ideally, the new product would be sufficiently reinforcing so as to attract smokers away from conventional cigarettes but not enough to encourage the widespread dependent use of the product by individuals who were previously nonusers, or who would have quit smoking."[36] There is a growing body of evidence suggesting that non-combusted ENDS products such as Vuse Solo could serve this function.

The current study design was based on FDA guidance regarding assessments of human abuse potential of drugs[38] and the application of these methods to tobacco products.[1,39] Notably, studies were performed with current experienced adult smokers to ensure study subjects were familiar with the effects of tobacco products. Subjective measures of product liking were included as one of the primary endpoints with the timing of the subjective measures aligned with the nicotine pharmacokinetic assessments. Additional

subjective, safety, and physiological measures were evaluated. The study design also included abuse liability assessment of two control products. A combustible cigarette was used as the positive control as it represents a nicotine product with a known, high AL. Nicotine gum was used as a reference control as it is generally accepted to be a product with low AL.

Hong et al. (2021), in this issue, provides a description of Vuse Solo Gen 1 and Gen 2. The intent of the current study was to confirm the results from the previous studies and to evaluate the strengths and weaknesses of adapting the previous ambulatory study to a confinement study design. This paper is the first in a three-part series reporting on findings from several clinical studies related to Vuse Solo.

Previous clinical studies have demonstrated reduced nicotine uptake, reduced abuse liability, and reduced biomarkers of exposure after short term use of Vuse Solo, a closed system ENDS product, compared to use of combustible cigarettes (CC).[21,22,39] These studies evaluated the first generation of Vuse Solo cartridges, termed Generation 1 (Gen 1). Additional studies have been conducted to evaluate Vuse Solo Generation 2 (Gen 2) cartridges, to confirm the results from the previous studies, and to provide additional evidence demonstrating that Vuse Solo is appropriate for the protection of the public health. and are reported in this three-part series describing the clinical assessment of Vuse Solo Gen 2, referred to hereafter as Vuse Solo.

The current study reports on the relative AL of the slightly modified Vuse Solo Gen 2 compared to CC and nicotine gum and assesses the strengths and weaknesses of adapting the previous ambulatory study to a confinement study design. Part Two describes the nicotine pharmacokinetics (PK) of Vuse Solo across four e-liquid flavors.[40] Part Three presents the results of 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 days.[41]

Results

This was a randomized, controlled, open-label crossover study to assess elements of AL in smokers following use of three closed system ENDS, including Vuse Solo Gen 2 Original (tobacco flavor), Vuse Ciro Original, and Vuse Vibe Original, relative to CC and nicotine gum. After a period of product familiarization for each assigned study product, subjects participated in 4-hour test sessions in which they used the assigned product ad libitum for 10 min (CC or ENDS) or 30 min (NRT) and subjective measures and blood samples for PK assessment were collected prior to, during and for 240 min following the start of product use. No comparisons were made between the ENDS. For the purposes of this manuscript, only the data for Vuse Solo and the high- and low-AL comparators are reported; data for Vuse Ciro and Vuse Vibe relative to the comparator products will be reported in a separate publication.

Study Population

Of the 93 subjects screened, 40 were randomized and 38 (95%) completed the three test sessions for CC, nicotine gum, and Vuse Solo. One subject was withdrawn from the study by the investigator following a blood draw-related vasovagal reaction before administration of study product in the first test session. Another voluntarily withdrew from participation at the beginning of the second test session due to discomfort with the repeated blood draws.

Three subjects had nicotine T_{max} values ≥120 minutes (two during the nicotine gum test session and one during the Vuse Solo test session) and were considered not to have used the products effectively during the test session. Data collected from these and the withdrawn participants were excluded from the statistical analyses. The demographic and baseline characteristics of all randomized subjects are summarized in **Supplementary Table 1**. The study population was predominantly male (70%), white (95%), and the majority were non-Hispanic (95%) with a mean age of 41.2 years. Mean individual cigarette use was 18 cigarettes per day and the mean smoking duration was 20 years. All subjects were self-reported smokers of CC with limited ENDS experience. The level of cigarette dependence at screening was moderate based on Fagerström Test for Nicotine Dependence scores (mean total score 5.5).[42]

Product use

Pre-to-post-use product weight differences for Vuse Solo were assessed following the prescribed 10 minutes of *ad libitum* product use for the relevant test session to confirm product use. The mean e-liquid weight difference, and thus the amount of e-liquid used, was 0.034 g ± 0.022 g (range 0.005 g to 0.107 g). This amount of e-liquid corresponds to approximately 1.63 mg of nicotine.

