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

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Study Overview

Purpose

- Determine changes in exposure to selected HPHCs by measuring biomarkers in adult smokers who completely switch from smoking to use of on!® Nicotine Pouches (on!® NP) compared to those who continue smoking cigarettes or stop using all tobacco products
- To support the on!® NP MRTPA submission

Study Design

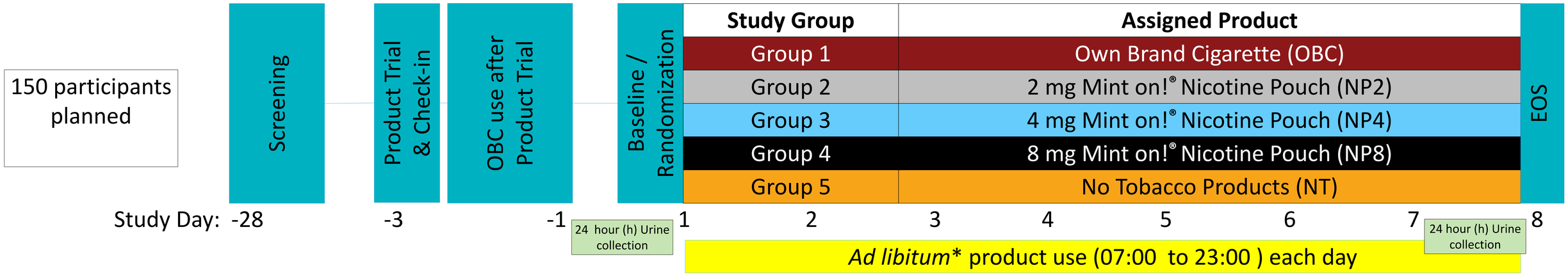
- In-clinic, randomized, controlled, open-label study
- Five study arms
  - Day 1 - 7 *ad libitum* use of assigned product

Study Group	Assigned Product
Group 1	Own Brand Cigarette (OBC)
Group 2	2 mg Mint on!® Nicotine Pouch (NP2)
Group 3	4 mg Mint on!® Nicotine Pouch (NP4)
Group 4	8 mg Mint on!® Nicotine Pouch (NP8)
Group 5	No Tobacco Products (NT)

Objectives

- Primary
  - Compare 24-hour (h) urinary total NNAL between on!® NP groups and OBC group
- Secondary
  - Other BoEs (besides NNAL)
  - Compare BoEs pouch groups to OBC & NT groups
  - Characterize product use behavior (cigarettes per day, pouches per day, duration)

Study Design



*NP Groups were required to use at least one NP at three different time points (11:00 h, 15:00 h, & 19:00 h) each day for at least 10 minutes.

Inclusion Criteria

- Healthy adult males and females, 21 to 65 years of age
- Smoking history (self-reported at screening) of at least 10 to 30 combustible cigarettes daily for at least 12 months prior to screening
- Positive urine cotinine ($\geq$ 500 ng/mL) at screening
- Willing to use the assigned study product
- Voluntary consent to participate

Exclusion Criteria

- Use of any type of tobacco- or nicotine-containing products other than OBC in the seven days prior to check-in
- Self-reported puffers (i.e., smokers who draw smoke from the cigarette into the mouth and throat but do not inhale)
- Planned to quit smoking
- Any clinically significant conditions that, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results

