Evaluation of Biomarkers of Exposure in Adult Cigarette Smokers During Dual and Exclusive Use of VERVE® Discs and Chews

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ABSTRACT

SIGNIFICANCE: Many adult smokers (AS) are interested in alternatives to traditional cigarettes. VERVE® Discs and Chews are non-dissolvable oral products that contain tobacco derived nicotine (~1.5mg per unit) without tobacco. The objective of this study was to evaluate the change in exposure in AS using a minimum of 3 VERVE® Discs and Chews per day. **METHODS:** AS were randomized into the following - CS: subjects (n = 40) continued smoking their own brand; DDU: subjects (n = 42) reduced their cigarettes by >50% and used VERVE® Discs; CDU: subjects (n =41) reduced their cigarettes by >50% and used VERVE® Chews; DEU: subjects (n = 30) stopped smoking and used VERVE® Discs; CEU: subjects (n = 30) stopped smoking and used Verve Chews; NT: subjects (n = 30) were not allowed to use tobacco products during the 7-day study. 20 biomarkers of exposure (BOE) were measured at baseline and Day 5 and Day 7 and included 24-hr urinary metabolites of tobacco specific nitrosamines, nicotine, aromatic amines, acrolein, benzene, polycyclic aromatic hydrocarbon; mutagenicity; and carboxyhemoglobin (blood). **RESULTS:** Cigarettes ranged from ~17-18 per day across the groups at baseline and CS smoked ~17 cigarettes on Day 7. On Day 7, VERVE® use ranged from ~5-6 per day with ~8-9 cigarettes per day, in the DDU and CDU groups, and ~8-10 VERVE® per day in the CEU and DEU groups. All biomarkers were lower in the DDU and CDU groups compared to CS, with statistically significant ($p < .05$) reductions in the majority BOEs at day 5 or 7. Even larger reductions were observed in the DEU and CEU groups compared to CS. In addition, for the DEU and CEU, no statistically significant differences were observed in any BOEs measured (except for nicotine) compared to the NT. **CONCLUSION:** A >50% reduction in cigarettes while using VERVE® products results in some exposure reductions, however, switching completely to VERVE® results in exposure reductions similar to no tobacco use (except for nicotine). VERVE® may offer cigarette smokers a non-combustible alternative to cigarettes and provide a potential product lower on the continuum of risk.

BACKGROUND & PURPOSE

Cigarettes are the most harmful of tobacco products and cause serious diseases. Adult smokers unable or unwilling to quit cigarettes may benefit by switching to non-combustible tobacco products lower on the continuum of risk. We present here results regarding innovative oral tobacco products, VERVE discs and chews. These products do not contain cut, ground, powered or leaf tobacco. They contain United States Pharmacopeia (USP) grade tobacco-derived nicotine (approximately 1.5 mg/piece) and food or biocompatible medical grade non-tobacco ingredients including flavors.

These products are designed for adult smokers interested in oral tobacco products. The VERVE discs have a firm, flexible texture. The VERVE chews have a soft, flexible texture. Both product types are placed in the mouth and, once chewed, removed and discarded.

The purpose of this study was to evaluate changes in exposure to selected HPHCs, subjective effects, and product use behavior in adult smokers who partially or completely switch to VERVE® Chews or Discs compared to those who continue smoking cigarettes or stop using all tobacco products for 7 days.

VERVE® Product
VERVE® Chews, VERVE® Discs

TABLE 1. Biomarkers Assessed

BOE	HPHC	Classification
1-OHP	Polycyclic Aromatic Hydrocarbons (1-hydroxypyrene)	CA, CT
GAMA	Acrylamide	CA
HEMA	Ethylene oxide	CA, RT, RDT
AAMA	Acrylamide	CA
1-OHPhe	Polycyclic Aromatic Hydrocarbons	CA, CT
NNAL	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	CA
3-HMPMA	1,3-Butadiene	CA, RT, RDT
2-OHFle	Polycyclic Aromatic Hydrocarbons	CA, CT
2-Naphthol	Naphthalene	CA, RT
COHb	Carbon monoxide	RDT
3-HPMA	Acrolein	RT, CT
2-HPMA	Propylene oxide	CA, RT
CEMA	Acrylonitrile	CA, RT
4-ABP	4-Aminobiphenyl	CA
Urine Mutagenicity	Mutagenic compounds*	-
S-PMA	Benzene	CA, CT, RDT
2-AN	2-Aminonaphthalene	CA
2-MHBMA	Crotonaldehyde	CA
NNN	N-Nitrosonornicotine	CA
NE	Nicotine	RDT, AD