Subjective Measures

As illustrated in Table 1, use of Vuse Solo resulted in scores for product liking (area under the effect curve [$AUEC_{15-240}$], E_{max}, and overall product liking), and intent to use again (E_{max}) that were consistently significantly lower ($p < 0.0001$) than those for CC and significantly higher than those for nicotine gum ($p \leq 0.0003$). Positive effects scores after use of Vuse Solo were intermediary between smoking CC and use of nicotine gum (statistically significant differences [$p \leq 0.0224$] for all comparisons). Conversely, negative effects scores for Vuse Solo were significantly lower as compared to nicotine gum ($p \leq 0.006$ for both $AUEC_{15-240}$ and E_{max}) with no significant differences compared to scores for CC.

Table 1
Statistical comparisons of subjective measures parameters

Parameter [a]	Vuse Solo	Usual brand cigarette	Nicotine gum
	(N=37)	(N=38)	(N=36)
Product liking ($AUEC_{15-240}$)	1245.18*†	1735.65	866.68
Product liking (E_{max})	6.61*†	8.83	5.04
Overall product liking	5.56*†	8.14	3.58
Overall intent to use again (E_{max})	4.19*†	8.98	2.24
Positive effects ($AUEC_{15-240}$)	757.14*†	925.74	578.44
Positive effects (E_{max})	6.13*†	7.02	4.23
Negative effects ($AUEC_{15-240}$)	356.32†	341.43	499.50
Negative effects (E_{max})	2.58†	2.91	4.32
Urge to smoke ($AUEC_{0-15}$)	96.86*†	70.60	110.41
Urge to smoke ($AUEC_{0-240}$)	1776.12*	1609.04	1861.75
Urge to smoke (E_{min})	5.01*	2.68	5.84
Urge to smoke (T_{min}, minutes)	16.11†	14.66	33.04

[a] Least squares means from mixed-effect models are presented

* Significantly different from usual brand cigarette; $p < 0.05$

† Significantly different from nicotine gum; $p < 0.05$

Abbreviations: $AUEC_{15-240}$, area under the effect curve from 15 to 240 minutes after the start of product use; E_{max}, maximum effect score; $AUEC_{0-15}$, area under the effect curve from 0 to 15 minutes after the start of product use; $AUEC_{0-240}$, area under the effect curve from 0 to 240 minutes after the start of product use; E_{min}, minimum effect score; T_{min}, time to minimum urge to smoke.

Mean urge to smoke scores (UTS) during the first 15 minutes following initiation of product use ($AUEC_{0-15}$) were significantly higher for Vuse Solo than for CC ($p < 0.0001$) but significantly lower than for nicotine gum ($p = 0.0164$; Table 1). Over the entire 4-hour test session ($AUEC_{0-240}$), UTS scores for Vuse Solo were significantly higher than for CC ($p = 0.0080$) and equivalent to those for nicotine gum. Table 1 and Figure 1 indicate that UTS scores decreased more slowly and to a lesser extent after using Vuse Solo as compared to smoking, but more quickly and to a greater extent when compared to nicotine gum. By

150 minutes after product use, UTS scores for all products had converged and by 240 minutes they had returned to near-baseline values (Figure 1).

The differences in degree of effect ($AUEC_{0\text{-}15}$, $AUEC_{0\text{-}240}$ and E_{min}) for UTS scores between use of Vuse Solo and CC were significant (p = < 0.0001, 0.0080 and < 0.0001, respectively). Although Vuse Solo did not provide the same magnitude of smoking relief as CC, the time to minimum UTS (T_{min}) was not significantly different between Vuse Solo and CC (16.1 min and 14.7 min, respectively; Table 1). This is in contrast to the T_{min} comparison between Vuse Solo and nicotine gum, as use of Vuse Solo provided significantly greater relief of smoking urges during the first 15 minutes after the start of product use (p = 0.0164) and reached the minimum urge significantly faster (p = 0.0110) (Table 1).

