Abuse Liability Assessments of Vuse Alto Golden Tobacco in Adult Smokers

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Background and study design

Regulatory Requirement & Guidance:

- United States Food and Drug Administration (FDA) Center for Tobacco Products' PMTA Guidance for Electronic Nicotine Delivery Systems (ENDS) (2019)
- FDA's Center for Drug Evaluations and Research (CDER) Guidance on Assessment of Abuse Potential of Drugs (2017)

Study Design:

- A Randomized, Open-Label, Crossover Study to Assess Elements of Abuse Liability for Two Vuse Alto Golden Tobacco 2.4% and 5.0% Electronic Nicotine Delivery Systems in ENDS naïve subjects
- A 9-day confinement study with four test sessions preceded by product acclimation periods and 12-hr tobacco/nicotine abstinence periods

Study overview

Two nicotine levels of Vuse Alto Golden Tobacco

- 2.4% and 5.0% nicotine concentrations by weight

Comparator products

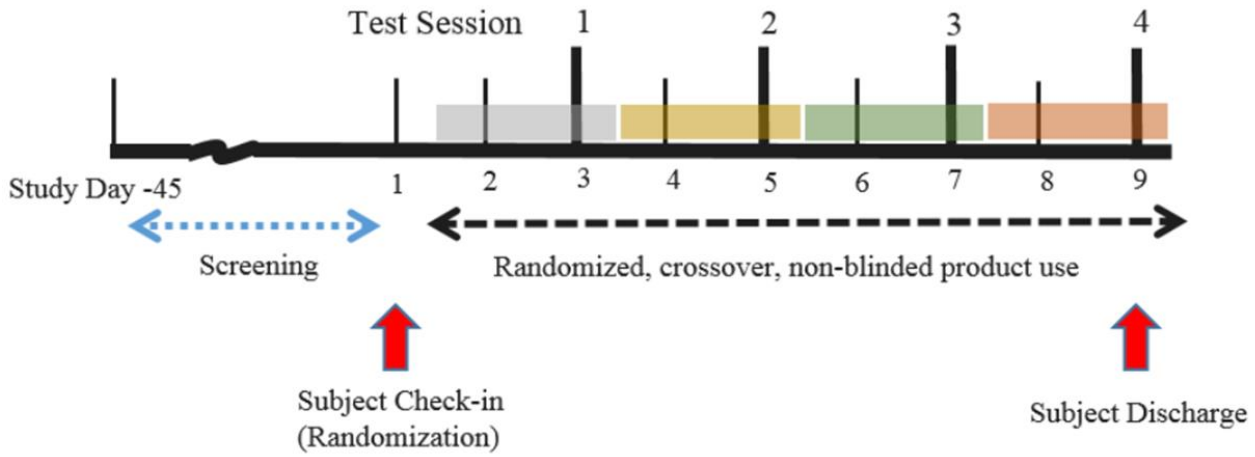
- High Abuse Liability (AL) comparator: Usual brand cigarette (UB CC)
- Low Abuse Liability (AL) comparator: Nicotine gum (NRT)

Test Session Product use and observation duration

- 10 minutes of *ad libitum* use for ENDS and UB Cigarette
- 30 minutes of *ad libitum* use for nicotine gum
- Observed duration of 240 minutes

Study overview

- 9-day confinement period
- Randomized 4-way cross-over study design
- IP familiarization over 1.5 days prior to Test Sessions:
  - At least 4 IP uses for both ENDS and NRT
- 4 Test Sessions (2 Study IP and 2 comparators) over 9 days
- 4-hour Test Sessions with PK/PD assessments (Days 3 through 9)



IP=Investigational Product; PD=Pharmacodynamic; PK=Pharmacokinetic; ENDS=Electronic Nicotine Delivery System; NRT=Nicotine Replacement Therapy.

Objectives

Subjective assessments:

- Product Liking (PL)*
- Overall Intent to Use Again (OIUA)*
- Product Effects (PE)
- Urge to Smoke (UTS)
- Overall Product Liking (OPL)

Pharmacokinetic assessments:

- Plasma nicotine uptake over the first 15 minutes and over 4 hours

Physiological measures:

