

Modern Oral Nicotine Pouch Abuse Liability and Nicotine Pharmacokinetics Assessed in a Randomized Crossover Clinical Study

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Abstract

Modern oral nicotine pouches (MO) are smokeless tobacco products containing nicotine without tobacco leaf and provide a compelling alternative to cigarettes for those who would otherwise continue to smoke. Tobacco Harm Reduction (THR): a science-driven public health strategy to reduce the harm of smoking cigarettes. There is an opportunity to offer adult smokers who do not wish to quit tobacco and nicotine products altogether evidence-based, innovative smokeless product choices that are potentially less risky than traditional combustible cigarettes. In an 8-way randomized crossover study, we evaluated the abuse liability (AL) of six Velo PLUS Nicotine Pouches with varying nicotine content (6–15 mg per pouch) and flavors based on subjective effects and selected nicotine pharmacokinetic (PK) parameters. These products were compared with high-AL (combustible cigarettes), overall PL, and overall intent to use again, were also significantly lower than cigarettes ($p < 0.05$) across all MO flavors and nicotine strengths. Nicotine uptake rate from MOs was slower than from cigarettes, as indicated by a longer $T_{\max}$ and lower $AUC_{\text{nic}0-15}$ relative to cigarettes, indicative of lower reinforcement potential. Flavor did not affect nicotine uptake. Taken together, these findings indicate that Velo MOs exhibit a composite AL profile lower than cigarettes, but similar to NRT gum, while providing sufficient nicotine delivery supporting their potential role in THR.

Methodology

Endpoints

Primary	
PD Subjective Measures - Product Liking (PL) over 4-h after start of investigational product (IP) use	• $AUEC_{\text{PL } 5-240}$ (Area under the effect curve) • $E_{\max \text{ PL}}$ (Maximum PL)
Secondary	
PD Subjective Assessments - Positive & Negative Product Effects (PE), Urge to Smoke (UTS), Overall PL (OPL) & Overall Intent to Use Again (OIUA) measures over 4-h after start of IP use	• PE: $AUEC_{\text{PEpos } 5-240}$, $AUEC_{\text{PEneg } 5-240}$, $E_{\max \text{ PEpos}}$, $E_{\max \text{ PEneg}}$ • UTS: $AUEC_{\text{UTS } 0-15}$, $AUEC_{\text{UTS } 0-240}$, $E_{\min \text{ UTS}}$ • OPL: $E_{\text{overall PL}}$ • OIUA: $E_{\text{overall IUA}}$
PK Assessments - Plasma nicotine uptake over the first 15 minutes & over 4-h after start of IP use	• $AUC_{\text{nic } 0-15}$ & $AUC_{\text{nic } 0-240}$ • $C_{\max}$ • $T_{\max}$
PD Physiological Measures - Changes in blood pressure & heart rate over 4-h after start of IP use	Mean maximum increases in systolic & diastolic blood pressures, & heart rate

Study Design and Population

Two-site, 9-day confinement, randomized, open label, 8-way crossover study (Figure 1). Generally healthy adult males & females, 21 to 60 years, who smoked at least 10 cigarettes per day for at least 6 months prior to screening and smoked their first cigarette within 30 minutes of waking.

Product Use and Data Collection Timepoints

30-min use of at least one of each nicotine pouch and one piece of nicotine gum on Check-in Day -1 (familiarization); required 30-min use of each IP (except UBCC which was 5 minutes¹) during 4-hour Test Session. Each Test Session followed a 12-hour minimum nicotine abstinence period.

