A Randomized, Controlled, Open-Label, In-Clinic Study Evaluating Changes in Biomarkers of Exposure in Adult Smokers Who Switch to on! Nicotine Pouches for Seven Days

Rensch, J; Edmiston, J; Liu, J; Wang, J; Jin, X; Sarkar, M.
Altria Client Services LLC, Richmond, VA 23219
Center for Research and Technology
American College of Clinical Pharmacology (ACCP)
N Bethesda, MD; September 25-27, 2022

Abstract

Innovative oral tobacco products like on![®] nicotine pouches (NP) (Test Products) are a rapidly emerging category of tobacco products. These NPs contain tobacco-derived nicotine, flavors, and other ingredients. The purpose of this study was to assess biomarkers of exposure (BoEs) to select Harmful and Potentially Harmful Constituents (HPHCs), in adult smokers (AS) switching to Test Products compared to continuing to smoke cigarettes (CS) and completely quitting all tobacco products (NT). This open-label, randomized, controlled, in-clinic, five parallel-group study evaluated changes in NNAL and 18 BoEs to select HPHCs in AS (N=144). The AS smoked their own brand cigarettes for two days in-clinic for baseline assessments and were then randomly assigned to use mint-flavored 2, 4, or 8 mg Test Products, CS, or NT for seven additional days. Linear mixed models for analysis of covariance were used to assess the Day 7 BoE levels between the groups. The creatinine (Cr) adjusted total urinary NNAL and all other BoE levels, other than nicotine, on Day 7 were significantly lower (p< 0.0003) among all test product groups compared to CS; Geometric Least Square Means (GLSM) were reduced for all BoEs, except nicotine, by ~96-44% compared to the CS group and similar to the NT group. The GLSM for the urinary excretion of nicotine equivalents was 3.93 mg/g Cr (95%CI:2.46-6.29), 5.19 mg/g Cr (95%CI:3.48-7.74), and 7.98 mg/g Cr (95%CI:5.15-12.4) for the 2, 4, and 8 mg test product groups, respectively, relative to 7.89 mg/g Cr (95%CI:5.21-11.9) for the CS group and were not significantly different. The substantial reduction in HPHC exposure suggests that complete switching from cigarettes to test products may present a harm reduction opportunity for AS.

Introduction

Background:
The harm caused by tobacco product use is primarily attributable to cigarette smoking. Smoking is the primary causal factor for many serious diseases including lung cancer, COPD, and heart disease. The scientific evidence has clearly established that smoking cessation leads to a significant reduction in smoking-related morbidity and mortality.[1,2,3,4] Public health authorities, including the FDA, have acknowledged a continuum of risk among tobacco products, with combustible cigarettes at the highest end and smoke-free products on the lower end of that spectrum.[5,6] While cessation is the most desirable outcome, many adult smokers, who are unable or unwilling to quit, may benefit by switching from cigarettes to smoke-free products. Oral Tobacco-Derived Nicotine (OTDN) products are smoke-free products intended for adult tobacco consumers seeking alternatives. The OTDN category is one of the fastest growing tobacco product segments in the United States.

Objectives:
Compare 24-hour urinary NNAL in participants using on![®] NP for 7 days versus participants who continue smoking
Compare BoEs in participants using on![®] NP for 7 days versus participants who continue to smoke
Compare BoEs in participants using on![®] NP for 7 days versus participants who stopped using tobacco products
Characterize product use (cigarettes per day, NPs used per day, NPs per use, average duration of each use).

Conclusion

- Switching from Cigarettes to on![®] NP for seven days resulted in:
  - Lower levels for all evaluated BoEs (except for Nicotine Equivalent (NE)) compared to use of cigarettes over the same time period
  - Levels of the evaluated BoEs (other than nicotine) that were similar to those who abstained from using any nicotine product for the same time period.
  - While on![®] NP 2 mg and 4 mg were directionally lower for NE, none of the pouch groups were statistically significantly different than the OBC
- The substantial reductions in HPHC exposure indicate that complete switching from cigarettes to on![®] NP presents a harm reduction opportunity for Adult Smokers.

References

1. IARC. Tobacco Control: Reversal of Risk after Quitting Smoking [Internet]. [cited 2019 Mar 29]. Available from: http://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Tobacco-Control-Reversal-Of-Risk-After-Quitting-Smoking-2007
2. World Health Organization / WHO report on the global tobacco epidemic 2011 [Internet]. [cited 2019 Mar 29]. Available from: http://www.who.int/tobacco/global_report/2011/en/
3. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014 [Internet]. [cited 2019 Mar 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK179276
4. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ. 1994; Oct 8;309(6959):901-911.
5. Zeller M, Hatsukami D. The Strategic Dialogue on Tobacco Harm Reduction: A Vision and Blueprint for Action in the US. Tob Control. 2009;18(4):324-332.
6. Hatsukami DK, Joseph AM, Lesage M, et al. Developing the Science Base for Reducing Tobacco Harm. Nicotine Tob Res. 2007;9 Suppl 4(0 4):S537-553

Methods

Study Design:
Open-label, randomized, five parallel-groups clinical study evaluating changes in exposure to selected HPHCs and product use behavior in adult smokers

Key Inclusion Criteria:
- Voluntary consent to participate in the study
- Healthy adult males and females, 21 to 65 years of age
- Smoking history of an average of at least 10 but no more than 30 factory-manufactured combustible cigarettes daily for at least 12 months prior to screening
- Positive urine cotinine (> 500 ng/mL) at screening

