Evaluation of Abuse Liability of Two Velo Nicotine Lozenge Tobacco Products Compared to Combustible Cigarettes and NRT Lozenge in Smokers

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Abstract

To examine the abuse liability (AL) of two mint-flavored Velo Hard and Velo Soft dissolvable nicotine lozenges (NL), we conducted a two-arm, five-way crossover study in confinement with healthy smokers. Subjects participated in five daily test sessions (each following a 12-hour minimum nicotine abstinence period) with randomized use of one of five products each session: usual brand combustible cigarette (CC / high-AL comparator), nicotine replacement therapy lozenge (NRT / low-AL comparator), one NL, or simultaneous use of two or four NLs. Results of subjective measures and nicotine pharmacokinetic parameters after use of NLs were compared with results after use of the high and low-AL comparators. Blood samples, subjective measures, vital signs, and adverse events (AEs) were collected over the course of 6 hours prior to, during, and following product use.

Results demonstrated that total nicotine uptake over 6 hours ($AUC_{0\text{-}360min}$) was statistically significantly lower for a single NL than for either CC or NRT. $AUC_{0\text{-}360min}$ after use of two and four NLs was similar to or higher than for CC or NRT. Mean scores for several product liking subjective measures were statistically significantly lower for all NLs compared to CC and not different from NRT. The mean scores for "positive effects" after use of all NLs were generally similar to those for NRT, however, mean scores for "negative effects" increased with the number of lozenges used simultaneously. Mild AEs such as hiccups, nausea, and throat irritation were similar among NLs and NRT, and for the NLs, increased with increasing number of lozenges. Results demonstrate that these NLs have AL profiles less than CC and similar to NRT lozenge and suggest that they have a low risk of abuse.

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Introduction

The FDA CTP 2019 Guidance for Industry on ENDS Premarket Tobacco Product Applications (PMTAs) recommends that PMTAs include "abuse liability evaluations, including pharmacokinetic evaluations, [and] should consider the addictiveness and abuse and misuse potential of the new product and the exposure to nicotine during product use." FDA further recommends that such evaluations 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 pharmacodynamic (PD) data (subjective and physiological measures) and pharmacokinetic (PK) data, along with general study design considerations.

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 Duration and Milestones

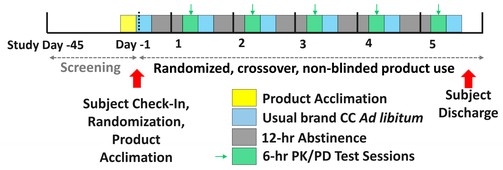
- **6-day** confinement study with **two** independent study arms conducted sequentially (Arm 1= Velo Hard NL [n=37]; Arm 2=Velo Soft NL [n=35])
- **Product familiarization** with use of one NRT and one NL on Day -1
- **5 days of 6-hour Test Sessions** (one for each of five investigational products) with PD/PK assessments (Days 1 through 5). Each Test Session followed 12-hour minimum nicotine abstinence periods
- Assessments were taken at baseline and at 5, 7.5, 10, 15, 20, 30, 45, 60, 120, 180, 240, and 360 minutes after product administration. CCs were smoked in their entirety and lozenges used to completion

Investigational Products (IPs)

- Usual brand of combustible cigarettes (*high abuse liability comparator*)
- Nicorette® Mint lozenge, 4 mg nicotine (NRT) (*low abuse liability comparator*)
- Velo Hard and Velo Soft NLs in three nicotine levels: 2 mg, 4 mg, and 8 mg nicotine (4 and 8 mgs of nicotine were achieved with simultaneous use of 2 or 4 NLs, respectively)

Study population

- Generally healthy males and females, aged 21 to 60 years, who smoked greater than 10 cigarettes per day for at least 6 months prior to screening and smoked their first cigarette within 30 minutes of waking



Results

Demographics & Baseline Characteristics

Characteristic	Study Population*
Enrolled Subjects, n (Complete)	72 (70)
Sex, n (%) Male / Female	55 (76.4) / 17 (23.6)
Race, n (%) White / Non-White	25 (34.7) / 47 (65.3)
Ethnicity, n (%) Hispanic or Latino / Not Hispanic or Latino	4 (5.6) / 68 (94.4)
Age, mean years (range)	38.3 (22-59)
Average Years Smoked / **Average CPD** (mean)	19.54 / 14.70

* Study population across both study arms. The demographic data was similar for both study arms.
CPD = cigarettes per day