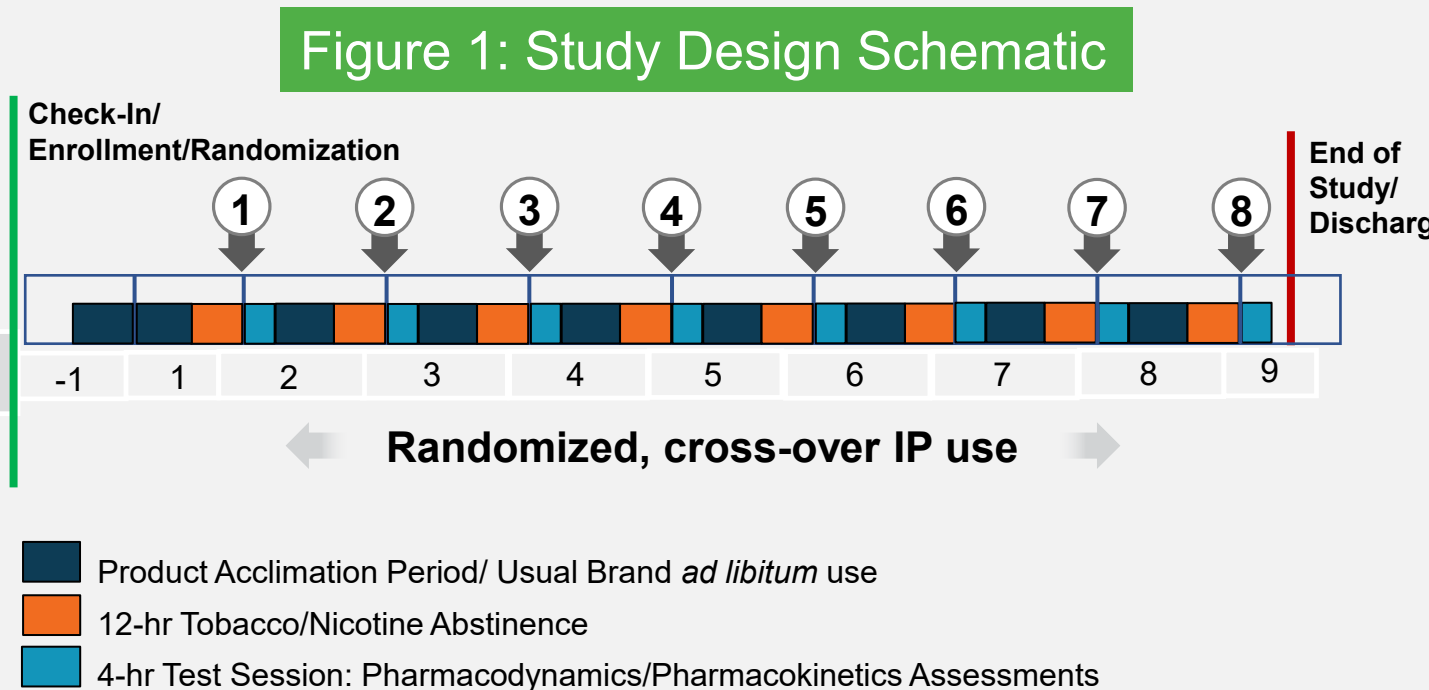
PD/PK Assessments: at baseline (-1) and at 5, 8, 10, 15, 20, 25, 30, 35, 40, 60, 120, and 240 minutes after start of IP use.

Investigational Products

Velo PLUS Pouch (nicotine level) Cool Mint (6, 12, 15 mg), Smooth (6 mg), Wintergreen (6 mg), and Dragon Fruit (6 mg)

Subjects' usual brand (UB) of cigarette (high-AL comparator)

Nicorette® White Ice Mint gum 4 mg nicotine (NRT) (low-AL comparator)



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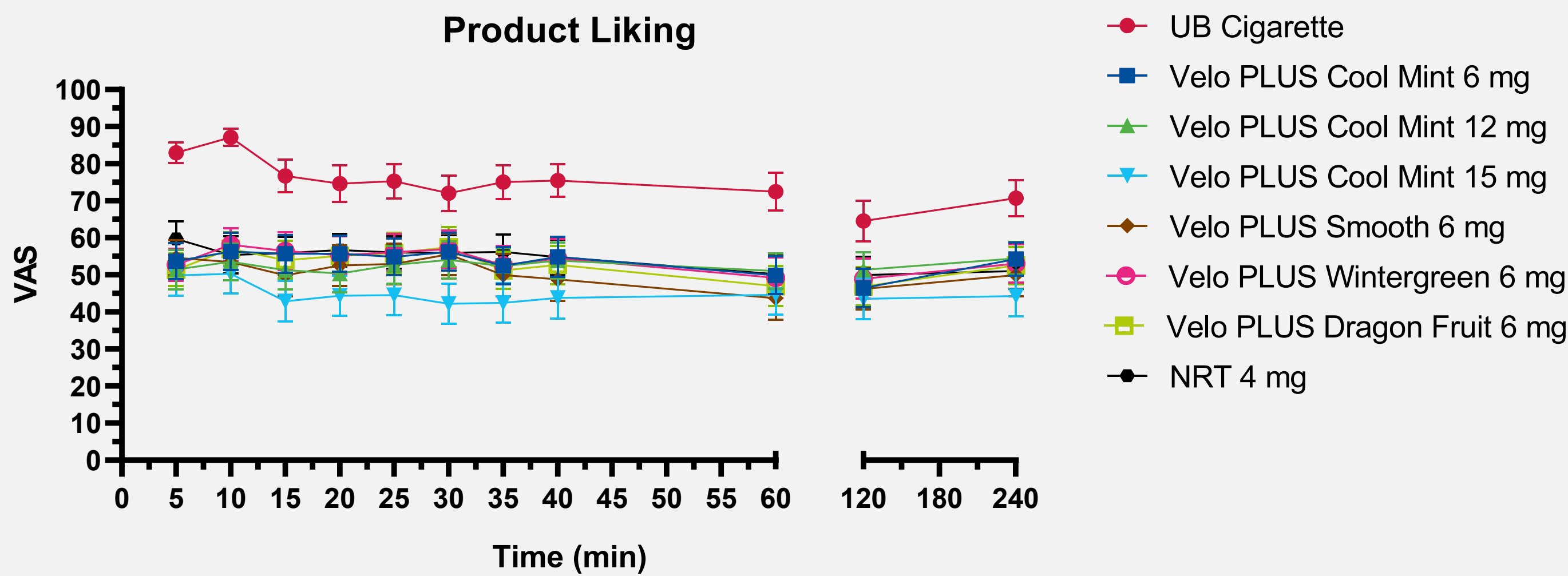
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Results