- Mean maximum heart rate and blood pressure

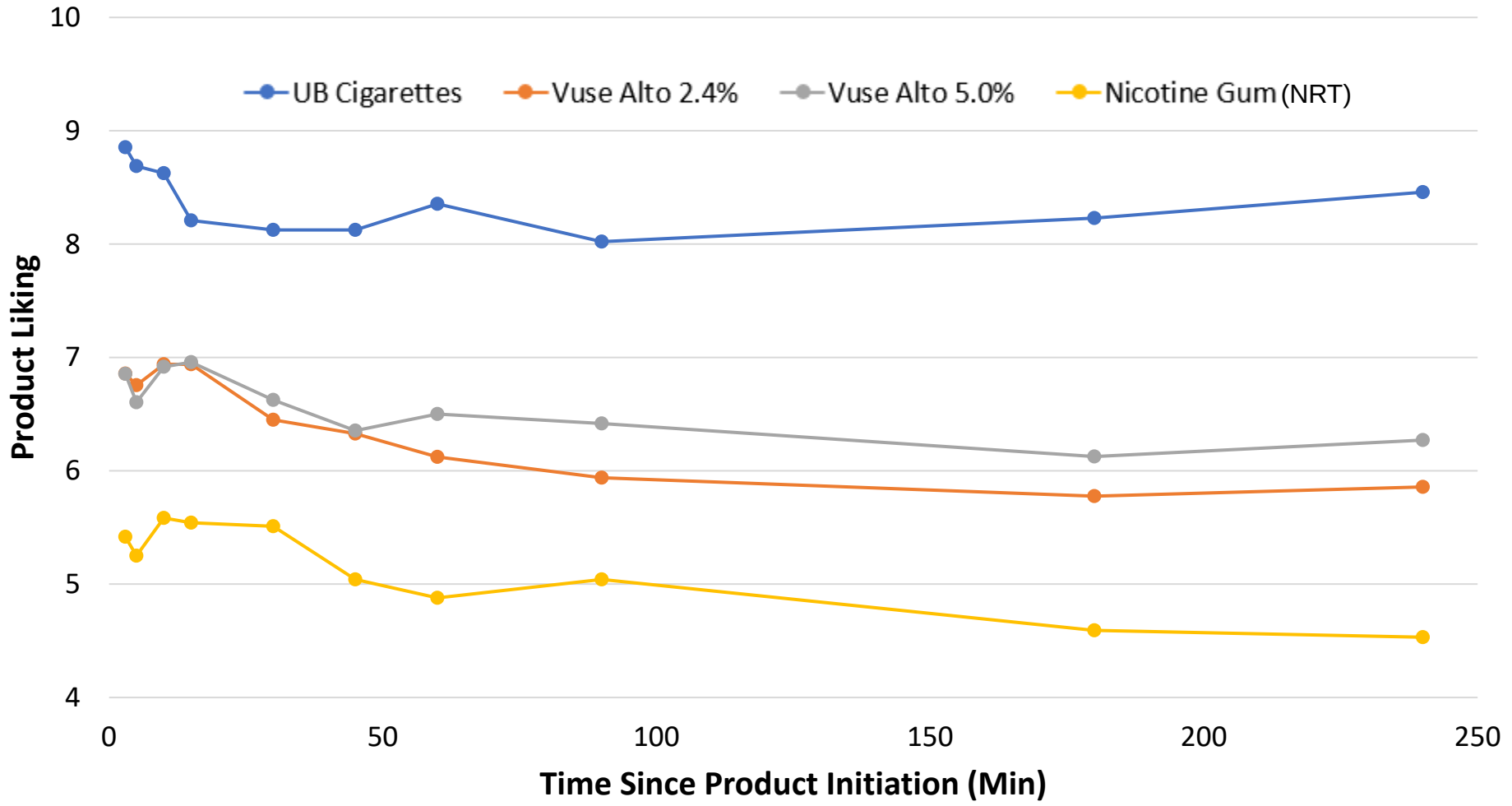
* Primary outcome measures

Study population

	Product Sequence				Total
	ABCD	BDAC	CADB	DCBA	
Number of Subjects [Enrolled (Completers)]	12 (11)	12 (11)	13 (13)	13 (13)	**50 (48)**
Average Age (yrs)	38.3	43.3	44.1	35.8	**40.4**
Sex (M/F)	5 / 7	9 / 3	7 / 6	6 / 7	**27 / 23**
Ethnicity [n (%)]	Non-Hispanic 10 (83.3)	Non-Hispanic 12 (100)	Non-Hispanic 10 (76.9)	Non-Hispanic 12 (92.3)	**Non-Hispanic 44 (88.0)**
Race [n (%)]	White 10 (83.3)	White 9 (75.0)	White 11 (84.6)	White 10 (76.9)	**White 40 (80.0)**
Average BMI (kg/m^2)	32.6	29.0	31.0	28.9	**30.4**
Average Years Smoked	25	23	27	20	**24**
Average Cigarettes consumed per day	21	19	15	15	**17**