Subjective Effects Measures

	Velo Hard	Velo Hard (2)*	Velo Hard (4)*	CC	NRT*
$AUEC_{PL\ 5\text{-}360}$	16457[aa]	16240[a]	15684[a]	27473	15819
$E_{max\ PL}$	65.1[a]	61.7[a]	64.1[a]	90.1	63.6
$E_{max\ PEpos}$	73.7[a]	69.1[a]	75.8[a]	88.3	73.7
$E_{max\ PEneg}$	47.2[a]	51.6[a]	60.5[a,b]	34.1	45.4
OIUA	46.7[a]	44.4[a]	43.4[a]	83.6	40.1
	Velo Soft	**Velo Soft (2)***	**Velo Soft (4)***	**CC**	**NRT***
$AUEC_{PL\ 5\text{-}360}$	15391[a]	16104[a]	14126[a]	27890	13992
$E_{max\ PL}$	56.8[a]	57.9[a]	59.1[a]	93.6	53.9
$E_{max\ PEpos}$	56.0[a]	60.1[a]	66.1[a]	88.3	59.8
$E_{max\ PEneg}$	39.7	41.4	55.0[a]	29.2	44.8
OIUA	36.8[a]	37.7[a]	34.1[a]	82.7	35.5

* (2) and (4) indicate the number of lozenges used at the same time to achieve 4 and 8 mg nicotine, respectively; the NRT contains 4 mg nicotine
[a] Statistically significantly different from CC
[b] Statistically significantly different from NRT
Subjective effects questionnaires were administered electronically using a 100 mm visual analogue scale (VAS) and are summarized with least squares (LS) means.

Nicotine Uptake Measures

	Velo Hard	Velo Hard (2)*	Velo Hard (4)*	CC	NRT*
$AUC_{0\text{-}15}$ (ng*min/mL)	10.6[a,b]	20.5[a]	33.4[a,b]	145	23.2
$AUC_{0\text{-}360}$ (ng*min/mL)	751[a,b]	1358[b]	2281[a,b]	1427	1579
C_{max} (ng/mL)	4.3[a,b]	7.9[a]	12.4[a,b]	15.0	8.9
T_{max} (min)	59.5[a]	44.5[a]	44.5[a]	9.5	44.5
	Velo Soft	**Velo Soft (2)***	**Velo Soft (4)***	**CC**	**NRT***
$AUC_{0\text{-}15}$ (ng*min/mL)	6.7[a,b]	7.9[a,b]	12.4[a]	114	14.8
$AUC_{0\text{-}360}$ (ng*min/mL)	824[a,b]	1401[b]	2285[a,b]	1384	1633
C_{max} (ng/mL)	4.9[a,b]	7.8[a,b]	11.5[b]	12.0	9.2
T_{max} (min)	58.6[a]	59.5[a]	59.5[a,b]	9.5	44.6

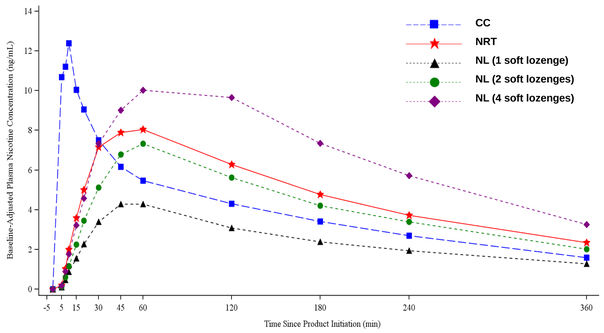
* (2) and (4) indicate the number of lozenges used at the same time to achieve 4 and 8 mg nicotine, respectively; the NRT contains 4 mg nicotine
[a] Statistically significantly different from CC
[b] Statistically significantly different from NRT
Geometric LS means are presented for the C_{max} and AUC parameters; median is presented for T_{max}.

Adverse Events (AEs)

	Velo Hard	Velo Hard (2)*	Velo Hard (4)*	NRT*
# Subjects	36	35	34	36
# of Subjects with CRAEs (21 of 37 total subjects)	6 (16.7%)	11 (31.4%)	17 (50.0%)	8 (22.2%)
# of CRAEs (56 of 63 total AEs)	8	13	23	12
Most Common AEs	Hiccups Cough	Nausea Hiccups Throat Irritation	Nausea Hiccups Throat Irritation	Diarrhea Nausea Hiccups
	Velo Soft	**Velo Soft (2)***	**Velo Soft (4)***	**NRT***
# Subjects	35	35	35	35
# of Subjects with CRAEs (16/35 Total Subjects)	4 (11.4%)	5 (17.1%)	11 (31.4%)	7 (20%)
# of CRAEs (45/49 Total AEs)	4	8	20	13
Most Common AEs	Nausea	Hiccups	Hiccups Nausea Throat Irritation	Nausea Dizziness

* (2) and (4) indicate the number of lozenges used at the same time to achieve 4 and 8 mg nicotine, respectively; the NRT contains 4 mg nicotine
CRAEs = Causally Related Adverse Events; were assessed by the Principal Investigator to be "Related" & "Possibly Related" to use of the IPs.
No AEs were reported for CC.