Figure 2: Mean Product Liking Scores Over Time



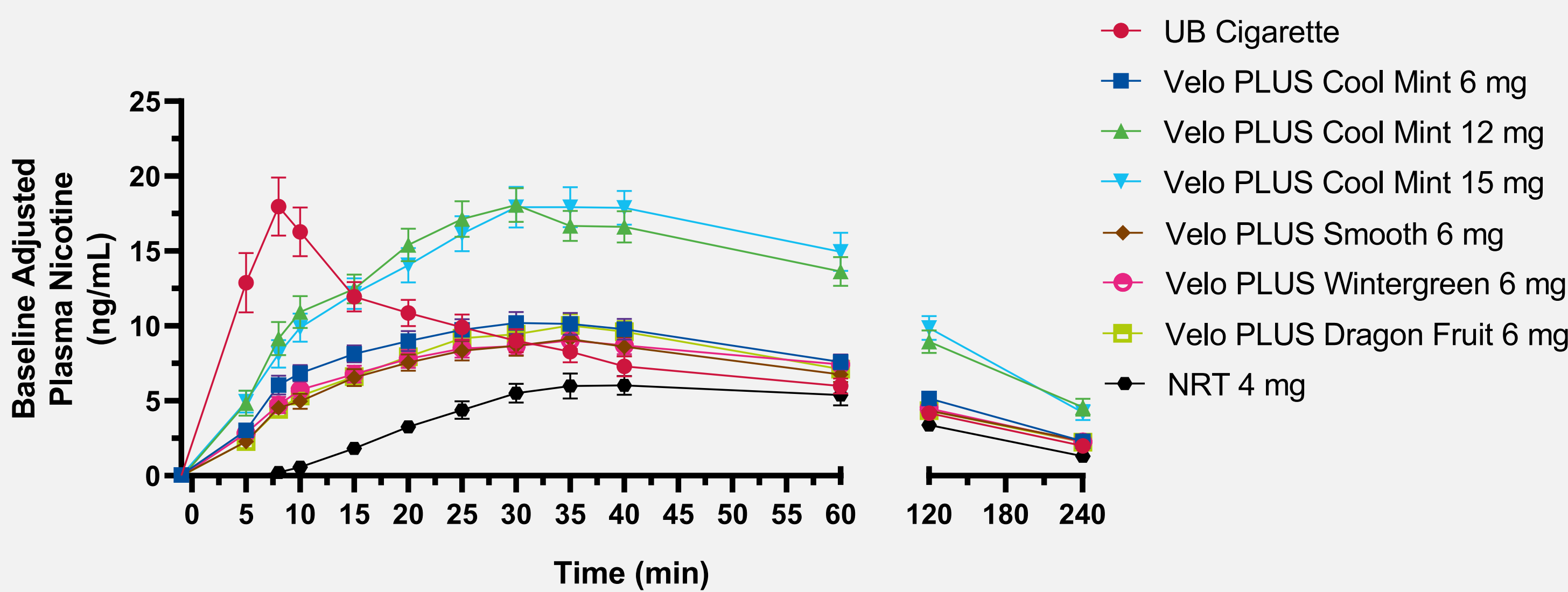
Each Velo PLUS Product elicited lower Product Liking scores than UB Cigarette