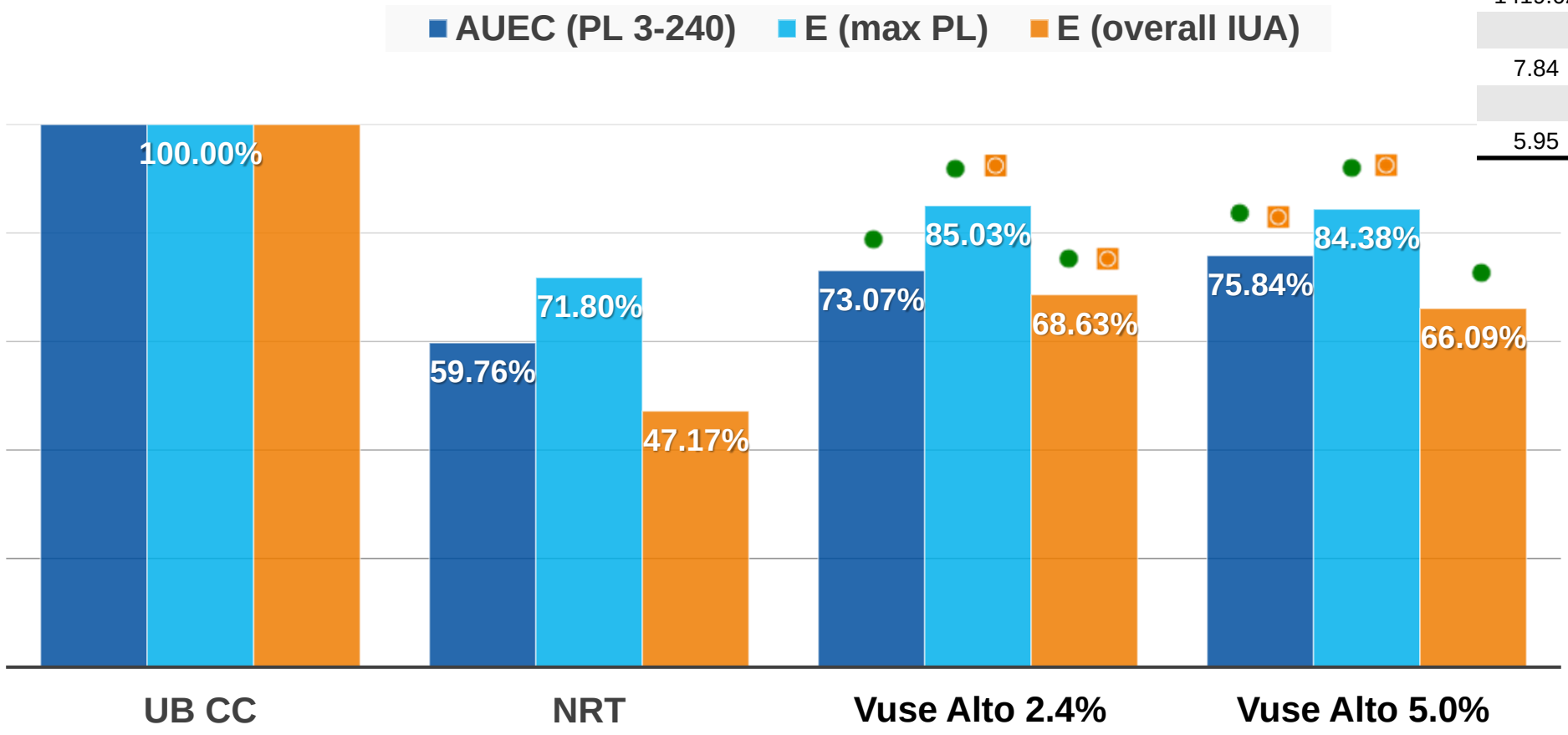
Product A: UB filtered, combustible cigarette**; Product B**: Vuse Alto Golden Tobacco, 2.4% nicotine;
Product C: Vuse Alto Golden Tobacco, 5.0% nicotine; **Product D**: 4 mg nicotine polacrilex gum

Vuse Alto use resulted in higher product liking and overall intent to use again vs. NRT



Vuse Alto use resulted in higher product liking and overall intent to use again vs. NRT

