A set of single arm, randomized cross over studies in confinement to assess abuse liability and nicotine pharmacokinetics of Vuse Alto ENDS

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Introduction

Cigarette smoking continues to be the 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 conditions. Whereas smoking conventional cigarettes requires combustion of tobacco, use of electronic nicotine delivery systems (ENDS) does not. 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 and reduced toxicant exposure to consumers who switch from cigarettes to ENDS. Public health authorities, such as Public Health England, Royal College of Physicians, and National Academies of Sciences, Engineering, and Medicine, have recognized the potential public health benefit of current smokers switching to ENDS. In addition, several recent publications by Goldenson et al., 2021, Foulds et. al., 2021, Dyer et. al., 2021, and Gades et. al., 2022 suggest that both nicotine concentrations and availability of flavors, along with strict youth access to ENDS, may help facilitate complete switching to ENDS by the adult smoker who seeks to achieve tobacco harm reduction.

The final FDA guidance for the ENDS Premarket Tobacco Product Application (PMTA) recommends conduct of a human abuse liability (AL) study, including nicotine pharmacokinetic assessments, to provide evidence that ENDS may be appropriate for protection of public health. FDA guidance suggests studies assess the AL of the new product relative to tobacco products with known AL. Previous published AL studies of novel tobacco products have included comparators such as high and low abuse liability tobacco comparator products.

Results from AL and pharmacokinetic (PK) studies using the current formulation of e-liquids for Vuse Alto, shown here, demonstrate that use of Vuse Alto ENDS suppressed urge to smoke compared to combustible cigarettes (CC) and achieved similar likability to CC while exposing subjects to lower nicotine levels. The results from these studies will inform AL and nicotine exposure from the use of Vuse Alto products across an array of nicotine concentrations and flavor variants, as well as providing a basis for similar study design of future AL and PK studies.

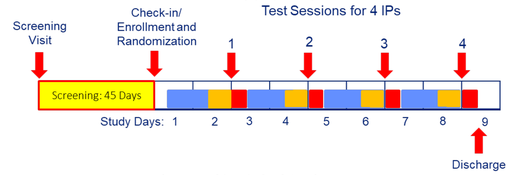
Study Design

Two clinical studies were completed, one focused on nicotine PK across various nicotine concentrations and flavors, the second evaluated AL across nicotine concentrations for one flavor. A total of 50 and 33 subjects were recruited with study completion rate of 96% and 97% for AL and PK studies, respectively. In both studies, subjects meeting all of the inclusion criteria and none of the exclusion criteria were enrolled, randomized to product use sequences based on Williams design, and confined at the study site for the duration of study conduct. For the AL study, subjective assessments and PK parameters of Vuse Alto tobacco flavor in 2.4% and 5.0% nicotine concentrations were compared against CC and NRT (nicotine gum), as the high and low AL comparators, respectively. In the PK study, nicotine PK parameters of Vuse Alto were assessed in eight e-liquid flavor variants at 1.8% and 2.4% nicotine concentrations.

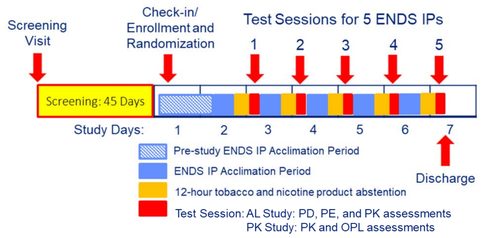
Matriculated subjects were randomly assigned to product use sequences to allow exposure to all investigational products (IPs) in each study. All subjects underwent product acclimation periods to allow familiarization with each products and underwent 12 hours of nicotine tobacco product abstention periods prior to taking part in a test session where subjects used CC or ENDS IP for up to 10 minutes *ad libitum*. Nicotine gum was used for 30 minutes *ad libitum*, as per product insert, in both the AL and PK studies. For both studies, each test session lasted for 240 minutes, during which, responses to subjective assessments (collected in numeric rating scale [NRS] from 0 to 10) and physiological assessments as well as serial blood samples to assess nicotine PK parameters were collected.