Nicotine Pharmacokinetics

As illustrated in Figure 2, plasma nicotine concentrations increased rapidly within 15 minutes of the start of CC and Vuse Solo use and more gradually after initiation of nicotine gum use, peaking at approximately 45 minutes. By 240 minutes, mean plasma nicotine levels had declined to approximately 2 ng/mL for all conditions. Statistical comparisons of baseline-adjusted nicotine PK parameters are summarized in Table 2. Geometric least square means were used for C_{max} and AUC statistical comparisons; median values were used for T_{max} comparisons. Mean nicotine uptake during the first 15 minutes following the start of product use ($AUC_{nic\ 015}$) was significantly lower (p < 0.0001) with use of Vuse Solo than with CC but was significantly higher (p < 0.0001) than with use of nicotine gum. Over the four-hour sampling period, the mean total nicotine uptake ($AUC_{nic\ 0-240}$) after use of Vuse Solo was significantly lower (p < 0.0001) than after smoking but not significantly different (p = 0.9029) than with use of nicotine gum. Further, the mean C_{max} was significantly lower with use of Vuse Solo than with CC (5.48 and 14.07 ng/ml, respectively; p < 0.0001) but was significantly higher than with use of nicotine gum (3.99 ng/ml; p = 0.0096). The median time to reach the maximum nicotine concentration (T_{max}) with use of Vuse Solo was slightly but significantly longer (p < 0.0001) than with use of CC, likely due in part to the CC being fully consumed before the end of the 10-minute product use window; T_{max} for Vuse Solo was significantly shorter (p < 0.0001) than for nicotine gum (Table 2).

Table 2
Statistical comparisons of baseline-adjusted plasma nicotine uptake parameters

PK Parameter[a]	Vuse Solo (Gen 2)	Usual brand cigarette	Nicotine gum	Vuse Solo[b] (Gen 1)
	(N=37)	(N=39)	(N=36)	(N=44)
C_{max} (ng/mL)	5.48*†	14.07	3.99	4.67
$AUC_{nic\ 0-15}$ (ng*min/mL)	46.83*†	140.7	4.67	42.64
$AUC_{nic\ 0-240}$ (ng*min/mL)	557.2*	1082	550.3	NA[e]
T_{max} (minutes)	10.13*†	7.62	45.03	15.15[c]

[a] Geometric least square means were used for the C_{max} and AUC statistical comparisons; median values were used for T_{max} statistical comparisons. Arithmetic means for C_{max} were 7.3, 15.0, and 4.6 ng/ml, respectively, for Vuse Solo Gen 2, UB, and nicotine gum.

[b] Data represents the 29 mg Vuse Solo product from Stiles et al., 2017.

[c] The published T_{max} of 21.83 represented the arithmetic LS mean. The median T_{max} value presented here was not included in Stiles et al., 2017.

[e] $AUC_{nic\ 0-360}$ was assessed in Stiles et al., 2017.

* Significantly different from usual brand cigarette; $p<0.05$.

† Significantly different from nicotine gum; $p<0.05$.

Abbreviations: C_{max}, maximum concentration; $AUC_{nic\ 0-15}$, area under the curve from 0 to 15 minutes after the start of product use; $AUC_{nic\ 0-240}$, area under the curve from 0 to 240 minutes after the start of product use; NA, not assessed, T_{max}, time to maximum concentration.

Physiologic Effects

Mean systolic and diastolic blood pressure and pulse rates at baseline before the start of use of all study products were similar, ranging from a mean of 109.8 to 110.3 mmHg, 68.6 to 69.4 mmHg, and 68.4 to 70.9 bpm, respectively. No statistically significant differences ($p > 0.05$) were seen between any products in maximum increase in systolic blood pressure (8.13, 8.62, and 8.34 mmHg with Vuse Solo, CC, and nicotine gum, respectively), diastolic blood pressure (5.93, 5.62, and 7.02 mmHg), or heart rate (9.90, 12.20, and 9.08 bpm).

Adverse Events

All study products were well tolerated under the conditions of use during the study. A total of 75 adverse events (AEs) were reported during the study, with 54 occurring during the Vuse Solo, CC, and nicotine gum

study periods reported in this manuscript. AEs associated with the Vuse Vibe and Vuse Ciro study periods will be reported elsewhere. Eight AEs were reported during the Vuse Solo study period, 12 during the CC study period, and 34 during the nicotine gum study period. None of the reported AEs were judged to be related or possibly related to use of Vuse Solo. All AEs were rated as mild. The AEs judged to be related or possibly related to nicotine gum use were abdominal distension (1), dizziness (3), dyspepsia (1), feeling hot (1), headache (3), hiccups (1), increased lymphocyte count (1); throat irritation (1), oral discomfort (1), and nausea (2). The AEs judged to be related or possibly related to cigarette use were dizziness (1), headache (1), and nausea (1). No serious adverse events were reported.

