Pharmacokinetics and Subjective Effects of the JL Electronic Nicotine Delivery System (ENDS) Compared to Five ENDS, a Heated Tobacco Product, and a Combustible Cigarette

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Introduction

- Electronic nicotine delivery systems (ENDS) comprise a heterogeneous and continually-evolving group of products; there are numerous technologies available on the marketplace.[1]
- Recent studies have assessed the nicotine delivery of the JL ENDS, a closed-system ENDS with a nicotine-salt formulation,[2-4] however there are limited data systematically comparing the nicotine pharmacokinetic (PK) profile and subjective effects of the JL ENDS to other tobacco products including ENDS and heated tobacco products.
- The primary objective of this study was to characterize the nicotine PK profiles and subjective effects of the JL ENDS 5.0%, five comparator ENDS products (*my*blu 2.4%, MarkTen 4.0%, VUSE Solo 4.8%, PHIX 5.0%, and NJOY Daily EXTRA 6.0%), a heated tobacco product (IQOS), and a combustible cigarette (Marlboro Red) across controlled and *ad libitum* puffing conditions among adult smokers.

Methods

- Adult smokers (N=25; 72.0% male; mean age [SD] = 30.44 [10.18]) completed a randomized, open-label, 16-arm within-subjects cross-over product-administration study over the course of three days.
- There was a total of eight study test products:
  1) JL ENDS Virginia Tobacco 5.0%
  2) *my*blu Original 2.4%
  3) MarkTen Bold Classic 4.0%
  4) VUSE Solo Original 4.8%
  5) PHIX Original Tobacco 5.0%
  6) NJOY Daily EXTRA Rich Tobacco 6.0%
  7) IQOS HeatStick Regular
  8) Marlboro Red
- Each product was administered under controlled (10 puffs; 3 seconds in duration, taken at 30 second intervals) and *ad libitum* (4.5 minutes) puffing conditions (16 total conditions).
- Each administration period was separated by a wash-out period of at least 120 minutes.
- Blood samples were collected 5 minutes prior (-5) to and 1.5-, 3-, 5-, 6-, 7-, 8-, 10-, 12-, 15-, 30-, and 60-minutes post-product administration. The time course of plasma nicotine concentration (PK curve) was evaluated and the following PK parameters were assessed:
  - Baseline-adjusted maximum plasma level ($C_{max\text{-}BL}$)
  - Rate of plasma nicotine rise (speed of absorption; ($C_{max\text{-}BL}/T_{max}$)
  - Total nicotine exposure (baseline-adjusted area under the curve [$AUC_{0\text{-}60\text{-}BL}$])
  - Time to maximum plasma nicotine level (T_{max})
- The modified Product Evaluation Scale (mPES)[5] was administered following completion of the 30-minute blood sample collection.
- All analyses were stratified by puffing condition (controlled vs. *ad libitum*). A repeated measures ANOVA model was used to compare the natural log of $C_{max\text{-}BL}$ and $AUC_{0\text{-}60\text{-}BL}$ between the JL ENDS and other test products. T_{max} between the JL ENDS and other test products was analyzed using a Wilcoxon signed-rank test. Multi-level linear models were used to conduct post-hoc pairwise comparisons in rate of plasma nicotine rise and mPES composite subscales between the JL ENDS and other test products.

Results

PK Parameters (Figures 1-2 and Table 1)

- Across both puffing conditions:
  - The combustible cigarette had the highest mean $C_{max\text{-}BL}$, rate of plasma nicotine rise, and $AUC_{0\text{-}60\text{-}BL}$.
  - Mean $C_{max\text{-}BL}$, rate of plasma nicotine rise, and $AUC_{0\text{-}60\text{-}BL}$ for the JL ENDS generally did not differ significantly from the IQOS tobacco HeatStick (except rate of plasma nicotine rise, *ad libitum* condition) and the PHIX (except $C_{max\text{-}BL}$, controlled condition) and NJOY Daily EXTRA (except rate of plasma nicotine rise) ENDS products.
  - Mean $C_{max\text{-}BL}$, rate of plasma nicotine rise, and $AUC_{0\text{-}60\text{-}BL}$ for the JL ENDS were significantly greater than the VUSE Solo, *my*blu, and MarkTen ENDS products.
  - Mean T_{max} for the for the JL, VUSE Solo, and NJOY Daily EXTRA ENDS products was somewhat faster than the combustible cigarette but these differences were not statistically significant—a likely explanation for the cigarette's slower T_{max} is that its mean $C_{max\text{-}BL}$ was the highest, thus the time it took to reach its peak level was longer.