Both the AL and PK studies were a single center, open-label, randomized, two-arm, within-arm crossover studies designed to evaluate elements of AL including subjective effects and physiological measures (pharmacodynamics [PD]), along with plasma nicotine uptake (PK) during and following ad libitum use of the ENDS IPs in generally healthy smokers.

Abuse Liability (AL) Study



Pharmacokinetic (PK) Study



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- Gades, M.S. et al. The role of nicotine and flavor in the abuse potential and appeal of electronic cigarettes for adult current and former cigarette and electronic cigarette users: A systematic review. Nicotine Tob Res Online ahead of print. doi: 10.1093/ntr/ntac073 (2022).
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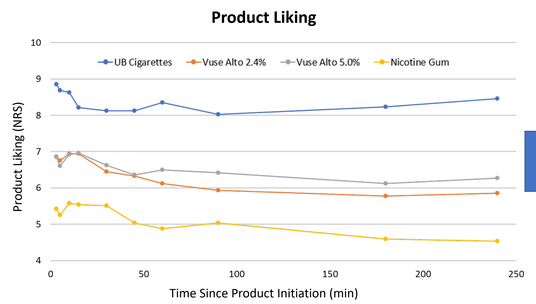
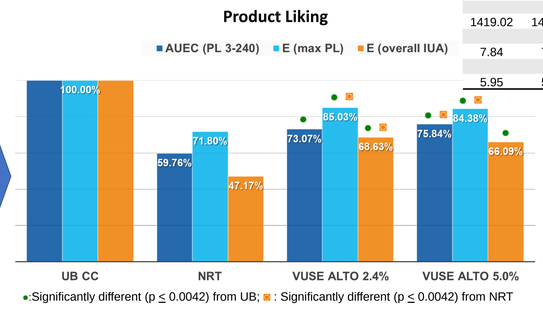
Results

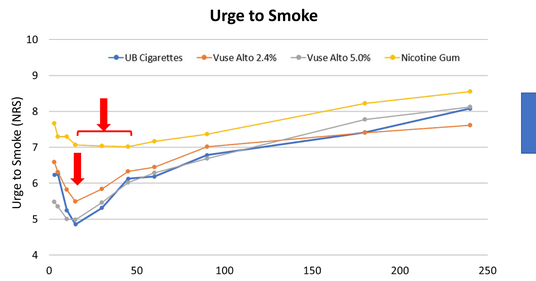
Abuse Liability Study

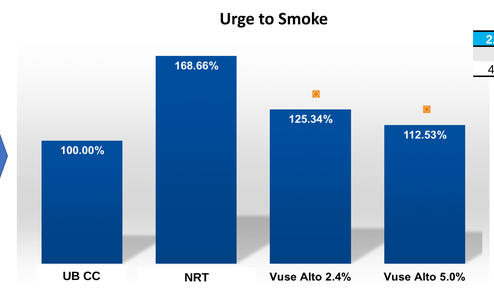




	2.4%	5.0%	UB CC	NRT
$AUEC_{PL\ 3\text{-}240}$	1419.02	1472.84	1941.93	1160.58
$E_{max\ PL}$	7.84	7.78	9.22	6.62
$E_{overall\ IUA}$	5.95	5.73	8.67	4.09

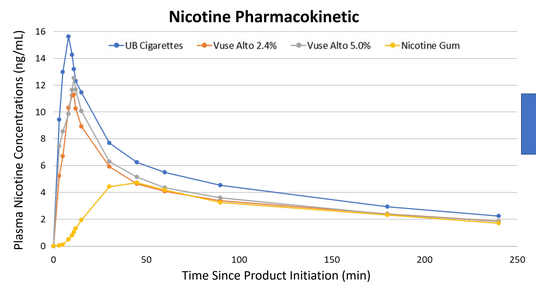
●:Significantly different ($p \leq 0.0042$) from UB; ■: Significantly different ($p \leq 0.0042$) from NRT