Discussion

This study was designed to compare elements of AL for Vuse Solo to high- (CC) and low- (nicotine gum) AL comparators using a framework generally similar to that proposed by the FDA CTP (US DHHS, 2019), but using a single nicotine level with subjective measures collected using a numeric rating scale. Overall, the results demonstrate that subjective measure scores for Vuse Solo Gen 2 were substantially higher than nicotine gum but not as high as CC, and the nicotine uptake parameters for Vuse Solo were closer to those of nicotine gum than CC. Peak nicotine uptake was four times faster after use of Vuse Solo as compared to nicotine gum and produced lower urge to smoke scores in the first 15 minutes after product use. Based on the endpoints evaluated in this study, the data indicate that the AL for Vuse Solo Gen 2 falls between that of the high- and low-AL comparators. This is consistent with previous RAIS evaluations of menthol and non-menthol Vuse Solo Gen 1 products tested with e-liquids containing three nicotine levels.[21,22]

These pharmacokinetic results suggest that Vuse Solo can serve as an appropriate replacement product for CC among adult smokers accustomed to a fairly rapid nicotine uptake and thus a faster onset of reduction in urge to smoke, and craving relief. Consistent with other published literature on ENDS, Vuse Solo was able to reduce early smoking urges to a significantly greater degree than nicotine gum, and time to maximum reduction of urges after Vuse Solo use was closer to that for CC use.[8,19,43]

The speed of nicotine uptake is associated with its reinforcing potential as well as craving relief. Acute nicotine cravings have been shown to lead to smoking lapse within 10 minutes.[44] Recent work administering nicotine to smokers using controlled intravenous infusions demonstrated that subjective effects, including alleviation of smoking urges, were more robust compared to placebo when the rate of delivery was faster.[45] The reinforcing effects of nicotine are strongly dependent on the speed of delivery to the central nervous system (slower onset, less reinforcing). Thus, when the onset of effect is delayed after use of some nicotine products such as smokeless tobacco and NRT, they are less reinforcing.[46–48] Along these lines, the continued use of NRT products is related to rate of nicotine uptake (faster rate of uptake correlates positively with continued use) suggesting that a product must deliver nicotine at a sufficient rate so as to adequately satiate the smoker and prompt switching.[48] from this study demonstrates that nicotine uptake within the first 15 minutes of Vuse Solo use was closer to that of CC

and faster than nicotine gum. The more rapid nicotine uptake profile for Vuse Solo may support product switching from CC.

Subjective effects in general, and product liking scores in particular, are considered important in evaluating AL of tobacco products and are a standard component of many clinical investigations of AL. The subjective measure questions were modified in the current study as compared to the previously published data by Stiles et al.[21,22] While the absolute scores are not directly comparable, the general conclusions are consistent; despite minor changes in product design and variability in individual nicotine uptake, Vuse Solo Gen 2, like Vuse Solo Gen 1, has an AL that falls between CC and NRT. Similarly, the results reported by Hong et al. demonstrated that pharmacokinetic parameters for Vuse Solo products with different e-liquid flavors were similar.[40] Furthermore, across all studies of Vuse Solo, the observed differences in product liking scores between the Vuse Solo products (Gen 1, Gen 2, and Gen 2 flavors) did not translate to substantial differences in nicotine PK parameters during acute *ad libitum* use.[21,22,40] We also note that the product liking scores are generally similar across studies, especially as compared to the scores we observe for CC.

A notable difference between this study and the earlier studies on Vuse Solo Gen 1 was the change from ambulatory to confinement. The confinement design successfully minimized the drop-out rate that was noted in the previous studies and ensured some product familiarization prior to each test session. Due to the profile of the PK curve and the known timeframe around nicotine elimination, the data collection period was reduced to 240 minutes from 360 minutes in the previous Stiles et al. studies.[21,22] This reduced the sampling burden on the subjects.

In the current study, subjects tended to use less e-liquid during the 10-minute test sessions compared to the previous study with Vuse Solo Gen 1 (Original) (0.034 g vs. 0.048 g), but the mean nicotine C_{max} and $AUC_{nic\ 0\text{-}15}$ were comparable (Stiles et al., 2017).[21] Additionally, the median time to maximum concentration (T_{max}) after use of Vuse Solo Gen 2 occurred slightly sooner (10.1 minutes) in the current study than in the previous study (15.2 minutes; Stiles et al., 2017).[21] One potential explanation for the differences in nicotine uptake across the studies could be increased familiarity with the product use with the addition of scheduled product acclimation sessions during confinement as opposed to self-reported use under ambulatory conditions. Other research with exclusive smokers has reported relatively low nicotine uptake with initial use of ENDS and increased uptake following experience with the product.[33,49–51] Other reasons for differences in nicotine uptake could be the characteristics of the sample populations or inherent variability in how the research participants used the product. A range of C_{max} values has been reported in other published studies of Vuse Solo. For example, in Part 2 of this series, Hong et al. (2021) report a mean C_{max} of 6.91 ng/ml (Vuse Solo Gen 2) after 10-minute *ad libitum* product use among a population of either exclusive smokers or dual users of cigarettes and ENDS.[40] A small sample of experienced ENDS users achieved relatively high nicotine uptake after five minutes of *ad*