Participant 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

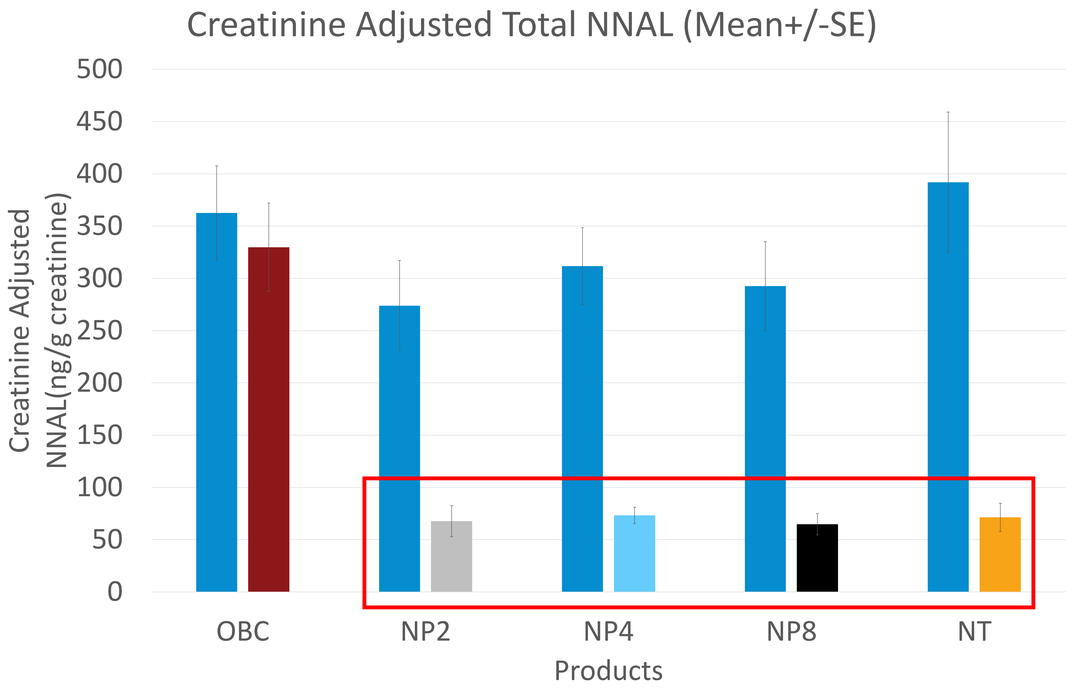
* Two subjects were enrolled but discontinued prior to being randomized to a group.

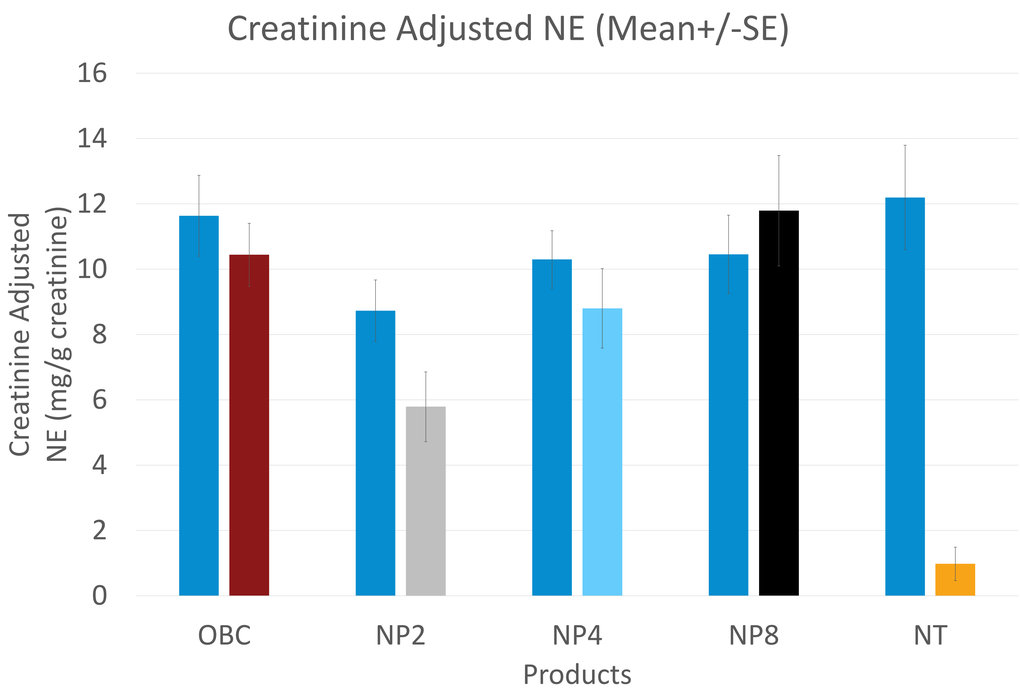
Biomarkers of Exposure (BoEs)

