Pharmacokinetic Evaluation of E-Liquid Flavors in Three Vuse Electronic Nicotine Delivery Systems (ENDS)

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Abstract

The impact of flavors on Electronic Nicotine Delivery Systems (ENDS) product use and nicotine exposure is an important factor in product regulation. As such, we evaluated the nicotine pharmacokinetics (PK) for three ENDS products (Vuse Ciro, Vibe and Solo) across four flavor variants for each product in single-blinded, randomized studies.

A total of 369 subjects (Ciro: 121; Vibe: 126; Solo: 122) who were primarily smokers completed the 2-day confinement study using one of three ENDS in one of four flavors. Nicotine contents of e-liquids for Ciro, Vibe and Solo were 1.5%, 3.0% and 4.8%, respectively.

Subjects acclimated to an assigned e-liquid flavor and product for one week prior to confinement. On the evening of Day 1, subjects were required to abstain from tobacco/nicotine products for 12 hours, followed by a test session on Day 2. During test sessions, subjects were required to use *ad libitum* their assigned ENDS for 10 minutes. Blood samples were collected before, during, and after a 10-minute *ad libitum* ENDS use session for 60 minutes after the start of ENDS use. Product liking was assessed at the end of test sessions.

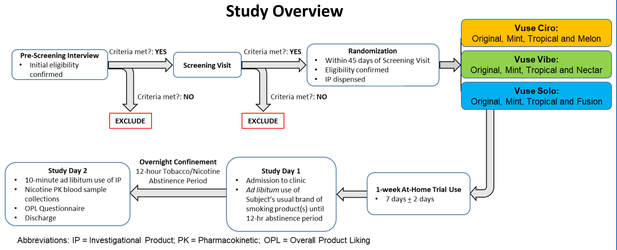
Baseline-adjusted geometric mean C_{max} ranged from 4.35 to 5.88 ng/mL (Ciro), 4.60 to 6.84 ng/mL (Vibe) and 6.53 to 8.21 ng/mL (Solo). Geometric mean $AUC_{nic0–60}$ ranged from 134.63 to 184.67 ng*min/mL (Ciro), 160.32 to 236.11 ng*min/mL (Vibe) and 206.87 to 263.52 ng*min/mL (Solo). The primary study endpoints were similar across the four flavors within each ENDS product as evidenced by overlapping 90% confidence intervals. This suggests that flavors may have a limited impact on nicotine exposure in these ENDS products in an acute exposure setting.

Introduction

To assess the impact of ENDS flavors on nicotine uptake, we conducted three separate nicotine PK studies in human subjects who used one of three different ENDS platforms marketed by RJ Reynolds Vapor Company. The platforms included Vuse Ciro with cartridges containing 1.5% nicotine by weight, Vuse Vibe with cartridges containing 3.0% nicotine by weight and Vuse Solo with cartridges containing 4.8% nicotine by weight.
Each of the three studies was executed following a parallel-group study design in which subjects were randomized to a single flavor variant. Subjects acclimated to the ENDS investigational products during 7 days of at-home use. This was followed by a PK test session in confinement to assess nicotine PK parameters from 10 minutes of *ad libitum* use of the IP. Plasma samples taken at timepoints of up to 60 minutes after the start of use were analyzed for overall nicotine exposure, maximum nicotine concentration and time to maximum concentration. In addition, overall product liking was assessed at the end of *ad libitum* product use during test sessions (13±1 minutes).

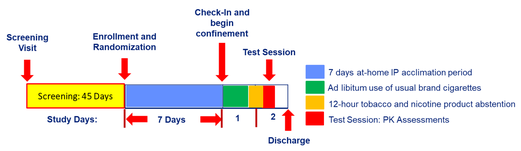
Study Design

Study Overview



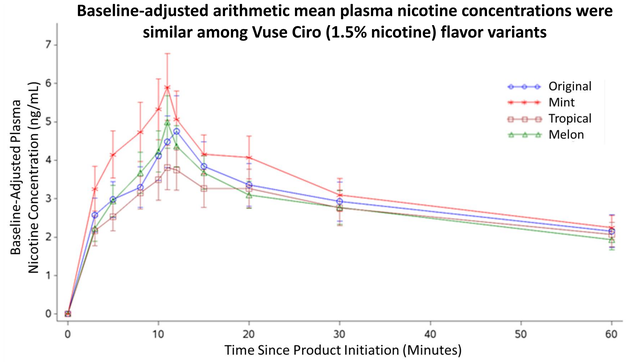
Abbreviations: IP = Investigational Product; PK = Pharmacokinetic; OPL = Overall Product Liking

Study Schematic

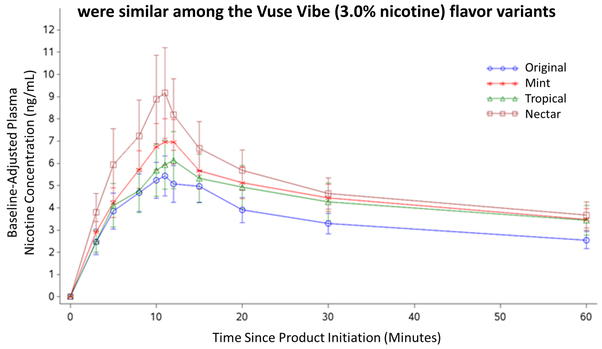


Results

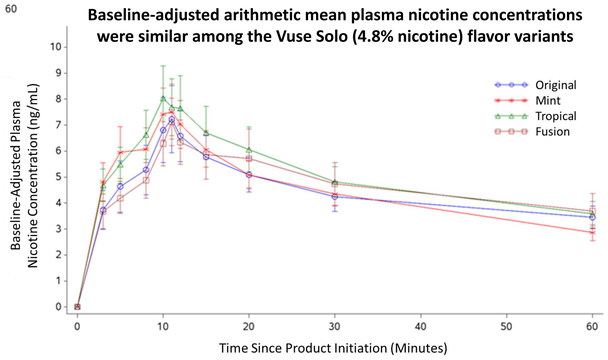
Baseline-adjusted arithmetic mean plasma nicotine concentrations were similar among Vuse Ciro (1.5% nicotine) flavor variants



