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Changes in Biomarkers of Exposure Associated with Switching for 5 Days from Combusted Cigarettes to Nicotine Salt Pod System

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Introduction:

The JUUL ENDS (JUUL Labs, San Francisco, CA) is a closed nicotine-salt pod system (NSPS) which aerosolizes an e-liquid solution through vaporization. A temperature control system integrated into the breath-actuated inhalation pathway is designed to maintain an operating temperature that is independent of puff intensity and to minimize the generation of combustion-related byproducts. The primary hypothesis is that switching from use of usual brand combustible cigarettes to exclusive use of four JUUL 5% ENDS (Virginia Tobacco, Cool Mint, Mango, or Creme Brulee) for 5 days will result in a significant decrease in primary biomarkers of exposure (BOEs) N-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 3-hydroxypropylmercapturic acid (3-HPMA), monohydroxybutenylmercapturic acid (MHBMA), S-phenyl mercapturic acid (S-PMA), and Carboxyhemoglobin (COHb). Each BOE was assessed relative to baseline on Day 5 in each of the six cohorts described below.*

Methods:

Ninety subjects were randomized into one of six cohorts: use of NSPS (n=15 for each of four flavors - Virginia Tobacco, Mint, Mango, Creme; all flavors 5% nicotine by weight), use of usual cigarette (n=15), or abstinence (n=15). Total nicotine equivalents, and the following biomarkers were measured in 24-hour urine collections at baseline (Day -1) and at Day 5: NNN, NNAL, 3-HPMA, MHBMA, S-PMA, HMPMA, CEMA, and 1-OHP. COHb was measured in blood.

The study population consisted of healthy smokers, age 22 to 62 inclusive, with a minimum 12-month history of smoking 10 or more king-size (or 100s) manufactured, combusted cigarettes per day. Participants were naïve to use of ENDS products and willing to be confined at the clinic for up to 7 days. The study was carried out in accordance with FDA and ICH guidelines regarding Good Clinical Practice and the ethical principles set forth in the Declaration of Helsinki. The study protocol and informed consent form were reviewed and approved by the Chesapeake Institutional Review Board (Columbia, Maryland, USA). Participants received monetary incentives for completing specific milestones related to the study.

Results:

Subjects on average were 39 years old, and smoked 16 cigarettes per day; 38% were female. All subjects randomized to the use of NSPS (n=60) and usual cigarettes (n=15) completed the study; four subjects from the abstinence arm terminated early (n=11; 73% completion rate in-arm).

Table 1: Baseline demographics and characteristics (safety population)[a]

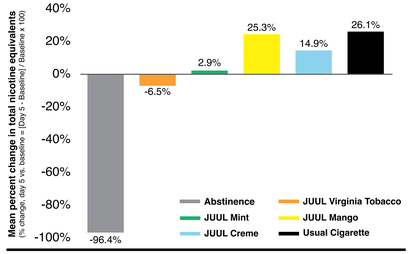
	NSPS Pooled	Usual Cigarettes	Abstinence	Overall
N	60	15	15	90
Age, y	39.0±10.59	40.3 ± 11.13	38.6 ± 14.26	39.1 ±11.40
Sex, male	37 (62%)	9 (60%)	10 (67%)	56 (62%)
Race				
Black or African American	9 (15%)	1 (7%)	3 (20%)	13 (14%)
White	49 (82%)	13 (87%)	10 (67%)	72 (80%)
Ethnicity				
Hispanic or Latino	2 (3%)	2 (13%)	0 (0%)	4 (4%)
Not Hispanic or Latino	58 (97%)	13 (87%)	15 (100%)	86 (96%)
BMI[JM2] , kg/m2	28.2 ± 5.31	27.8 ± 4.28	27.5 ± 5.67	28.0 ± 5.19
Fagerstrom Dependency Score	5.50 ± 1.55	4.87 ± 1.72	5.20 ± 1.42	5.34 ± 1.55
Cigarettes per day	16.5 ± 3.75	15.1 ± 3.66	16.2 ± 2.58	16.2 ± 3.64

[a]Data are presented as n (%) or mean ± standard deviation

Nicotine Consumption and Excretion:

Over the course of 5 days, mean total nicotine equivalents increased by 9% in the pooled NSPS group vs. 26% in the usual cigarette group (p-value for difference >0.05). Total nicotine equivalents were reduced by 96.4% in the abstinence group, consistent with compliance with no smoking or nicotine consumption for 5 days in that arm.