Classification: Carcinogen (CA), Respiratory Toxicant (RT), Cardiovascular Toxicant (CT), Reproductive or Developmental Toxicant (RDT), Addictive (AD)[3]

OBJECTIVES

- To compare 24-hour urinary total NNAL in adult smokers who reduce cigarette by ≥50% AND use VERVE® Chews or Discs (CDU/DDU) to those who continue to smoke (CS) for 7 days
- To compare CDU/DDU and Exclusive VERVE® (DIC/CWS) to CS and those who cease tobacco (NT) for 5 and 7 days on
  - Biomarkers of exposure (BOE, total = 20)
  - Subjective effects (mCEQ and Use the Product Again questionnaire)

METHODS

Study Product

TABLE 2. Products Assigned to Study

Group	Product Name	Flavor	Nicotine
Continue Smoking (CS)	Cigarette*	No restriction	Various
Discs Dual Use (DDU)	VERVE® Discs	Blue Mint & Green Mint	~1.5 mg/disc
Chews Dual Use (CDU)	Cigarette*	Blue Mint & Green Mint	~1.5 mg/chew
Discs Exclusive Use (DEU)	VERVE® Discs	Blue Mint & Green Mint	~1.5 mg/disc
Chews Exclusive Use (CEU)	VERVE® Chews	Blue Mint & Green Mint	~1.5 mg/chew
No Tobacco (NT)	(No tobacco/VERVE)	-	-

*** subject's own brand cigarette of any flavor and nicotine content**

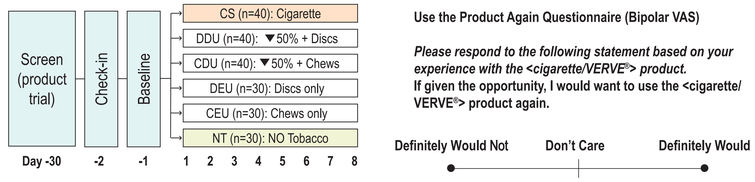
Study Design

An open label, randomized, 6 parallel-arm clinical study to evaluate changes in exposure to selected HPHCs, subjective effects and product use behavior in adult smokers who are randomly assigned to continue smoking, partially or completely switch to VERVE® Chews or VERVE® Discs products, or stop using any tobacco products for 7 days.

Key Inclusion/Exclusion Criteria:
Inclusion Criteria
- Healthy adult males & females 21 to 65 years of age
- Self-affirmed smokers of combustible manufactured cigarettes (at least 10 but not more than 30 cigarette per day [CPD], for at least 1 year)
- Positive Urine cotinine (≥500 ng/mL at screening)

Exclusion Criteria
- Planning to quit smoking in the next 30 days
- Self-reported puffers (draw smoke into mouth but don't inhale)
- History or presence of clinically significant disease or condition, that would jeopardize the safety of the subject or impact the validity of the study results

Figure 1. Study Design



Questionnaire

Use the Product Again Questionnaire (Bipolar VAS)

Please respond to the following statement based on your experience with the <cigarette/VERVE®> product.
If given the opportunity, I would want to use the <cigarette/ VERVE®> product again.

RESULTS

TABLE 3. Study Population & Product Use*

	CS	DDU	CDU	DEU	CEU	NT
Total (N)	40	42	41	30	30	30
Female/Male	13/27	19/23	15/26	15/15	12/18	12/18
Age (yrs, mean)	36.6	39.8	43.7	38.3	38.2	41.5
CPD Baseline	17.0	17.2	18.3	17.0	16.9	16.8
CPD Day 7	17.1	8.2	8.8	-	-	-
Discs Day 7	-	5.4	-	-	8.8	-
Chews Day 7	-	-	6.1	10.2	-	-

