Abuse Liability Evaluation of Velo Oral Nicotine Products Compared to Combustible Cigarettes and NRT Gum in Adult Smokers

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Abstract

This study investigated subjective measures and nicotine pharmacokinetic characteristics of portioned oral nicotine pouch product (investigational products [IPs]) use among healthy adult smokers. Results from this 5-way crossover study are reported for use of the IPs compared with use of subjects' usual brand combustible cigarette (CC) and nicotine replacement therapy (NRT) gum (high- and low-abuse liability [AL] comparators, respectively). During clinical confinement, subjects participated in five daily test sessions following a 12-hour nicotine abstinence period, in which they used 1 of 5 products per session based on a product randomization sequence: CC, NRT, one 2 mg nicotine pouch, one 4 mg nicotine pouch, or simultaneous use of two 4 mg nicotine pouches (8 mg nicotine). Blood samples, subjective measures, vital signs, and adverse events were collected prior to, during, and following product use over 4 hours.

Compared to CC, nicotine uptake over 4 hours ($AUC_{0\text{-}240\ min}$) was statistically significantly lower after use of the 2 and 4 mg IPs and not statistically different after use of the 8 mg IP. Compared to NRT, mean $AUC_{0\text{-}240\ min}$ was not statistically different for the 2 mg IP, but was significantly greater for the 4 and 8 mg IPs. The IPs demonstrated significantly lower scores for product liking (PL) and positive effects, and significantly higher urge to smoke (UTS) and negative effects scores compared to CC. Relative to NRT, PL and positive effects were significantly lower or not statistically different for the IPs, negative effects were greater, and UTS was generally similar to NRT. These results indicate the IPs have an AL profile lower than a CC and similar to or slightly lower than a commercial NRT gum.

Introduction

FDA CTP 2019 Guidance for Industry on ENDS Premarket Tobacco Product Applications (PMTAs) recommends that PMTAs:

- Include abuse liability evaluations, including pharmacokinetic assessments
- Should consider the addictiveness and abuse and misuse potential of the new product
- Evaluate exposure to nicotine during product use
- Describe the abuse potential of the new product in comparison to other relevant tobacco products

This study incorporates the CTP guidance as well as Center for Drug Evaluation and Research (CDER) guidance on Assessment of Abuse Potential of Drugs (2017), which recommends the inclusion of pharmacodynamics (PD) data (subjective and physiological measures) and pharmacokinetic (PK) data.

FDA Center for Tobacco Products. (2019). *Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems*.

FDA. (2017). *Guidance Document: Assessment of Abuse Potential of Drugs.*

Study Design

Study Design and Population **Clinical Trials.gov ID: NCT04372290**

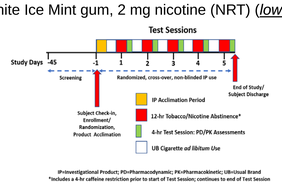
- Single site, randomized, open-label, 5-way crossover study
- Generally healthy males and females, ages 21 to 60 years, who smoked at least 10 combustible cigarettes (CC) per day for at least 6 months prior to screening and smoked their first cigarette within 30 minutes of waking

Study Duration and Milestones

- **6-day** confinement study
- **Product Familiarization:** 30-minute use of one 2 mg nicotine pouch and one 2 mg nicotine gum on Check-in Day -1
- **5 days of 4-hour Test Sessions:** one IP use per Test Session with PD/PK assessments (Days 1 through 5). Each Test Session followed a 12-hour minimum nicotine abstinence period.
- **PD/PK Assessments:** at baseline and at 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 120, 180 and 240 minutes after start of IP use
- **IP Use Times:** 30 minutes for both nicotine pouches and nicotine gum; CCs smoked in their entirety (up to 10 min)

Investigational Products (IPs)

- Velo Pouch Mint in three nicotine levels: 2 mg, 4 mg, and 8 mg nicotine (simultaneous use of two 4 mg nicotine pouches)
- Subjects' usual brand of CC, menthol or non-menthol (*high-AL comparator*)
- Nicorette® White Ice Mint gum, 2 mg nicotine (NRT) (*low-AL comparator*)