Nicotine Pharmacokinetics

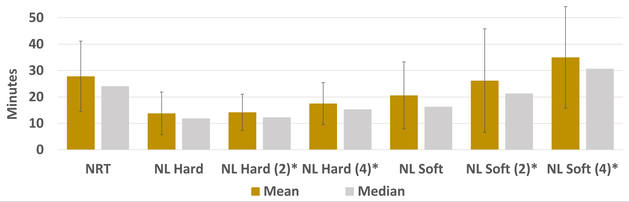


Arithmetic mean plasma nicotine levels over six hours after initiation of IP use. Results from both study arms showed similar trends, but only Velo Soft results are presented due to space limitations.

Physiological Effects

- Increases in all physiological measures (systolic blood pressure, diastolic blood pressure, and heart rate) were observed following use of the NRT and all NLs, but there were no consistent statistically significant differences in mean maximal increases between the NLs and either comparator.
- Plots of mean physiological measures over time showed a pattern similar to that of Figure 2, with changes seen most rapidly after use of CC.
- Maximum changes in heart rate increased with increasing number of NLs used simultaneously.

Time to Lozenge Completion



Objectives and Endpoints

Objectives	Endpoints
Primary	
Subjective assessments: In the moment Product Liking (PL) subjective measures over 6 hours after the start of IP use	Area under the Effects Curve-PL: $AUEC_{PL\ 5\text{-}360}$ Maximum PL: $E_{max\ PL}$
Secondary	
PK assessments: Plasma nicotine uptake over the first 15 minutes and over 6 hours after the start of IP use	$AUC_{nic\ 0\text{-}15}$, $AUC_{nic\ 0\text{-}360}$, C_{max} and T_{max}
Subjective assessments: Positive and Negative Product Effects (PE), and Overall Intent to Use Again (OIUA) subjective measures over 6 hours after the start of IP use	Product Effects (positive and negative): $E_{max\ PEpos}$ and $E_{max\ PEneg}$ Overall Intent to Use Again: $E_{overall\ IUA}$
Physiological measures: Changes in heart rate and blood pressure following IP use	Average maximum increases in systolic blood pressure, diastolic blood pressure, and heart rate

Statistical Methods

- Comparisons were made between each Velo Lozenge IP and the two comparator products (CC, high-AL; NRT, low-AL*); no* comparisons were made between the NLs within a study arm, nor between results of the two study arms.
- Comparisons for subjective assessment parameters were made using a mixed-effect model analysis of variance (ANOVA) and analyzed on the original scale.
- Individual plasma nicotine concentrations were baseline-adjusted using a model that assumed that nicotine elimination follows first-order kinetics; all PK parameters were calculated on baseline-adjusted plasma nicotine concentrations.
- 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 to compare the T_{max} between each NL IP and the two comparator products using the original scale.
- Statistical significance for primary endpoints was set at $p \leq 0.0042$, Bonferroni-adjusted to preserve an overall significance level of 0.05; secondary endpoints were compared without adjustment with a 0.05 significance level

Conclusions

- **Both Velo Hard and Velo Soft NLs have an abuse liability profile generally lower than CC and similar to commercially available NRT.**
- **Product liking** endpoints (**$AUEC_{PL\ 5\text{-}360}$** and **maximum PL** scores) were lower than CC and similar to those for the NRT lozenge.
- **Maximum positive effects** were generally similar to those of the NRT lozenge.
- The **maximum negative effects** and frequency of **AEs** increased with the number of NLs used simultaneously. Although nicotine uptake parameters from use of a single NL (~2 mg nicotine) were less than those of one 4 mg NRT lozenge, the subjective effects from use of the two products were generally similar.
- The mean **speed of nicotine uptake (T_{max})** and **maximum plasma nicotine concentrations (C_{max})** were greatest after use of CC.
- **Slower time to product completion** may have impacted early nicotine uptake for Velo Soft but there was no difference between products for overall nicotine uptake or subjective measures relative to the high and low AL comparators
- **T_{max} values** were not different between NRT and either NL. Nicotine uptake was substantially slower and consistent with use of oral nicotine products, with early uptake of nicotine trending with the time to completion. Other PK parameters were proportional to the number of lozenges used at a time (i.e., amount of nicotine ingested).
  - Use of one lozenge resulted in total nicotine uptake levels generally lower than CC or NRT.
  - Use of 2 or 4 lozenges resulted in total nicotine uptake levels similar to or higher than CC or NRT.
- The **Velo Hard and Velo Soft** NLs were well-tolerated with similar **AEs** and **physiological effects** as those seen with an FDA-approved commercially-available NRT.