Baseline-adjusted arithmetic mean plasma nicotine concentrations were similar among the Vuse Vibe (3.0% nicotine) flavor variants



Baseline-adjusted arithmetic mean plasma nicotine concentrations were similar among the Vuse Solo (4.8% nicotine) flavor variants



Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters and Following IP Use

	$AUC_{nic\ 0\text{-}60}$ (ng*min/mL) Geometric Mean (90% CI)	C_{max} (ng/mL) Geometric Mean (90% CI)	T_{max} (min) Median (Range)	Overall Product Liking Mean (SD)
Vuse Ciro (N=121)				
Original	138.11 (107.91, 176.75)	4.38 (3.39, 5.67)	11.06 (3.5-30)	6.0 (2.74)
Mint	184.67 (150.21, 227.04)	5.88 (4.69, 7.37)	10.51 (3-30)	5.8 (2.25)
Tropical	143.95 (110.97, 186.73)	4.35 (3.47, 5.47)	11.00 (3-30)	5.8 (2.52)
Melon	134.63 (106.49, 170.21)	4.68 (3.78, 5.80)	11.00 (3-30)	7.2 (1.93)
Vuse Vibe (N=126)				
Original	160.32 (121.59, 211.40)	4.60 (3.50, 6.04)	11.00 (2.8-60)	6.1 (2.87)
Mint	236.11 (190.36, 292.86)	6.84 (5.51, 8.48)	11.00 (7.6-61)	6.5 (2.49)
Tropical	180.62 (130.92, 249.18)	5.06 (3.72, 6.88)	11.00 (3-70.2)	6.9 (2.24)
Nectar	206.17 (157.14, 270.48)	5.85 (4.39, 7.80)	11.00 (3-30)	7.3 (2.29)
Vuse Solo (N= 122)				
Original	223.79 (180.13, 278.03)	6.91 (5.49, 8.70)	11.00 (5-60)	6.4 (2.50)
Mint	215.37 (175.92, 263.68)	6.53 (5.26, 8.10)	11.00 (3-30)	5.3 (2.46)
Tropical	263.52 (218.92, 317.20)	8.21 (6.87, 9.81)	11.00 (3-30.4)	7.5 (1.94)
Fusion	206.87 (156.70, 273.10)	6.67 (5.20, 8.56)	11.00 (3-30)	6.0 (2.53)

Objectives and Endpoints

The primary objectives of these studies were:

To assess the maximum baseline-adjusted plasma nicotine concentration (C_{max}) and the area under the baseline-adjusted plasma nicotine concentration-versus-time curve from time zero to 60 minutes ($AUC_{nic\ 0\text{-}60}$), with respect to the start of a 10-minute *ad libitum* product use period.

The secondary objectives of these studies were:

- To assess the time to maximum baseline-adjusted plasma nicotine concentration (T_{max}) and the area under the baseline-adjusted plasma nicotine concentration-versus-time curve from time zero to 15 minutes ($AUC_{nic\ 0\text{-}15}$), with respect to the start of a 10-minute *ad libitum* product use period.
- To measure overall product liking ($OPL_{overall}$) at 13 minutes ± 1 minute with respect to the start of the 10-minute *ad libitum* product use period.

Study Design and Methods

- Each was a single-center randomized study conducted at clinical research sites in New Jersey and Colorado
- Tobacco consumers ages 21-60 years who met all inclusion criteria (IC) and none of the exclusion criteria were enrolled. Key tobacco-specific IC were as follows:
  - Exclusive smokers - self-reported smoking ≥ 10 cigarettes per day (CPD) for at least 6 months prior to screening
  - Dual users - self-reported smoking ≥ 10 cigarettes per day (CPD) for at least 6 months prior to screening and used a nicotine-containing cig-a-like or tank-style ENDS at least weekly for at least 3 months prior to screening
  - Expired carbon monoxide levels > 10 ppm at Screening and at Check-in
- Informed consent was obtained from all subjects before any study procedures were performed

Subject Disposition

- Vuse Ciro Study: 143 subjects enrolled and randomized; 121 (84.6%) completed the study.
- Vuse Vibe Study: 144 subjects enrolled and randomized; 126 (87.5%) completed the study.
- Vuse Solo Study: 148 subjects enrolled and randomized: 122 (82.4%) completed the study.

The studies were reviewed and approved by an Institutional Review Board and 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.

Conclusions

- The primary study endpoints (C_{max} and $AUC_{nic\ 0\text{-}60}$), were similar across the four flavors within each ENDS product as evidenced by overlapping 90% confidence intervals.
- Our results suggests that flavors may have a limited impact on nicotine exposure from use of these ENDS products in an acute exposure setting.

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