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

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Abstract

Using a 2-arm, 5-way crossover study design, we investigated subjective measures and pharmacokinetic characteristics of a dissolvable nicotine lozenge (NL) (mint-flavored hard and soft forms) when used by healthy smokers. Results after use of NLs were compared with results after use of high and low-abuse liability comparators (subjects' usual brand combustible cigarette [CC] and a nicotine replacement therapy [NRT] lozenge, respectively). Adverse events (AEs) from product use were also collected. During confinement, subjects participated in 5 daily Test Sessions (following a 12-hour minimum tobacco/nicotine abstinence period) and were randomized to 1 of 5 products per session: CC, NRT, one NL, or simultaneous use of 2 and 4 NLs. Blood samples, subjective measures, vital signs, and AEs were collected over the course of 6 hours prior to, during, and following product use.

Results demonstrated that total nicotine uptake levels ($AUC_{0\text{-}360}$) over 6 hours were lower after use of a single NL than those for CC and NRT and similar to or higher than CC after use of 2 and 4 NLs. Mean scores for several product liking measures were statistically significantly lower for all NL sessions compared to CC and not different from NRT. While the mean scores for "liking of positive effects" after use of all hard and soft NLs were generally similar to those for NRT, the "disliking of negative effects" increased with the number of NLs 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 used simultaneously. Results suggest that the NLs included in this study have a low risk for abuse and an abuse liability less than CC and similar to NRT lozenge.

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 pharmacodynamics (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

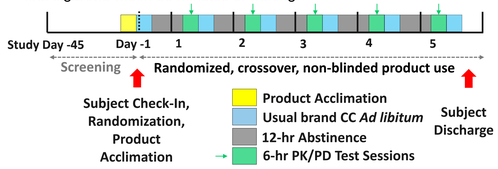
- **6-day** confinement study with **two** independent study arms (Arm 1=NL hard form [n=37]; Arm 2=NL soft form [n=35]) conducted sequentially
- **Product familiarization** with use of one NRT and one NL (Day -1)
- **5 days of 6-hour Test Sessions** (one for each investigational product) with PD/PK assessments (Days 1 through 5) following 12-hour minimum nicotine abstinence period
- Assessments taken at baseline and at 5, 7.5, 10, 15, 20, 30, 45, 60, 120, 180, 240, and 360 minutes after product administration (CC or 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*)
- NLs (hard and soft), 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 first cigarette within 30 minutes of waking.



Results

Table 1: 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 (mean)	19.54
Average Cigarettes per Day (mean)	14.70

* Study population across both study arms. The demographic data was similar for both study arms.

Table 2: Subjective Effects Measures

	NL Hard	NL Hard (2)*	NL Hard (4)*	CC	NRT*
$AUEC_{PL\ 5\text{-}360}$	16457[a]	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
	NL Soft	**NL Soft (2)***	**NL 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.

Table 3: Nicotine Uptake Measures

	NL Hard	NL Hard (2)*	NL 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
	NL Soft	**NL Soft (2)***	**NL 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

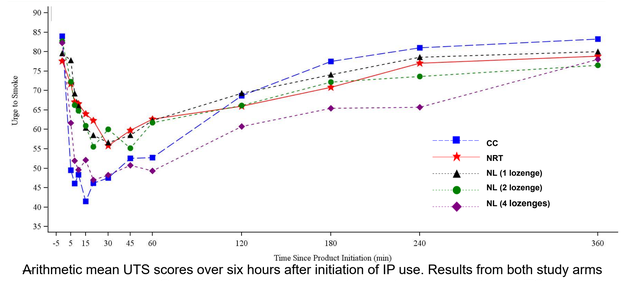
* (2) and (4) indicate the number of lozenges used at the same time to achieve 4 and 8 mg nicotine, respectively; the NRT contains 4 mg nicotine
[a] Statistically significantly different from CC
[b] Statistically significantly different from NRT
Geometric LS means are presented for the C_{max} and AUC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

Table 4: Adverse Events (AEs)

	NL Hard	NL Hard (2)*	NL 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
	NL Soft	**NL Soft (2)***	**NL 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

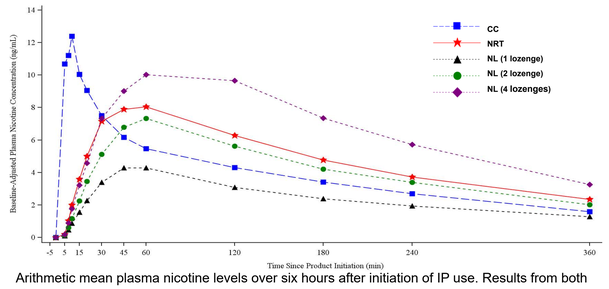
* (2) and (4) indicate the number of lozenges used at the same time to achieve 4 and 8 mg nicotine, respectively; the NRT contains 4 mg nicotine
CRAEs = Causally Related Adverse Events; were assessed by the Principal Investigator to be "Related" & "Possibly Related" to use of the IPs.
No AEs were reported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

Figure 1: Urge to Smoke



Arithmetic mean UTS scores over six hours after initiation of IP use. Results from both study arms showed similar trends. Only NL Soft results are presented due to space limitations. UTS scores were measured on a 100 mm visual analogue scale (VAS).

Figure 2: Nicotine Pharmacokinetics



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

Physiological Effects

- There were increases in all physiological measures (systolic blood pressure, diastolic blood pressure, and heart rate) 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.

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), Urge to Smoke (UTS), 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 physiological measures (i.e., heart rate and blood pressure) following IP use	Average maximum increases in systolic blood pressure, diastolic blood pressure, and heart rate

Statistical Methods

Within each study arm:

- Comparisons for PL, PE, and OIUA 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.
- 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.
- All PK parameters were calculated on the baseline-adjusted plasma nicotine concentrations.
- 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 significance level of 0.05.
- No comparisons were made between the NLs in a study arm, nor between results of the two study arms.

Conclusions

- **Both investigational 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 concentrations (C_{max})** were greatest after use of CC.
- **T_{max} values** for were not different between NRT and either NL. Nicotine uptake was substantially slower and consistent with use of oral nicotine products. 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 timing and scores for **Urge to Smoke** after use of a single NL were generally similar to those seen for other oral nicotine products.
- The NLs were well-tolerated with similar **AEs** and **physiological effects** as those seen with an FDA-approved commercially-available NRT.