libitum Vuse Solo use (mean C_{max} of 13.6 ng/ml; Hajek et al., 2017).[11] In another study with daily smokers, the mean C_{max} after ten minutes of controlled Vuse Solo use was 6.8 ng/ml.[52]

Several limitations of this study should be noted. First, this study was specifically designed to compare elements of AL between Vuse Solo and high- and low-AL comparators. This study did not include comparisons between Vuse Solo and other ENDS products or between nicotine levels of the same product. Instead, we focused on how adult smokers generally unfamiliar with ENDS experienced Vuse Solo during initial use, as experienced ENDS users, dual users of ENDS and CCs, and non-users of tobacco products were excluded from the study. These exclusions may limit the generalizability of these findings to consumers of different categories of tobacco products. However, exclusive smoking remains the most prevalent tobacco use behavior[53] and Vuse Solo is intended to be a product for smokers who choose to continue using nicotine-containing products but who want to switch product use to one that is lower on the risk continuum.

Another limitation was that subjects used the Vuse Solo product *ad libitum* during the first 10 minutes of the test session. Although a prescribed puffing regimen would have reduced variability in the nicotine uptake, self-selection of puffing behaviors provides ecological validity.[54] Thus, *ad libitum* use was included so that the measures of AL would more closely reflect actual product use by smokers. Lastly, because Vuse Solo Gen 2 e-liquid was manufactured with only one nicotine level, only one nicotine level was assessed in this study. As such, the impact of different nicotine concentrations on AL measures was not evaluated. The previous studies with Vuse Solo Gen 1 (Original and Menthol at three nicotine levels) showed that the AL for all the Vuse Solo products, regardless of nicotine level, was between that of the comparators.[21–22]

In summary, the findings of the current study are consistent with those observed in our previous evaluation of a first-generation Vuse Solo ENDS. They support the conclusion that the AL for Vuse Solo (4.8% nicotine, Original flavor) is lower than that for CC but higher than that for nicotine gum. The lower AL of Vuse Solo compared to CC is consistent with accumulating evidence for the overall ENDS category.[51,52,55,56] In this study, nicotine uptake within the first 15 minutes of Vuse Solo use was closer to that of CC use than to nicotine gum use. This profile suggests the potential for alleviation of smoking urges and cravings and increases the likelihood of product adoption.[44] Changes in product experience over time may influence nicotine delivery and uptake with ENDS, and other characteristics may need to be considered to optimize satisfaction of the experience for smokers to completely switch from CC.

Methods

Study Design and Participants

This was a randomized, open-label, crossover study (ClinicalTrials.gov identifier: NCT03126357) designed to evaluate subjective effects, plasma nicotine uptake, and physiological measures following

use of Original flavor Vuse Solo e-cigarettes with a second-generation cartridge design, relative to usual brand CC or nicotine gum. The crossover design was chosen to minimize variability and the number of subjects needed for evaluation. The study was completed at a single research center (Celerion, Lincoln, NE) and was reviewed and approved by Chesapeake Institutional Review Board (Columbia, MD). It was conducted in accordance with the ethical standards in the Declaration of Helsinki and applicable sections of the United States Code of Federal Regulations (21 CFR Parts 50, 54, 56, and 312 Subpart D), and ICH E6 Good Clinical Practice guidelines. Two additional Vuse product platforms (Vuse Vibe and Vuse Ciro) were included in the same study. The results for these products will be reported in a future publication.

Potential participants were recruited using standard advertising methods (print media, radio, and television) and from the study site's existing recruitment database. Informed consent was obtained from all potential participants before initiation of any study events. Eligibility was assessed during a screening process. The eligible target population was male and female smokers aged 21–60 years determined by the principal investigator to be in reasonably good health. Eligible participants also self-reported smoking 10 or more filtered CC per day for at least the previous 6 months, typically smoking their first cigarette of the day within 30 minutes of waking, and not using any ENDS for the prior 30 days. Smoking status was confirmed by expired breath carbon monoxide measurements of ≥ 15 ppm. Women who were pregnant, breastfeeding, or aged ≥35 years and currently using systemic estrogen-containing contraception or hormone-replacement therapy were excluded from participation. All potential participants who expressed an interest in quitting smoking were excluded from the study and were encouraged to quit. After enrollment, subjects were randomized to product presentation sequences using a Williams Design to minimize assignment bias.