*** Data are shown as mean**

FIGURE 3. 24-hour Urine NE & Total NNAL

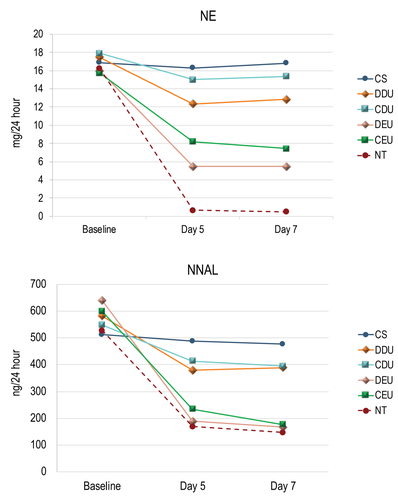
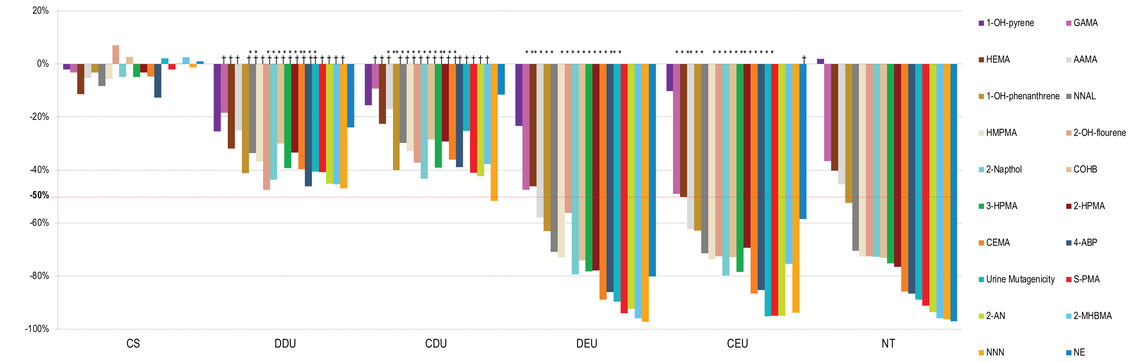


FIGURE 2. BOE – Percent Change at Day 7 from Baseline



*** Statistically significant lower relative to Continue Smoking (CS)**
† Statistically significant higher relative to No Tobacco (NT)
For illustration purposes, the percent changes from baseline are presented with the outliers removed. Statistical testing was conducted on the original values with all available data.

Figure 4. Study Product Use (Mean)

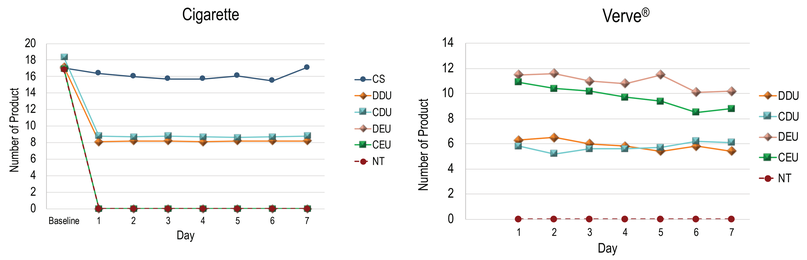
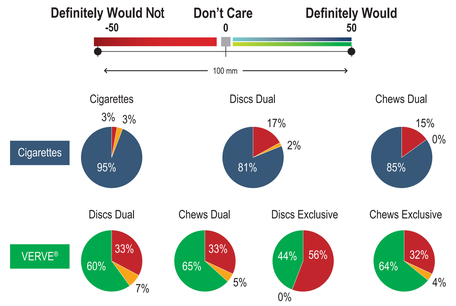


Figure 5. Use the Product Again



CONCLUSIONS

Overall, under the study conditions, reduction of BOEs appear to be proportional with the reduction in cigarettes. AS when reducing the number of cigarettes by 50% and using VERVE® discs or chews exhibited a corresponding ~50% reduction in BOEs. Complete switching to VERVE discs or chews results in reduction in exposure comparable to that observed from no tobacco use. Approximately 44% to 64% of AS indicated they would use the VERVE® product again. While dual use is not a desirable state, the results suggest that AS do not appear to exhibit compensatory smoking behavior and no increase in exposure is observed with dual use of cigarettes and VERVE® discs or chews.

STRENGTHS & LIMITATIONS

Strengths
- Study was conducted in a controlled clinical setting which ensured the product usage was according to the protocol
- The study included a cessation arm which provided the best-case scenario for BOE reduction

Limitation
- A 50% reduction in cigarettes for dual users may not reflect all dual use conditions in real world conditions

REFERENCES

1. Protecting American Families: Comprehensive Approach to Nicotine and Tobacco," Remarks by Scott Gottlieb, M.D., Commissioner of Food and Drug Administration (June 28, 2017).
2. Environmental Health Perspectives, 74:191.
3. U.S. Department of Health and Human Services (2012). Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a) (3) of the Federal Food, Drug, and Cosmetic Act.