Figure 1: Mean percent change in total nicotine equivalents at Day 5 vs. Baseline (Day -1) in urine[b]



[b]Data are presented as percent change (%, Day 5 vs. Baseline = [Day 5 - Baseline] / Baseline x 100)

Mean total nicotine equivalents excreted on day 5 was similar between the usual cigarette arm (19.0 mg/24h) and the NSPS pooled arms (18.3 mg/24h). The usual cigarette cohort consumed a mean of 19.3 cigarettes per day, and the NSPS cohorts consumed a mean of 0.79 grams per day. In this experimental setting with this population, this suggests that an NSPS pod, if completely consumed, would result in the mean total nicotine equivalents excreted associated with consuming 91% of a pack of cigarettes.

Table 2: Relative mean product consumption and mean total nicotine excreted[c]

Measure	Units	NSPS Pooled Groups	Usual Cigarettes
Num participants	ITT participants	n = 60	n = 15
Mean e-liquid consumed / day (days 4-5)	Grams (actual)	0.79 ± 0.39	
Mean cigarettes consumed / day (days 4-5)	Num cigarettes (actual)		19.3 ± 4.87
Mean pod equivalents consumed / day	Pod content equivalents (estimated; assuming 0.77 g per pod)[1]	1.03 ± 0.50	
Mean pack equivalents consumed / day	Pack equivalents (actual; assuming 20 cigarettes per pack)		0.97 ± 0.23
Mean total nicotine equiv excreted (day 5)	mg / 24h (actual)	18.3 ± 10.2	19.0 ± 4.53
Relative total nicotine equivalents excreted per pod or cigarette pack consumed	(estimated)	~91%	100%

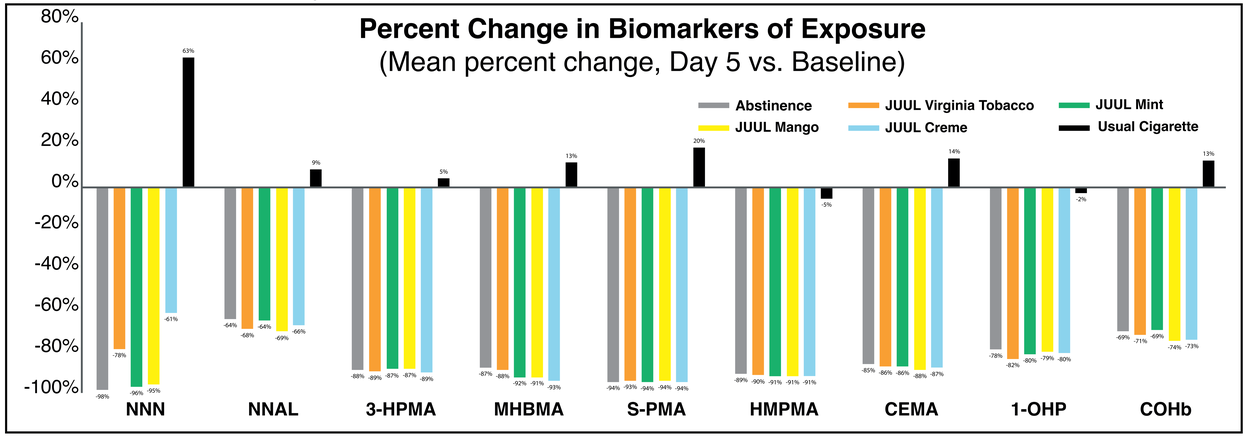
[c]Pod content equivalents consumed per day are calculated assuming e-liquid in pods is completely consumed. If pod is incompletely consumed, then relative ratio would be lower than 91%::100%.

Changes in Biomarkers of Exposure (Non-Nicotine):

Decreases in the mean levels of all non-nicotine BOEs were observed in the abstinence group and four NSPS groups at Day 5 compared to baseline (Day -1); the cigarette group demonstrated increases in all BOEs except for 1-OHP and HPMA. The eight non-nicotine urine BOEs were reduced by an average of 85.3% in the abstinence group and 85.0% in the pooled NSPS group (99.6% relative reduction in aggregate biomarkers; p-value for difference >0.05). Similar reductions were seen in the pooled NSPS and abstinence groups for each individual BOE (p>0.05 for each analyte). In the usual cigarette group, these BOEs increased by an average of 14.4% (pooled NSPS vs. usual cigarette; p<0.001 for each analyte). COHb was likewise reduced by 71.8% in the pooled switching group vs. 69.1% in the abstinence group (p-value for the difference >0.05), while increasing by 13.3% in the usual cigarette group (p<0.001).