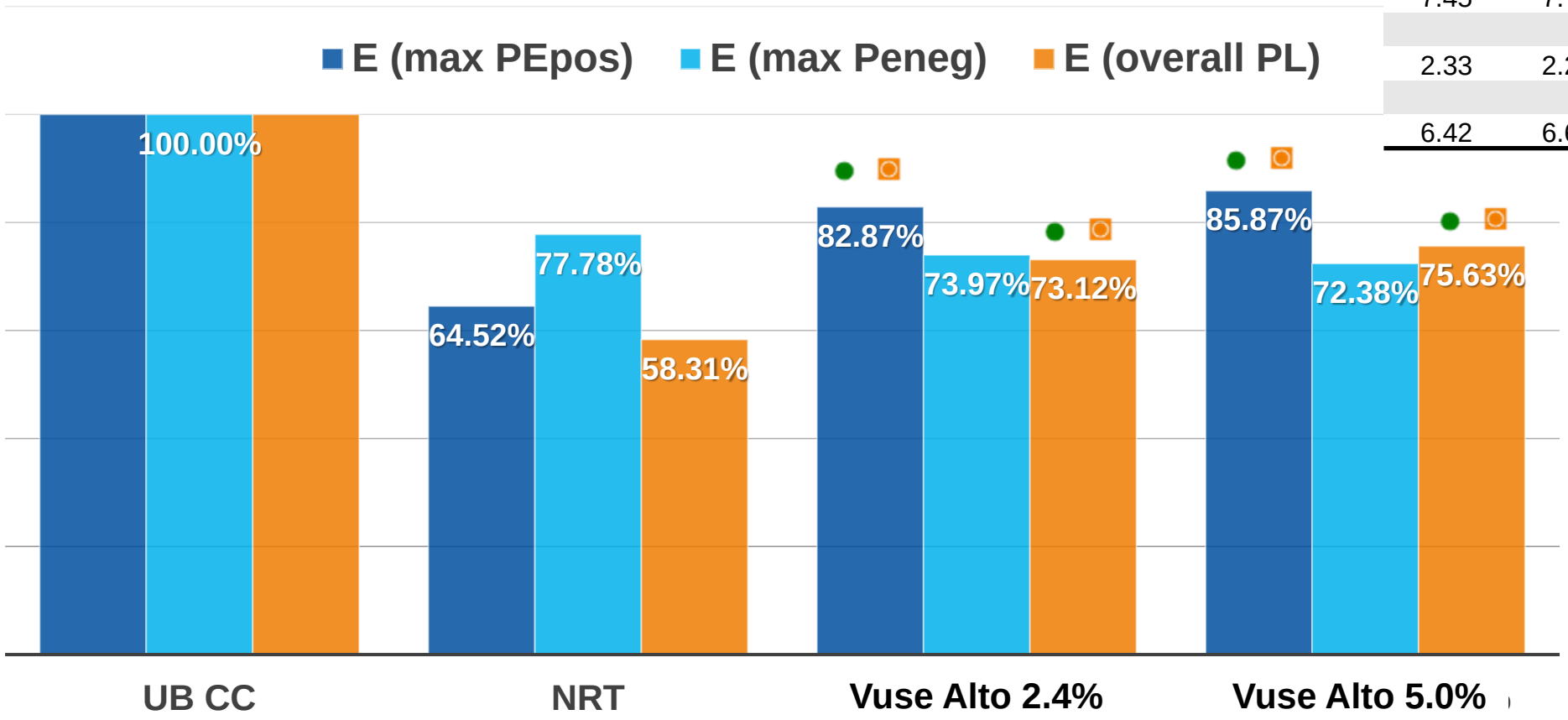
2.4%	5.0%	UB CC	NRT
$AUEC_{PL\ 3\text{-}240}$			
1419.02	1472.84	1941.93	1160.58
$E_{max\ PL}$			
7.84	7.78	9.22	6.62
$E_{overall\ IUA}$			
5.95	5.73	8.67	4.09



●:Statistically significantly different from UB CC; ◙ : Statistically significantly different from NRT.
For primary endpoints, $p \leq 0.0042$ is considered significant following Bonferroni adjustment.

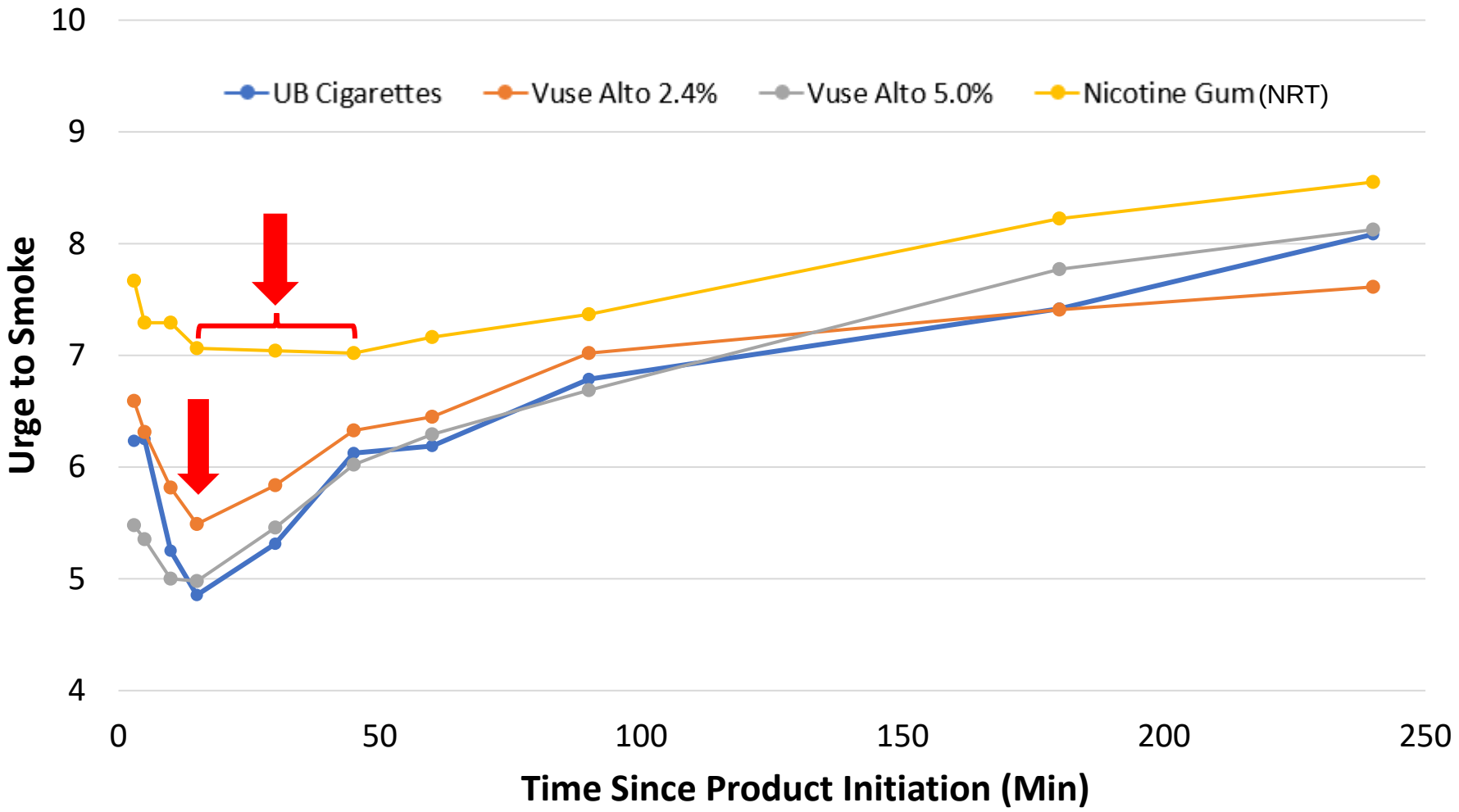
Vuse Alto use resulted in positive product effects and overall product liking