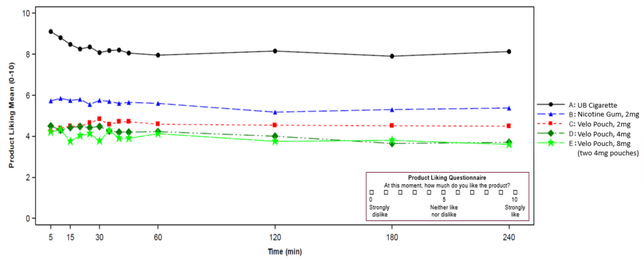
Results

Table 1: Demographics & Baseline Characteristics

Characteristic	Study Population
Enrolled Subjects, N (Completed)	42 (40*)
Sex, n (%) Male / Female	23 (54.8) / 19 (45.2)
Race, n (%) White / Non-White	34 (81.0) / 8 (19.0)
Ethnicity, n (%) Hispanic or Latino / Not Hispanic or Latino	1 (2.4) / 41 (97.6)
Age, mean years (range)	42.8 (23 - 60)
Average Years Smoked, mean (SD)	24.7 (11.4)
Average Cigarettes per Day, mean (SD)	18.9 (5.9)
CC Flavor, n (%) Non-menthol / Menthol	28 (66.7) / 14 (33.3)

* 2 subjects withdrew consent: one prior to start of Test Session 1; one after completing Test Session 1

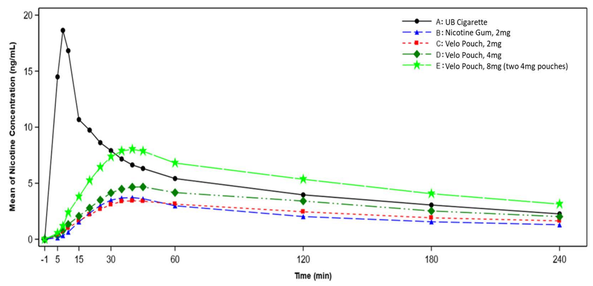
Figure 1: Mean Product Liking Scores over Time



- PL over time for Velo Pouches decreased with increasing levels of nicotine
- PL over time and maximum PL scores were lower for all Velo Pouches relative to NRT gum

Figure 2: Nicotine Pharmacokinetics

Arithmetic mean of baseline-adjusted plasma nicotine concentrations over four hours after start of IP use



Physiological Effects

Heart Rate

- Greatest mean maximum increase was observed with CC, followed by NRT gum, Velo Pouch 4 mg, Velo Pouch 2 mg, and Velo Pouch 8 mg
- Maximum increase was statistically significantly greater with CC compared to each Velo Pouch and was significantly greater with NRT gum compared to 2 mg and 8 mg Velo Pouches

Blood Pressure (BP)

- No statistically significant differences observed in maximum increase in BP for all Velo Pouches compared to CC and NRT gum (except SBP where CC > Velo Pouch 4 mg)

Table 2: Subjective Effects Measures

	Velo Pouch 2 mg	Velo Pouch 4 mg	Velo Pouch 8 mg*	CC	NRT**
Product Liking					
$AUEC_{PL\ 5\text{-}240}$	1072.09[a]	924.43[a,b]	896.50[a,b]	1889.81	1260.68
$E_{max\ PL}$	5.86[a]	5.46[a,b]	5.66[a]	9.34	6.76
Positive And Negative Product Effects					
$AUEC_{PEpos\ 5\text{-}240}$	681.31[a]	592.60[a,b]	602.35[a,b]	1155.97	864.79
$E_{max\ PEpos}$	5.47[a]	5.81[a,b]	5.31[a,b]	8.61	6.38
$AUEC_{PEneg\ 5\text{-}240}$	480.37[a,b]	436.88[a,b]	402.88[a,b]	198.88	225.81
$E_{max\ PEneg}$	4.33[a,b]	4.10[a,b]	5.15[a,b]	2.55	2.32
Urge to Smoke					
$AUEC_{UTS\ 0\text{-}15}$	116.05[a,b]	113.71[a]	110.96[a]	72.28	103.78
$AUEC_{UTS\ 0\text{-}240}$	1802.56[a]	1858.27[a]	1688.02[a]	1520.21	1706.90
$E_{min\ UTS}$	5.36[a]	5.31[a]	4.28[a]	2.73	4.76
Overall PL and IUA					
$E_{overall\ PL}$	4.12[a,b]	3.97[a,b]	3.60[a,b]	9.10	5.45
$E_{overall\ IUA}$	3.92[a]	3.50[a,b]	3.27[a,b]	9.37	4.92