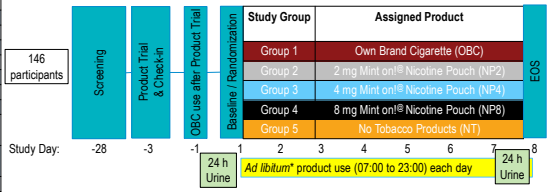
Key Exclusion Criteria:
- Use of any type of tobacco- or nicotine-containing products other than manufactured cigarettes in the seven days prior to check-in
- Self reported puffers (i.e., adult smokers who draw smoke from the cigarette into the mouth and throat but do not inhale)
- Planning to quit smoking within 30 days after the screening visit

Table 1. Demographics

Demographics	OBC (n=29)	NP2 (n=28)	NP4 (n=30)	NP8 (n=30)	NT (n=29)	Overall (n=146)*
Age (years)						
Mean	34.2	33.6	35.9	31.7	35.5	34.2
Sex, n (%)						
Male	16	16	17	17	17	83 (56.8%)
Female	13	12	13	13	12	63 (43.2%)
Race, n (%)						
White	21	20	17	14	17	89 (61.0%)
Black or African American	8	7	13	16	10	54 (37.0%)
American Indian or Alaska Native					2	2 (1.4%)
Multiple		1				1 (0.7%)
Cigs per Day						
Mean	16.03	16.14	16.23	16.57	16.69	16.34

*2 subjects were enrolled but discontinued prior to being randomized to a group.

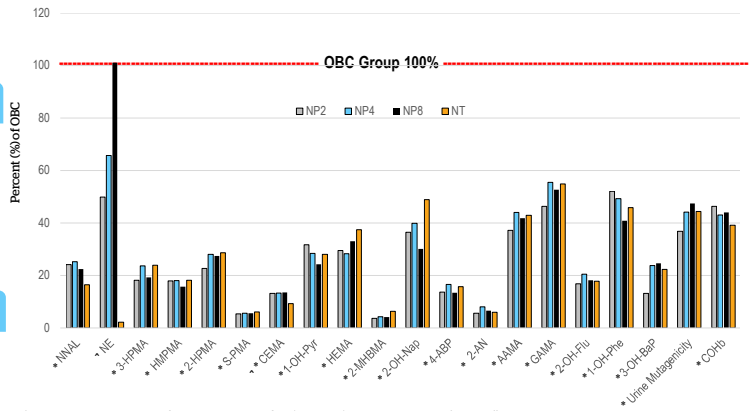
Figure 1. Study Design



* Subjects in the NP groups were requested to use at least 1 pouch at 3 different timepoints (11:00, 15:00, & 19:00) for at least 10 minutes, to ensure product was used each day.

Results

Figure 2. Substantial Reductions in BoEs are Observed in on![®] NP and Smoking Abstinence Groups



* NP groups compared to the Cigarette group – all BOEs (except NE) were statistically significantly different between the NP groups and the continued smoking group (p-values were ≤ 0.0003)
^ NP groups compared to the No Tobacco group – only the NE and CEMA were statistically significantly different
Least Squared (LS) Means comparisons of each group compared to OBC Group

Associated toxicants: NNK (NNAL), Nicotine (NE), Acrolein (3-HPMA), Crotonaldehyde (HMPMA), Propylene Oxide (2-HPMA), Benzene (SPMA), Acrylonitrile (CEMA), Pyrene (1-OH-Pyr), Ethylene Oxide (HEMA), 1,3 Butadiene (2-MHBMA), Naphthalene (2-OH-NAP), 4-Aminobiphenyl (4-ABP), 2-Aminonaphthalene (2-AN), Acrylamide (AAMA), Acrylamide (GAMA), Fluorene (2-OH-Flu), Phenanthrene (1-OH-Phe), Benzo-a-pyrene (3-OH-BaP), Mutagens (Urine Mutagenicity), Carbon Monoxide (COHb)

Figure 3. Baseline and End of Study Levels of NNAL

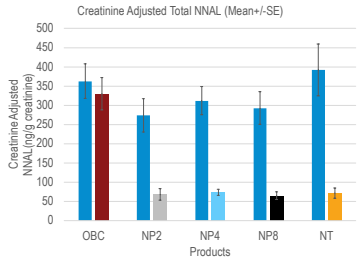


Figure 4. Baseline and End of Study Levels of NE

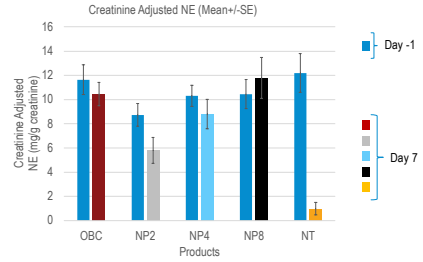


Figure 5. Cigarettes Per Day

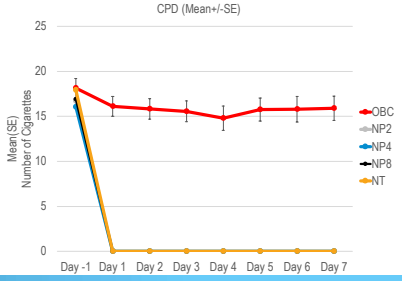
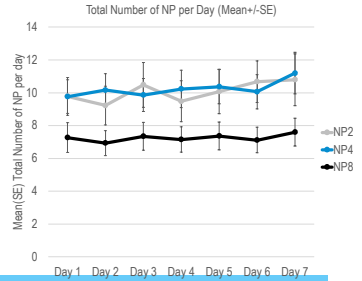


Figure 6. Nicotine Pouch Product Use



Altria Science