2.4%	5.0%	UB CC	NRT
$E_{max\ PEpos}$			
7.45	7.72	8.99	5.80
$E_{max\ PEneg}$			
2.33	2.28	3.15	2.45
$E_{overall\ PL}$			
6.42	6.64	8.78	5.12



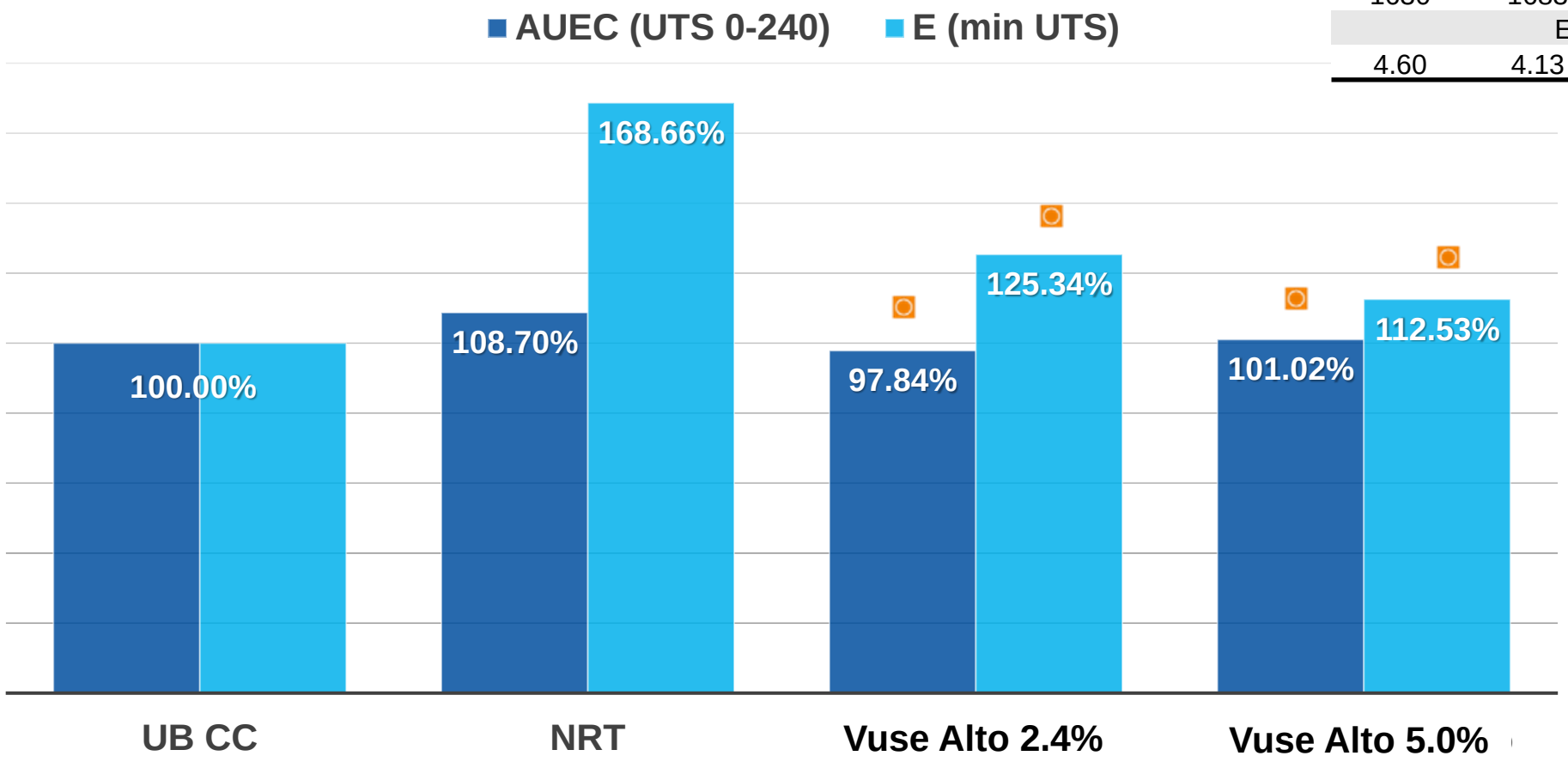
●:Statistically significantly different from UB CC; ◙ : Statistically significantly different from NRT. For secondary endpoints, $p \leq 0.05$ is considered significant.