Subjective effects questionnaires were administered using an 11-point numeric rating scale (0 to 10). Subjective effects endpoints were statistically compared using least squares (LS) means.
[a] Statistically significantly different from CC; [b] Statistically significantly different from NRT
* Simultaneous use of two 4 mg nicotine pouches
** NRT gum contains 2 mg nicotine

Table 3: Nicotine Uptake Measures

	Velo Pouch 2 mg	Velo Pouch 4 mg	Velo Pouch 8 mg*	CC	NRT**
Geometric LS Means					
$AUC_{0\text{-}15}$ (ng*min/mL)	6.62[a]	8.67[a,b]	14.59[a,b]	165.67	4.90
$AUC_{0\text{-}240}$ (ng*min/mL)	492.75[a]	632.70[a,b]	1002.25[b]	1022.49	450.34
C_{max} (ng/mL)	3.42[a]	4.62[a,b]	7.46[a,b]	17.29	3.49
Median					
T_{max} (minutes)	40[a]	40[a]	37.5[a]	7.5	40

[a] Statistically significantly different from CC; [b] Statistically significantly different from NRT
* Simultaneous use of two 4 mg nicotine pouches
** NRT gum contains 2 mg nicotine

Table 4: Adverse Events (AEs)

	Velo Pouch 2 mg	Velo Pouch 4 mg	Velo Pouch 8 mg*	NRT**
Subjects Receiving IP, n	41	40	40	40
Subjects with Causally Related AEs, n (%)	2 (4.8%)	6 (15%)	3 (7.5%)	1 (2.5%)
Number Causally Related AEs (21 of 34 total AEs) (%)	2 (5.9%)	8 (23.5%)	9 (26.5%)	2 (5.9%)
Most Common AEs	Nausea Headache	Nausea Headache Hiccups Mouth/Throat Irritation	Nausea Headache Hiccups Mouth/Throat Irritation	Throat Irritation

All Causally Related AEs were mild in severity; all resolved prior to study discharge.

Causally Related Adverse Events = AEs assessed by the Principal Investigator to be "Related" and "Possibly Related" to use of the IPs
* Simultaneous use of two 4 mg nicotine pouches
** NRT gum contains 2 mg nicotine

Objectives and Endpoints

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

Statistical Methods

- Comparisons were made between each Velo Pouch IP and the two comparator products (CC, high-AL; NRT, low-AL)
- Comparisons for PL, PE, OPL and OIUA parameters used a mixed-effect model analysis of variance (ANOVA) analyzed on the original scale. UTS parameters were compared using a mixed-effect analysis of covariance (ANCOVA) model, with baseline UTS included as a covariate.
- A mixed-effects model ANOVA was used to compare plasma nicotine uptake parameters ($AUC_{nic\ 0\text{-}15}$, $AUC_{nic\ 0\text{-}360}$, C_{max}) on the natural log scale. A Wilcoxon signed-rank nonparametric test was used in the comparisons for T_{max} using the original scale.
- Individual plasma nicotine concentrations were baseline-adjusted using a model that assumed that nicotine elimination follows first-order kinetics.
- $p \leq 0.0042$ (Bonferroni-adjusted for multiple comparisons) was considered statistically significant for primary endpoints; $p \leq 0.05$ (unadjusted) was considered significant for secondary endpoints.

Summary and Conclusions

Summary Points

- ***Compared to CC,*** Velo Pouches demonstrated…
  - Significantly lower scores for **PL endpoints** and **positive PE**
  - Significantly higher **UTS** and **negative PE** scores
- ***Compared to NRT gum,*** Velo Pouches demonstrated…
  - Significantly lower scores or scores not significantly different for **PL endpoints, positive PE, OPL** and **OIUA**
  - Significantly higher **negative PE scores**
  - Generally similar **UTS parameters**
- **Nicotine uptake parameters** increased with increasing levels of nicotine in the Velo Pouches
- **OPL and OIUA** decreased with increasing levels of nicotine in the Velo Pouches
- Velo Pouches were well-tolerated with **AEs** similar to those seen with an FDA-approved commercially-available NRT.

Conclusions

- Velo Pouches have an AL profile lower than a CC and similar to or slightly lower than that of a commercially available NRT gum.
- Velo Pouches have a low risk of dependence, similar to NRT gum, and may provide levels of nicotine that enable some adult cigarette smokers to transition away from smoking to use of oral nicotine pouches.

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