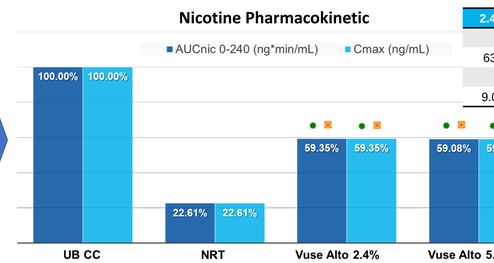




	2.4%	5.0%	UB CC	NRT
$E_{min\ UTS}$	4.60	4.13	3.67	6.19

●:Significantly different ($p \leq 0.05$) from UB; ■: Significantly different ($p \leq 0.05$) from NRT

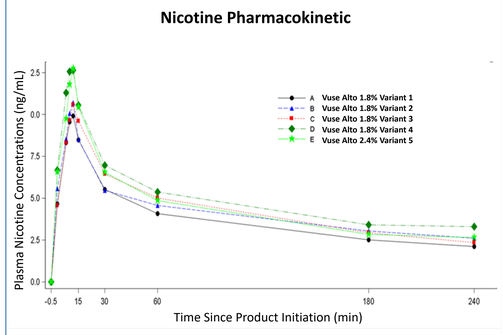




	2.4%	5.0%	UB CC	NRT
$AUC_{nic\ 0\text{-}240}$ (ng*min/mL)	631	678	1058	464
C_{max} (ng/mL)	9.08	9.04	15.3	3.46

●:Significantly different ($p \leq 0.05$) from UB; ■:Significantly different ($p \leq 0.05$) from NRT. *Note: The log-transformed PK parameters. ($AUC_{nic\ 0\text{-}240}$ and C_{max}) were analyzed using a mixed effect model, with fixed effects for IP, period, sequence; and subject nested within sequence as random effect.*

Pharmacokinetic Study



Pharmacokinetic Comparison Between Studies

Parameter	Statistics	Pharmacokinetic Study					Abuse Liability Study	
		Vuse Alto 1.8% Variant 1	Vuse Alto 1.8%, Variant 2	Vuse Alto 1.8%, Variant 3	Vuse Alto 1.8%, Variant 4	Vuse Alto 2.4% Variant 5	Vuse Alto 2.4%	Vuse Alto 5.0%
$AUC_{nic0\text{-}15}$ (ng*min/mL)	n	33	33	32	32	33	44	44
	GM	78.08	81.54	76.62	99.39	96.26	85.742	85.680
	95% CI Lower	57.11	60.70	56.44	73.62	71.27	62.18	60.92
	95% CI Upper	106.75	109.53	104.22	134.18	130.01	113.45	120.55
$AUC_{nic0\text{-}240}$ (ng*min/mL)	n	33	33	33	32	33	44	44
	GM	679.38	666.28	747.33	850.28	798.51	659.592	669.254
	95% CI Lower	517.86	472.38	558.49	629.23	601.56	543.77	490.23
	95% CI Upper	891.28	939.77	1000.02	1148.98	1059.94	815.43	871.45
C_{max} (ng/mL)	n	33	33	33	32	33	44	44
	GM	8.43	8.89	8.29	10.60	10.78	9.632	9.049
	95% CI Lower	6.32	6.61	6.19	7.79	8.22	7.58	7.22
	95% CI Upper	11.24	11.95	11.11	14.42	14.13	11.72	13.38
$E_{overall\ PL}$	n	33	33	33	32	33	44	43
	Mean	5.5	5.8	5.8	6.9	5.7	6.4	6.7
	CV%	40.35	46.46	50.27	29.05	42.88	46.67	43.39
	Median	6.0	6.0	6.0	7.5	5.0	7.0	7.0

$AUC_{nic0\text{-}15}$: baseline-adjusted area under the plasma nicotine concentration-versus-time curve from zero to 15 minutes after the start of IP use; **$AUC_{nic0\text{-}240}$**: baseline-adjusted area under the plasma nicotine concentration-versus-time curve from zero to 240 minutes after the start of IP use; **C_{max}**: maximum baseline-adjusted plasma nicotine concentration; **CI**=confidence interval; **GM**=geometric mean; **PK**=pharmacokinetic; **SD**=standard deviation; Note: 95% CI are based on the estimation of geometric mean.