Table 1. PK Parameters of Test Products in the Controlled 10-Puff and *Ad Libitum* Puff Conditions

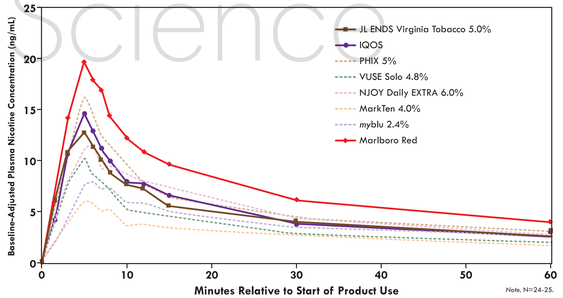
PK Parameters in Each Puffing Condition	JL ENDS Mean (SD)	IQOS Mean (SD)	VUSE Solo Mean (SD)	*my* blu Mean (SD)	MarkTen Mean (SD)	PHIX Mean (SD)	NJOY Daily EXTRA Mean (SD)	Combustible Cigarette Mean (SD)
$C_{max\text{-}BL}$ (ng/mL)								
Controlled	14.2 (7.3)	16.1 (7.7)	11.5 (5.4)*	9.9 (5.6)*	7.6 (3.4)*	17.4 (9.6)*	13.6 (7.6)	21.2 (11.7)*
Ad Libitum	17.4 (10.0)	17.4 (7.3)	12.1 (6.7)*	7.9 (3.8)*	7.5 (4.0)*	18.4 (14.0)	15.8 (7.7)	27.9 (19.6)*
Rate of Plasma Nicotine Rise (ng/mL per Minute)								
Controlled	3.3 (2.3)	3.3 (2.1)	2.2 (1.3)*	1.7 (1.1)*	1.3 (0.9)*	3.3 (2.1)	2.3 (1.6)*	4.2 (3.4)*
Ad Libitum	4.3 (3.2)	3.3 (1.6)*	2.3 (1.4)*	1.3 (0.8)*	1.5 (1.3)*	3.7 (4.2)	2.9 (1.6)*	5.0 (3.8)*
$AUC_{0\text{-}60\text{-}BL}$ (hrs*ng/mL)								
Controlled	4.98 (2.15)	5.15 (2.32)	3.68 (1.59)*	4.01 (2.17)*	2.88 (1.03)*	5.72 (2.65)	5.26 (2.47)	7.67 (3.56)*
Ad Libitum	5.81 (2.70)	5.72 (1.88)	3.92 (2.43)*	3.18 (1.51)*	3.21 (1.76)*	5.71 (3.75)	5.52 (2.81)	9.76 (5.69)*
T_{max} (mins)								
Controlled	5.20 (1.85)	5.41 (1.36)	6.32 (3.04)	6.64 (2.14)*	8.12 (5.55)*	5.82 (1.33)	6.63 (2.24)*	6.71 (5.11)
Ad Libitum	4.88 (2.18)	6.38 (5.06)	5.57 (1.25)	6.32 (1.79)*	6.84 (3.82)*	6.05 (1.54)*	5.77 (1.26)*	5.84 (1.36)

Note: N=24-25.
*Significantly different than the JL ENDS ($p<0.05$).