Vuse Alto use reduced the urge to smoke



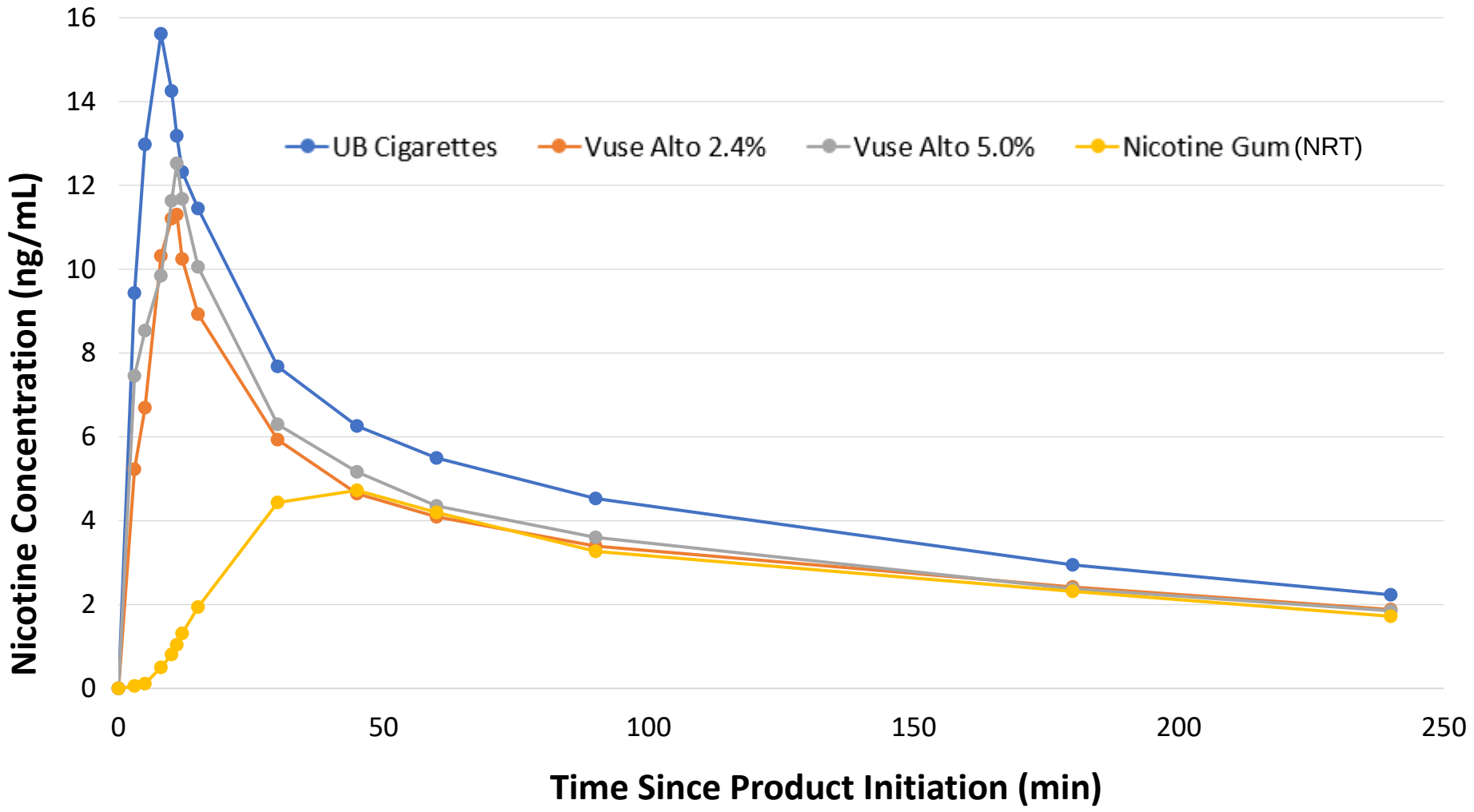
Vuse Alto use reduced the urge to smoke

2.4%	5.0%	UB CC	NRT
AUEC (UTS 0-240)			
1630	1683	1666	1811
$E_{min\ UTS}$			
4.60	4.13	3.67	6.19