BoE Abbreviation	Associated Toxicant	FDA toxicant classification*
NNAL	**NNK: 4-[Methyl(nitroso) amino]-1-(3-pyridinyl)-1-butanone**	**CA**
NE	Nicotine	RDT, AD
3-HPMA	Acrolein	RT, CT
HMPMA	Crotonaldehyde	CA
2-HPMA	Propylene oxide	CA, RT
SPMA	Benzene	CA, CT, RDT
CEMA	Acrylonitrile	CA, RT
1-OH-Pyr	Pyrene	-
HEMA	Ethylene oxide [carcinogen, respiratory, reproductive or developmental]	CA, RT, RDT
2-MHBMA	1,3 butadiene [carcinogen, respiratory, reproductive or developmental]	CA, RT, RDT
2-OH-Nap	Naphthalene [not listed]	-
4-ABP	4-aminobiphenyl [carcinogen]	CA
2-AN	2-aminonaphthalene [carcinogen]	CA
AAMA	Acrylamide [carcinogen]	CA
GAMA	Acrylamide [carcinogen]	CA
2-OH-Flu	Fluorene [not listed]	-
1-OH-Phe	Phenanthrene [carcinogen, cardiovascular]	CA, CT
3-OH-B[a]P	Benzo-a-pyrene [carcinogen]	CA
Urine Mutagenicity	- [not listed]	-
COHb	Carbon monoxide [reproductive or developmental]	RDT

* Classification abbreviations: AD = addictive; CA = carcinogen; CT = cardiovascular toxicant; RDT = reproductive or developmental toxicant; RT = respiratory toxicant.

Baseline and End of Study Levels of NNAL and NE





Day -1

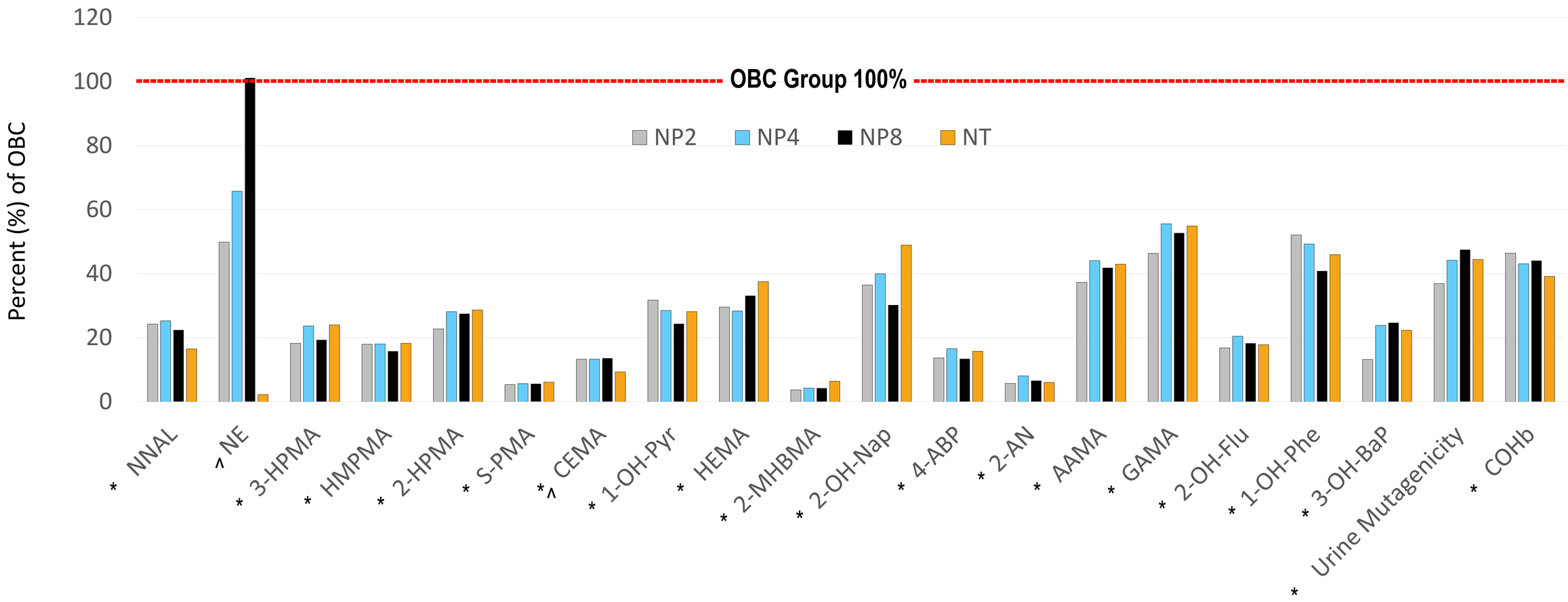
Day 7

What about the other BoE's?