Table 1: Nicotine Uptake Measures

Parameter	Cool Mint 6 mg	Cool Mint 12 mg	Cool Mint 15 mg	Smooth 6 mg	Wintergreen 6 mg	Dragon Fruit 6 mg	UBCC	NRT
Geometric Means								
AUC_{0-15} (ng*min/mL)	68.1 ^{a,b}	94.6 ^{a,b}	96.9 ^{a,b}	46.5 ^{a,b}	56.5 ^{a,b}	52.8 ^{a,b}	134	10.3
AUC_{0-240} (ng*min/mL)	1380 ^{a,b}	2230 ^{a,b}	2290 ^{a,b}	1180 ^b	1240 ^b	1260 ^b	1170	779
$C_{\max}$ (ng/mL)	11.4 ^{a,b}	18.9 ^b	19.1 ^b	9.48 ^{a,b}	9.87 ^{a,b}	10.5 ^{a,b}	15.4	5.81
Median								
$T_{\max}$ (minutes)	29.5 ^{a,b}	30.0 ^{a,b}	30.0 ^{a,b}	35.0 ^{a,b}	34.0 ^a	34.0 ^{a,b}	8.0	39.0

UBCC = UB Combustible Cigarette; a,b = Significantly different from UBCC and NRT gum at $p \leq 0.05$, respectively.

Figure 3: Nicotine Pharmacokinetics



Each Velo PLUS Product had a lower $C_{\max}$ in the first 15 minutes and higher $T_{\max}$ than UB Cigarette

Results (cont.)

Table 2: PD Subjective Effects Measures

Parameter	Cool Mint 6 mg	Cool Mint 12 mg	Cool Mint 15 mg	Smooth 6 mg	Wintergreen 6 mg	Dragon Fruit 6 mg	UBCC	NRT
Product Liking								
$AUEC_{\text{PL } 5-240}$	11880 ¹	12110 ¹	10388 ¹	11690 ¹	12058 ¹	12003 ¹	16079	11970
$E_{\max \text{ PL}}$	73.05 ¹	69.26 ¹	63.05 ¹	70.41 ¹	72.13 ¹	69.82 ¹	91.41	72.69
Positive and Negative Product Effects								
$AUEC_{\text{PEpos } 5-240}$	10944 ^a	11330 ^a	10315 ^a	11162 ^a	10955 ^a	11761 ^a	14224	11175
$AUEC_{\text{PEneg } 5-240}$	5333 ^{a,b}	6656 ^{a,b}	7323 ^{a,b}	4942	3771	3800	3603	3578
Urge to Smoke								
$AUEC_{\text{UTS } 0-15}$	1203 ^a	1154 ^a	1141 ^a	1176 ^a	1148 ^a	1168 ^a	862	1174
$AUEC_{\text{UTS } 5-240}$	17448 ^a	17126	16954	16764	16687	17281 ^a	15530	16517
Overall PL and IUA								
$E_{\text{overall PL}}$	53.4 ^a	47.57 ^a	41.91 ^a	52.18 ^a	54.5 ^a	53.44 ^a	75.15	46.32
$E_{\text{overall IUA}}$	42.63 ^a	40.94 ^a	40.32 ^a	42.88 ^a	48.18 ^a	44.35 ^a	73.76	39.62

UBCC = UB Combustible Cigarette; 1 = Significantly different from UBCC at $p \leq 0.0021$; a,b = Significantly different from UBCC and NRT gum at $p \leq 0.05$, respectively.

Summary & Conclusions

- Nicotine uptake parameters of Velo PLUS Nicotine Pouches increased with higher levels of nicotine were generally similar across product flavors at the same nicotine level.
- Compared to UB cigarette, Velo PLUS Nicotine Pouches had:
 - significantly lower scores of PL endpoints: OPL, OIUA, and Positive PE
 - significantly higher UTS during the first 15 minutes of product use
- Compared to NRT gum, Velo PLUS Nicotine Pouches had:
 - similar scores for PL endpoints and Positive PE
 - generally similar UTS parameters
- Velo PLUS Nicotine Pouches were well-tolerated; no SAEs or death reported; AEs were similar to those observed with commercially-available FDA-approved NRT gum.
- The AL profile of Velo PLUS Nicotine Pouches falls between that of UB cigarettes and a commercially-available NRT gum, but generally closer to NRT gum.
- Similar to NRT gum, Velo PLUS Nicotine Pouches have a low risk of dependence and may provide levels of nicotine that enable adult cigarette smokers to transition from smoking to use of the Velo PLUS Nicotine pouches.



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