Subjective Effects (Table 2)

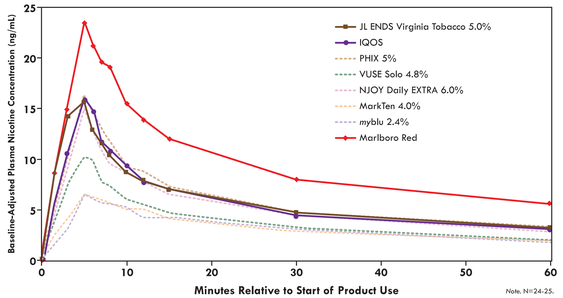
- Across both puffing conditions, the cigarette had the highest mean mPES "Satisfaction" and "Psychological Reward" composite subscale scores.
- For the mPES "Satisfaction" composite subscale:
  - In the controlled puffing condition, the mean score for the JL ENDS was significantly higher than the *my*blu, MarkTen, PHIX, and NJOY Daily EXTRA ENDS products, but not significantly different from the IQOS tobacco HeatStick and the VUSE Solo ENDS product.
  - In the *ad libitum* puffing condition, the mean score for the JL ENDS was significantly greater than the IQOS tobacco HeatStick and the *my*blu, MarkTen, and NJOY Daily EXTRA ENDS products, but not significantly different from the VUSE Solo and PHIX ENDS products.

Figure 1. Test Product Average Baseline-Adjusted Plasma Nicotine Concentration by Nominal Time in the Controlled 10-Puff Condition



Note: N=24-25.

Figure 2. Test Product Average Baseline-Adjusted Plasma Nicotine Concentration by Nominal Time in the *Ad Libitum* Puff Condition



Note: N=24-25.

- For the mPES "Psychological Reward" composite subscale:
  - In the controlled puffing condition, the mean score for the JL ENDS was significantly higher than the VUSE Solo and MarkTen ENDS products, but not significantly different from the IQOS tobacco HeatStick and the *my*blu, PHIX, and NJOY Daily EXTRA ENDS products.
  - In the *ad libitum* puffing condition, the mean score for the JL ENDS was significantly greater than the *my*blu and MarkTen ENDS products, but not significantly different from the IQOS tobacco HeatStick and the VUSE Solo, PHIX, and NJOY Daily EXTRA ENDS products.

Table 2. mPES Satisfaction and Psychological Reward Composite Subscale Scores among Test Products in the Controlled 10-Puff and *Ad Libitum* Puff Conditions

	mPES Satisfaction Subscale		mPES Psychological Reward Subscale	
Test Product	**Controlled Mean (SD)**	***Ad Libitum* Mean (SD)**	**Controlled Mean (SD)**	***Ad Libitum* Mean (SD)**
JL ENDS	3.71 (1.17)	3.74 (1.12)	2.83 (1.15)	2.86 (1.35)
IQOS	2.91 (1.39)	2.95 (1.48)*	2.77 (1.17)	2.61 (1.08)
VUSE Solo	3.32 (1.07)	3.45 (1.10)	2.51 (1.24)*	2.73 (1.34)
*my*blu	2.45 (1.36)*	2.18 (0.97)*	2.46 (1.30)	2.21 (0.87)*
MarkTen	2.61 (1.05)*	2.84 (1.16)*	2.38 (1.17)*	2.35 (1.04)*
PHIX	3.14 (1.27)*	3.85 (1.21)	2.71 (1.13)	2.88 (1.29)
NJOY Daily EXTRA	2.64 (1.35)*	2.72 (1.36)*	2.74 (1.19)	2.66 (1.39)
Marlboro Red	5.24 (1.25)*	5.16 (1.36)*	3.90 (1.30)*	4.07 (1.35)*

Note: N=23-25.
*Significantly different than the JL ENDS ($p<0.05$).
All items were answered on seven-point response scales from 1 ("Not at all") to 7 ("Extremely").

Conclusions

- Out of all the tobacco products assessed, the combustible cigarette had the highest peak nicotine levels, speed of nicotine absorption and total nicotine exposure and was rated highest on subjective measures of satisfaction and reward.
- The PK and subjective effects profiles of the JL ENDS were within the range of other marketed ENDS products and similar to that of the IQOS tobacco HeatStick.

References

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