Substantial Reductions in BoEs are Observed in on!® NP and Smoking Abstinence Groups

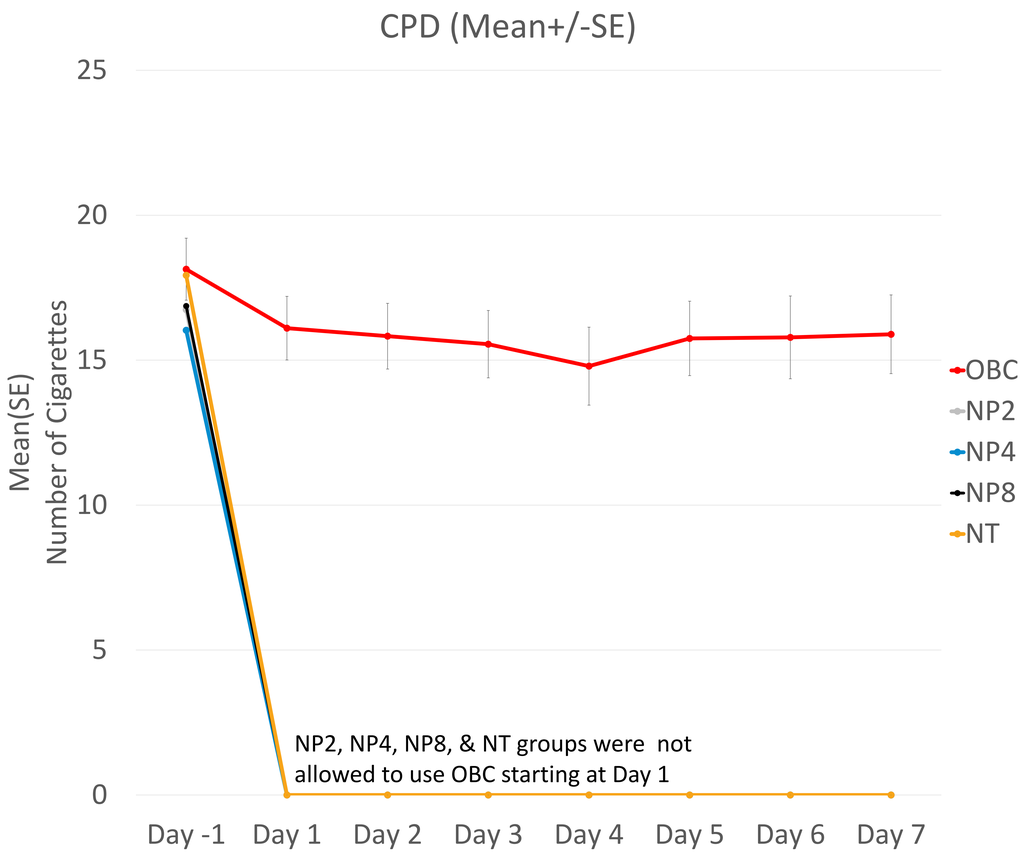
* NP groups compared to the Cigarette group – all BOEs (except NE) were statistically significantly different between the NP groups and the continued smoking group (p-values were ≤ 0.0003)