Study Products

The Vuse Solo pre-filled, closed vapor cig-a-like product (RJR Vapor Company, Winston-Salem, North Carolina) evaluated in this study was commercially available in the US at the time of the study and was similar to a product previously reported but with minor modifications to the cartridge design used in Stiles et al., 2017.[21] There was no change to the e-liquid formulation, which contained nicotine (4.8% by weight [58 mg/mL]), propylene glycol, glycerin, flavorings, and water. Detection of a pressure differential during puffing by users activated aerosol generation.

The high- and low-AL comparators (usual brand cigarettes and Nicorette® White Ice Mint nicotine polacrilex gum 4 mg [GlaxoSmithKline], respectively) were chosen in accordance with the 2017 FDA Guidance on Assessment of Abuse Potential of Drugs which discusses the use of positive and negative controls when designing studies.[38] Vuse Solo and nicotine gum were provided to the participants free of charge, whereas smokers provided their own usual brand cigarettes.

Study Procedures

The 11-day confinement period was divided into five different 48-hour Study Periods which each lasted from mid-day on Study Period Day 1 until the end of the PK test session at mid-day on Study Period Day

3 (Supplementary Figure S1). During each study period, subjects participated in six scheduled Trial Use Sessions with their assigned product Days 1 and 2 to gain familiarity with the product. The test sessions occurred on Day 3 of each Study Period.

Product use parameters for ENDS and gum during the Trial Use Sessions and test sessions were as follows: ad libitum use of ENDS for approximately 10 minutes or one piece of nicotine gum for approximately 30 minutes of use according to the package insert (i.e., “chew and park” method). During the CC test session, a single CC was smoked to completion. Subjects could request additional trial use of non-CC assigned study product during days 1 and 2 of the respective Study Period and could request their usual brand CC for *ad libitum* use throughout the study except during scheduled use of other products and one hour prior to scheduled nicotine gum use. Subjects abstained from all nicotine-containing product use for at least 12 hours overnight prior to test sessions to minimize the impact that residual nicotine might have on subjective effects. A new study period began upon completion of the test session of the preceding study period.

Test sessions were held on the morning of each Study Period Day 3 and involved product use as described above and subjective measures assessments, blood sampling for nicotine uptake, and physiologic measurements. Use of the three types of products during the test sessions occurred in separate areas of the clinic to avoid potential sensory cues that may have impacted responses to the subjective measures. Vuse Solo products were provided to the subjects with fully charged batteries, and the cartridges were weighed before and after use to determine the amount of e-liquid aerosolized.

Study Assessments

Five different subjective effects questionnaires were administered during the study on paper forms and were slightly modified from questionnaires used in previous studies. Each questionnaire was provided to subjects on the day of study check-in for training purposes. The product liking (“At this moment, how much do you like the product?”) and product effects (“Rate the degree to which you feel positive/negative effects of the product at this moment”) questionnaires were completed at 15, 30, 45, 60, 90, 120, 150, 180, and 240 minutes following the start of product use during each test session. The urge to smoke (“How strong is your current urge to smoke your usual brand cigarette?”) questionnaire was completed prior to and at 5, 15, 30, 45, 60, 90, 120, 150, 180, and 240 minutes following the start of product use during each test session. The overall product liking (“Overall, how much do you like the product?”), and overall intent to use again (“Rate the degree to which you would like to use the product again”) questionnaires were completed only at the 240-minute time point. All questionnaires were administered as 11-point numeric rating scales of 0 to 10, with “strongly like/dislike,” “no urge,” “no positive/negative effects,” or “not at all” on the left anchor (“0”) and “strongly like/dislike,” “extremely strong urge,” “extremely positive/negative effects,” or “very much” on the right anchor (“10”). A midpoint descriptor “Neither like nor dislike” was included for the product liking and overall product liking questionnaires.

Venous blood samples for plasma nicotine concentration measurement were collected at 5, 0.5, 5, 7.5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, and 240 minutes relative to the start of product use during each

test session with the -0.5-minute sample used as the preferred baseline sample. Samples were analyzed and nicotine concentrations determined in plasma using a validated liquid chromatography tandem mass spectrometry method at Celerion Global Bioanalytical Services (Lincoln, NE).