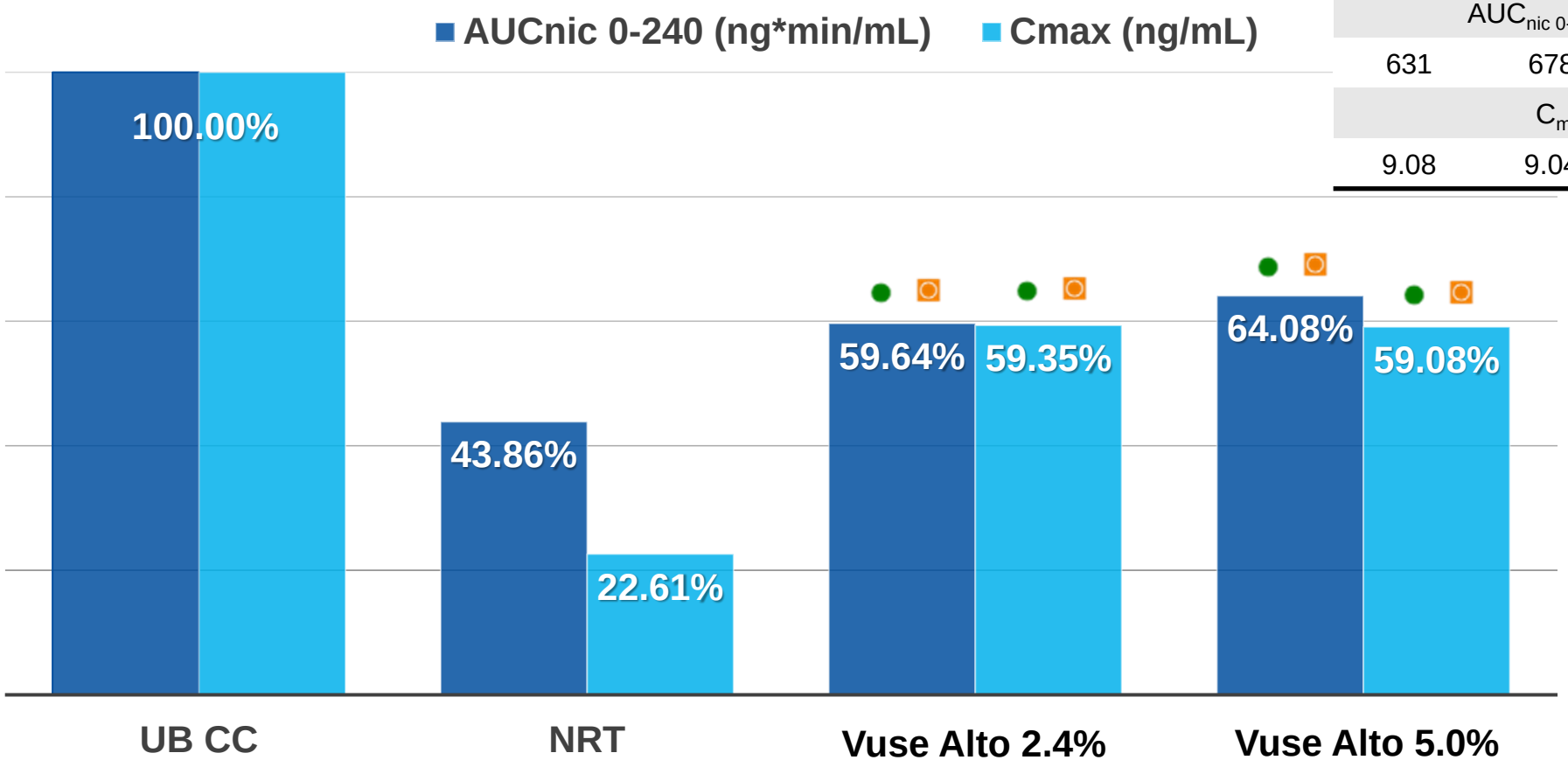


●:Statistically significantly different from UB CC; ◙ : Statistically significantly different from NRT.
For secondary endpoints, p ≤ 0.05 is considered significant.