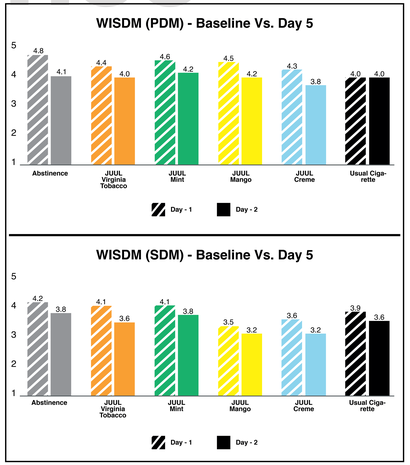
In contrast to combusted cigarettes, NNAL, 3-HPMA, MHBMA, S-PMA, HMPMA, CEMA, 1-OHP, and COHb were significantly reduced in the blood and urine of smokers who switched to any of the NSPS flavors, and the mean percent reduction was similar to the percent reduction seen in the abstinence arm. For NNN, the mean percent reduction was not statistically different from abstinence for all flavors. However, within two cohorts, a subject showed increase in NNN, which impacted our primary hypothesis (median reduction similar to NNN, but mean reduction not statistically different from mean). Furthermore, an increase of 63% was seen in NNN in the cohort which continued smoking their usual cigarette. This will be further evaluated in future studies.

Figure 2: Mean change in biomarkers of exposure (BOE's)[d]



[d]Data are presented as percent change (%, Day 5 vs. Baseline)

Figure 3: WISDM (Primary Dependence Motives, PDM); WISDM (Secondary Dependence Motives, SDM)[e]

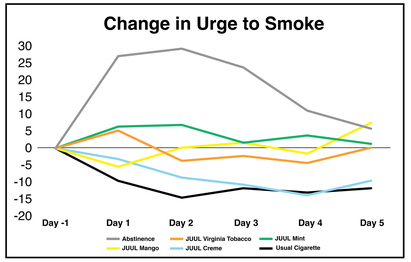


[e]Data are presented as mean value (absolute score, 1 = low dependence, 7 = high dependence)

Changes in Psychometric Measures:

Mean primary dependency motives (WISDM-PDM) were reduced for the abstinence arm and for all four flavors of NSPS, but not for the usual cigarette arm. Secondary dependence motives (WISDM-SDM) were reduced for all products (Figure 3). Urge to smoke increased in subjects in the abstinence arm, and this moderated over time. For NSPS and usual cigarettes, mean urge to smoke did not similarly increase during the first 4 days, or decreased (Figure 4). Note that a limitation of the scale used is it does not clearly specify whether urge to smoke refers to cigarettes or urge to use any tobacco product, including e-cigarettes, and this will be further explored in future studies.

Figure 4: Change in Urge to Smoke[f]



[f]Data are presented as change in Smoking Urge Assessment sale (Day n minus Baseline). Scale ranges from 1 (no urge to smoke) to 100 (extreme urge to smoke)

Conclusion:

For the non-nicotine urinary biomarkers studied, for adult smokers who switched to NSPS, an aggregate mean reduction of 99.6% was observed relative to the reduction associated with five days of abstention. Likewise, blood COHb was similarly reduced in the NSPS and abstention arms. These results support the objective that complete switching from cigarettes to the NSPS may lead to meaningful reductions in multiple key, short-term biomarkers of exposure observed with combustible use. Nicotine delivery and subjective measures are consistent with acceptability of JUUL as substitute for combusted cigarette for adult smokers.

Limitation:

Incomplete switching from cigarettes to NSPS (dual-use) was not studied.

Note: An earlier version of the poster said that the primary endpoint of this study was 'reduction in NNN compared to baseline.' This poster was amended on 2019-10-09 to accurately reflect the primary endpoints, which are described in the study protocol as 'the Day 5 values for each JUUL 5% product . . . compared to baseline' for six biomarkers of exposure (BOE), and to restate the study's primary hypothesis. This change does not impact the results of the study.

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Note: Consistent with applicable laws and regulations, JUUL Labs does not, and cannot, promote its products as being less harmful than cigarettes.