Blood pressure and heart rate were measured prior to product administration and at 15, 30, 45, 60, 120, 180, and 240 minutes following the start time of product use during each test session. Where the measurements coincided with blood sampling, the blood pressure and heart rate were taken after blood sampling to minimize the impact on nicotine PK results.

Safety and tolerability were evaluated based on data collected from physical and oral examinations, clinical laboratory tests, electrocardiograms, and adverse events.

Statistical Analysis

Based on data from a previous study of the similar first-generation product (Stiles et al., 2017), the minimum number of subjects needed to complete all test sessions was 30 to allow for 80% power to detect the hypothesized 20% differences between Vuse Solo and CC with the significance threshold set at p=0.0013 level (Bonferroni-adjusted for multiple comparisons) for the primary endpoints. The significance threshold for secondary endpoints was 0.05. Forty (40) subjects were initially randomized in order to ensure that 30 subjects completed all test sessions.

Data management and statistical analyses were performed by Celerion (Lincoln, NE). Statistical summarizations and comparisons were calculated using SAS version 9.3 (SAS, Cary, NC). Phoenix® WinNonlin® version 6.3 (Certara, Princeton, NJ) was used to calculate non-compartmental nicotine pharmacokinetics and subjective measure response parameters.

In all analyses, Vuse Solo was compared to CC and nicotine gum. Mixed effects models for analysis of variance were used to compare product liking, intent to use again, and product effects. Sequence, period, and product were included as fixed effects and subject-nested-within-sequence was included as a random effect. A mixed model analysis of covariance was used to compare the urge to smoke parameters, with sequence, period, and product included as fixed effects, subject-nested-within-sequence as a random effect, and baseline score as a covariate. All subjective effects parameters were analyzed on the original scale.

Measured plasma nicotine concentrations that were below the lower limit of quantitation (0.200 ng/mL) were set to one-half of the lower limit of quantitation for data summarization and statistical analysis. Individual nicotine concentrations were adjusted for the presence of nicotine at baseline, as described by Shiffman et al. (2009),[57] and all pharmacokinetic parameters were calculated from the adjusted concentrations. A mixed-effects model was used to compare the nicotine uptake parameters. AUCs and C_{max} were analyzed on the natural log scale. Sequence, period, and investigational product were included as fixed effects and subject-nested-within-sequence was included as a random effect. Wilcoxon signed rank test was used in T_{max} comparisons. Any subjects with $T_{max} \geq 120$ minutes were considered not to

have used the study products effectively during the test session, and the subjective effects and PK data analyses were performed both with and without those subjects. Data presented herein excludes those subjects.

The maximum increase in systolic and diastolic blood pressures and heart rate were compared using a mixed-effects model. If there was no increase from baseline (prior to product use) and the difference was zero or less, zero was reported for the maximum increase.

Data Availability

The applicable data generated or analyzed during this study are included in this manuscript (and its supplementary Tables). Additional datasets generated and/or analyzed during the study are available from the corresponding author on reasonable request.

Declarations

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Author Contributions

Study concept and design: E.R., S.B., C.C.

Acquisition of the data: C.C., T.J., E.S.

Drafting of the manuscript: C.C.

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

C.C., T.J., E.S., E.R., and S.B. are full-time employees of RAI Services Company, and P.N. is a former full-time employee 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