Baseline-adjusted plasma nicotine concentrations over time



Vuse Alto use resulted in lower nicotine exposure vs. UB CC

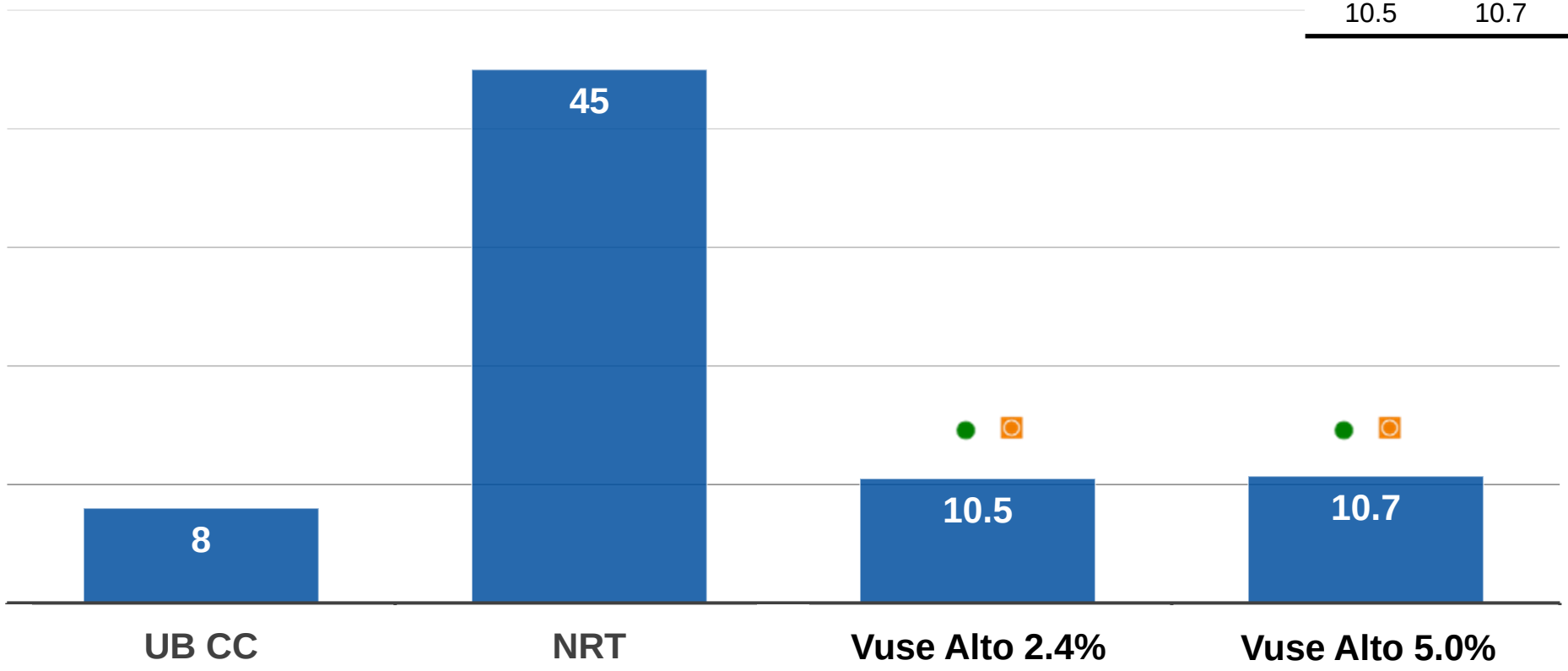


2.4%	5.0%	UB CC	NRT
$AUC_{nic\ 0-240}$ (ng*min/mL)			
631	678	1058	464
C_{max} (ng/mL)			
9.08	9.04	15.3	3.46

●:Statistically significantly different from UB CC; ◙ : Statistically significantly different from NRT. For secondary endpoints, $p \leq 0.05$ is considered significant.

T_{max}* (minutes)

2.4%	5.0%	UB CC	NRT
T_{max} (min)*			
10.5	10.7	8.00	45.0



*: Median value presented. ●:Statistically significantly different from UB CC; ▣ : Statistically significantly different from NRT. For secondary endpoints, p ≤ 0.05 is considered significant.

Physiological responses were transient and similar to comparator products

	Vuse Alto 2.4%	Vuse Alto 5.0%	UB CC[1]	NRT[2]
Max. increase in Systolic Blood Pressure (mmHg)	10.8	11.7[1]	7.61	12.3
Max. increase in Diastolic Blood Pressure (mmHg)	8.45[1]	7.70[1]	5.13	8.55
Max. increase in Heart Rate (bpm)	13.2[2]	14.2[2]	14.1	8.52

Values presented are mean maximum change from baseline. For secondary endpoints, $p \leq 0.05$ is considered significant

Adverse events were mild

Investigational Products (IP)	Alto Golden Tobacco (2.4% & 5%)	
Subjects in safety population	49	
Total number of AE (Subjects reporting AE)	22 (13)	
Most Common AE(s) for All IPs (% of subjects)	Headache Presyncope Others	10 (14.3%) 3 (6.1%) 1 (<1%)
AE per IP	5 / Vuse Alto 2.4%, 6 / Vuse Alto 5.0% 7 / UB CC 3 / NRT 1/ Pre-IP Administration	

Summary

- Product liking scores were higher for Vuse Alto as compared to NRT
- Positive product effects for Vuse Alto were higher than NRT
- All IPs showed similar negative product effects indices
- Vuse Alto resulted in reductions in UTS that were not statistically different from UB CC
- Nicotine PK measures fell between UB CC and NRT
- Physiological responses were transient and consistent with the comparators

Conclusions

- Subjective effects and PK data for Vuse Alto fell between UB CC and NRT
- Data supports that the Abuse Liability of Vuse Alto lies between UB CC and NRT
- Vuse Alto reduces UTS similar to UB CC
- AEs were mild in severity and no AE caused discontinuation of ENDS IP use or subject discontinuation from the study

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