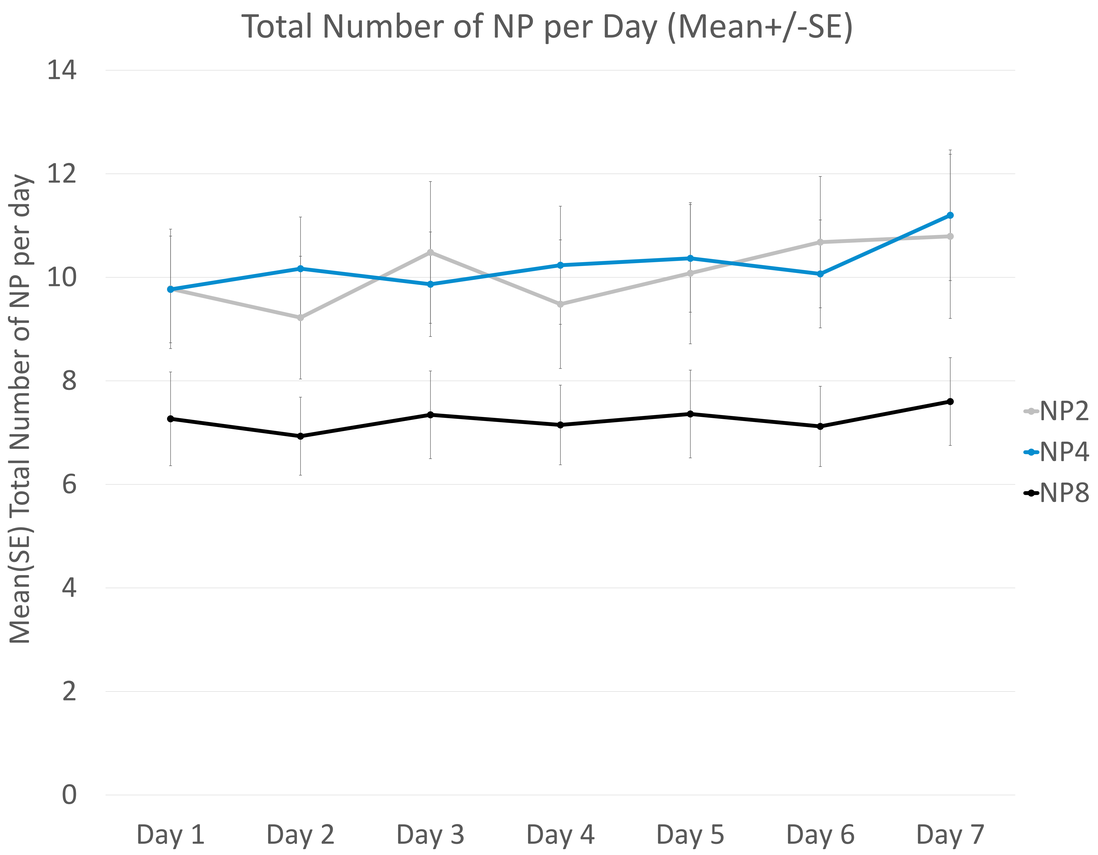
^ NP groups compared to the No Tobacco group – only the NE and CEMA were statistically significantly different



LS Means comparisons of each group compared to OBC group

Product Use


CPD (Mean+/-SE)
Mean(SE) Number of Cigarettes
25
20
15
10
5
0
Day -1
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
OBC
NP2
NP4
NP8
NT
NP2, NP4, NP8, & NT groups were not allowed to use OBC starting at Day 1


Total Number of NP per Day (Mean+/-SE)
Mean(SE) Total Number of NP per day
14
12
10
8
6
4
2
0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
NP2
NP4
NP8

Product Emergent Adverse Events

- Product-related AEs
  - Were mostly mild in severity (33 of 38 events)
  - 5 events were moderate in severity
- No AEs were identified as severe
- Number of Product-related AEs per Group:
  - OBC Group (n=29) – 1 product related AE (headache), mild in severity
  - NP Groups (n= 88) – 25 product related AEs (most common Headache and Nausea)
    - NP2 Group (n= 28) – 8 product related AEs, all mild in severity
    - NP4 Group (n= 30) – 6 product related AEs, 4 mild/2 moderate in severity
    - NP8 Group (n= 30) – 11 product related AEs, 10 mild/2 moderate in severity
  - NT Group (n= 29) – 5 product related AEs, 4 mild/1 moderate in severity
- All products were well tolerated

Key Takeaways

- Switching from Cigarettes to on!® NP for seven days resulted in:
  - lower levels for all evaluated BoEs (except for NE) compared to *ad libitum* 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
  - nicotine exposures that were not statistically significantly different in the on!® NP groups compared to cigarettes

- The substantial reductions in HPHC exposure indicate that complete switching from cigarettes to on!® NP presents a harm reduction opportunity for Adult Smokers.

Thank you!

Any Questions?

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