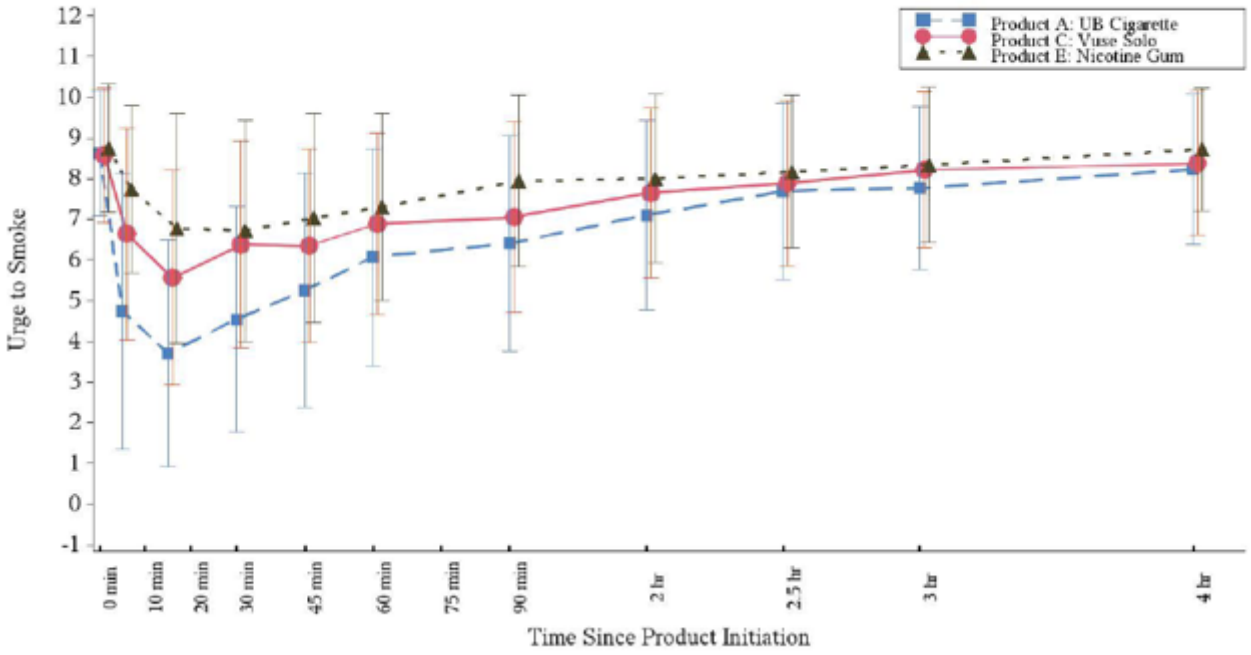

Figure 1

Arithmetic mean (SD) urge to smoke response profiles over four hours after initiation of product use.

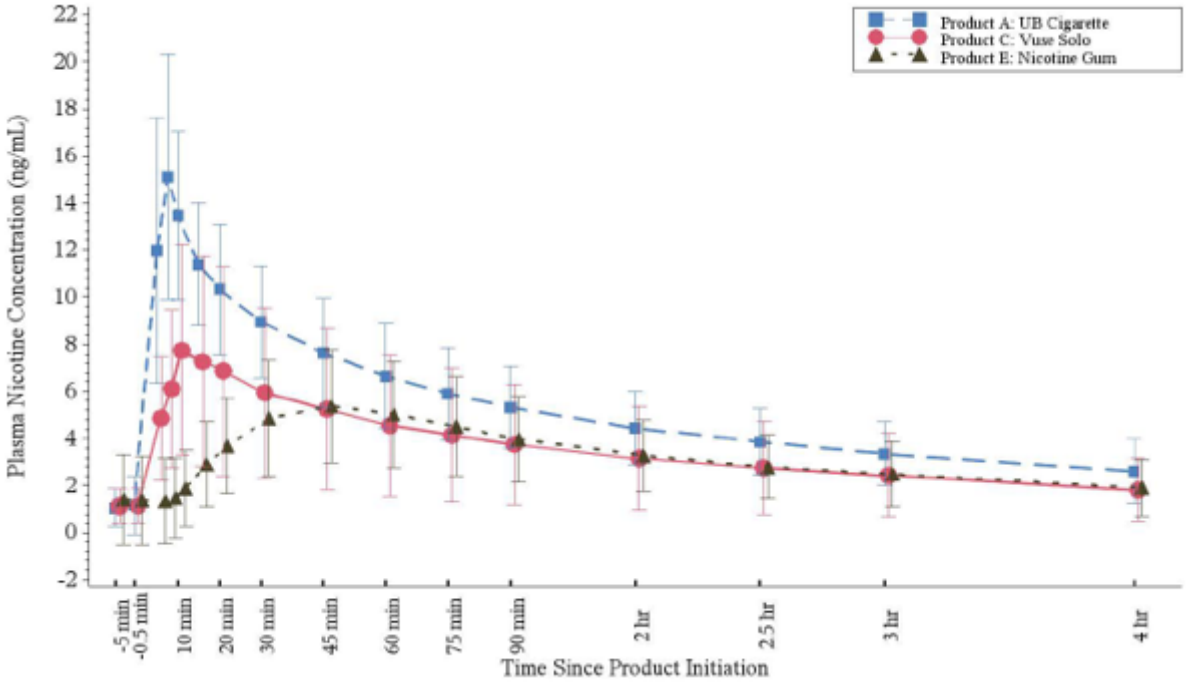

Figure 2

Arithmetic mean (SD) baseline-adjusted plasma nicotine concentration profiles.

Supplementary Files

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- VuseSoloPart1SuppCampbellAL8Nov2021.docx