Objectives and Endpoints

Unless otherwise noted, all endpoints were collected over 4 hours during/after the start of IP use

Abuse Liability Study Endpoints

Primary Endpoints:

- Product Liking [PL] parameters ($AUEC_{PL\ 0\text{-}240}$ and E_{maxPL})
- Overall Intent to Use Again [OIUA] ($E_{overall\ IUA}$)

Secondary Endpoints:

- Baseline-adjusted nicotine PK parameters ($AUC_{nic\ 0\text{-}240}$, $AUC_{nic\ 0\text{-}15}$, C_{max} and T_{max})
- Product Effects [PE] and Urge to Smoke [UTS] parameters.
- Overall Product Liking [OPL] assessed at then end of 4 hours after the start of IP use.
- Mean maximum change in physiological measures (i.e., heart rate and blood pressure)

Pharmacokinetic Study Endpoints

Primary Endpoints:

- Overall nicotine uptake ($AUC_{nic\ 0\text{-}240}$).
- Maximum plasma nicotine concentration (C_{max}).

Secondary Endpoints:

- Nicotine uptake during first 15 minutes ($AUC_{nic\ 0\text{-}15}$).
- Time to maximum plasma nicotine concentration (T_{max}).
- Overall Product liking [OPL] assessed at the end of 4 hours after the start of IP use.

Materials and Methods

Generally healthy adult (21 to 60 years of age) male and female primary smokers of filtered menthol or non-menthol cigarettes with occasional or episodic ENDS use were recruited. All subjects provided informed consent prior to initiating any study procedures. Matriculated subjects agreed to reside in the study center for 9 (AL Study) or 7 (PK Study) days.

Subjects in both studies were confined at the study center for the duration of clinical conduct and used all study products during product acclimation sessions on the first 2 days. The ENDS IPs used in both studies (Vuse Alto) are comprised of a non-adjustable power unit with a rechargeable battery and a non-refillable pod containing approximately 1.8 mL of e-liquid of varying flavors and nicotine contents of 1.8%, 2.4% and 5.0% by weight.

Results and Conclusions

Product Liking (AL Study)

- Maximum product liking for both ENDS IPs assessed in the AL study were significantly lower than cigarette and greater than nicotine gum.
- Product liking (PL) over 4 hours for both ENDS IPs in the AL study were significantly lower than cigarettes and the ENDS IP with 5.0% nicotine content was significantly greater than nicotine gum.
- Overall intent to use again for both ENDS in the AL study IPs were significantly lower than cigarette, but only ENDS IP with 2.4% nicotine content was significantly greater than nicotine gum.

Plasma Nicotine Uptake (PK) Endpoints (AL and PK study)

- Plasma nicotine delivery profiles of both ENDS IPs in the AL study were similar but lower than cigarettes and greater than nicotine gum.
- Plasma nicotine delivery profiles and PK parameters from the PK study were similar among flavor variants as evidence by overlap of 95% confidence intervals.

Urge to Smoke (AL Study)

- ENDS IPs relieved urge to smoke similar to cigarette, and significantly better than nicotine gum.

Product Effects (not shown)

- Both ENDS IPs in the AL study resulted in significantly higher reported positive product subjective effects than nicotine gum but lower than cigarettes.
- Negative product effects for both ENDS IPs in the AL study were not significantly different from cigarette or nicotine gum.

Overall Product Liking (AL and PK study)

- Overall Product Liking parameters were similar between ENDS IPs in the AL study; significantly higher than nicotine gum but lower than cigarette.
- Overall Product Liking of ENDS IPs in PK study were similar among the flavors and between nicotine contents (1.8% versus 2.4%) and these results were also similar to AL study results.

Overall Conclusion

- Abuse liability potentials of Vuse Alto with 2.4% and 5.0% nicotine are lower than cigarette and greater than nicotine gum.
- PK parameters from both studies indicate nicotine delivery from ENDS products may not be solely driven by the nicotine content but also driven by the individual use pattern.

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