Biomarker of Exposure Reductions Upon Switching for 5 Days From Cigarettes to a Carbon Heated Tobacco Product (CHTP 1.0)

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Introduction and Objectives

Background

Carbon Heated Tobacco Product (CHTP 1.0) is a heat-not-burn tobacco product designed to heat tobacco without burning it in order to reduce formation of, and consequently exposure to, harmful and potentially harmful constituents (HPHCs) as compared to cigarettes, and to replicate the ritual, taste, sensory characteristics and nicotine uptake of cigarette smoking.

Main Objectives

To assess the extent of reduced exposure to a number of HPHCs upon complete switch to CHTP 1.0 use compared to continued cigarette smoking. Nicotine uptake and subjective effects were also evaluated.

Methods

Design

Randomized, controlled, open-label, 2-arm, parallel group, confinement study in 80 healthy adult smokers who used *ad-libitum* CHTP 1.0 (n=41) or continued to smoke their own brand of cigarettes (n=39) for 5 days. The study was conducted in Poland between July 4th and Aug 25th 2015 and measured 15 selected HPHCs assessed in 24-hour urine or blood.

Participants

- Subjects judged healthy at screening by the Investigator
- 21+ years of age Caucasians, smoking ≥10 commercially available non-menthol cigarettes (maximum ISO nicotine yield of 1 mg per cigarette) per day for the last 6 weeks prior to admission
- Smoking cigarettes during the last 3 years prior to admission.
- Not planning to quit smoking in the forthcoming 3 months, but ready to switch from cigarettes to CHTP 1.0 use for 5 days

Participants willing to quit smoking after enrolment were encouraged to do so and referred to a smoking cessation counselor.

Screening n=124
Unmet criteria n=39

↓

Enrollment n=85

Safety population n=85
Discontinued n=5

↓

Randomization
n=80

CHTP 1.0 n=41 | Cigarettes n=39

Completion
n=80

Sample size estimation

A total of 80 participants randomized at a ratio of 1:1 to the CHTP 1.0 or cigarette group, were considered sufficient to attain >80% power to show a reduction of ≥50% in the concentrations of COHb, 3-HPMA, MHBMA, and S-PMA in the CHTP 1.0 group relative to the cigarette group, using a one-sided test with 2.5% type I error probability.

Statistical methods

- Analysis of covariance on log-transformed Day 5 values to estimate the ratios between the study groups.
- Adjustment for sex, cigarette use over the 6 weeks before enrollment, and the baseline values of the analyzed biomarkers.

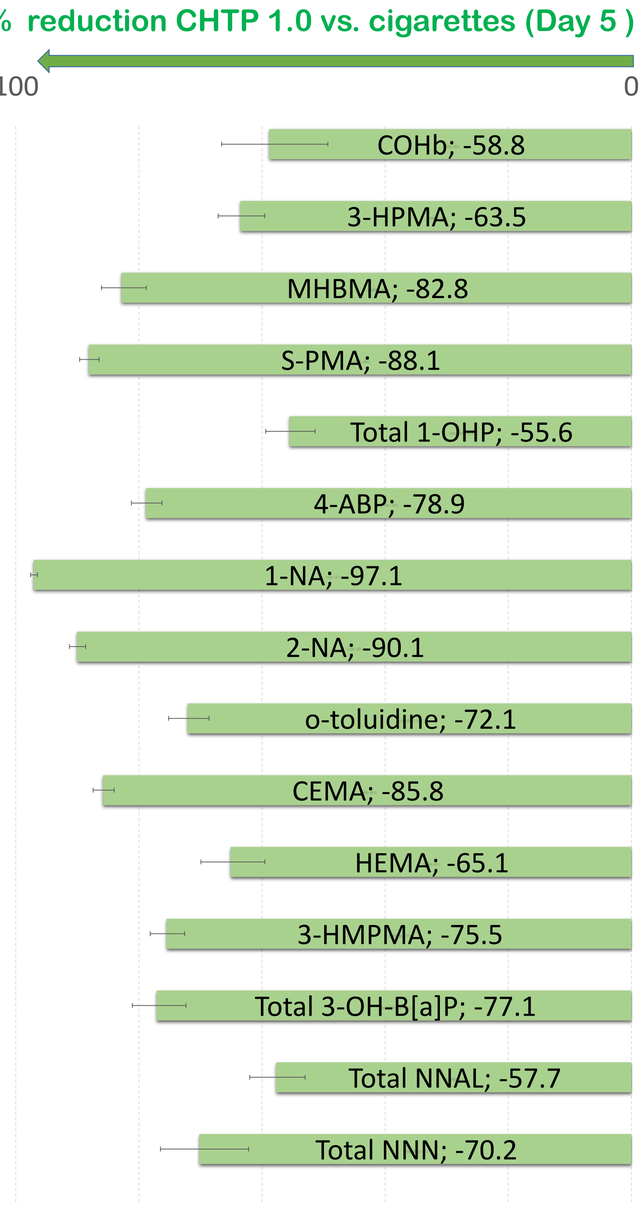
Product

- CHTP 1.0 is a heat-not-burn product that does not involve the combustion of tobacco.
- The product generates a nicotine-containing aerosol which has significantly lower levels of harmful and potentially harmful constituents (HPHCs) than cigarettes.
- CHTP 1.0 has been designed to resemble a cigarette as closely as possible.

Key Points

- Completely switching to CHTP 1.0 use reduced exposure to HPHCs, compared to cigarettes.
- CHTP 1.0 use led to nicotine uptake comparable to cigarette smoking.
- CHTP 1.0 use led to similar urge-to-smoke results as cigarette smoking.

Results



Demographics

	CHTP	CC
Female n (%)	21 (51.2%)	20 (51.3%)
Age (Mean ± SD)	34.1±10.5	32.7±11.0
Daily CC Consumption n (%)		
10-19 cig/day	21 (51.2%)	19 (48.7%)
> 19 cig/day	20 (48.8%)	20 (51.3%)
ISO Nicotine n (%)		
≤ 0.6mg	32 (78.0%)	34 (87.2%)
> 0.6-1 mg	9 (22.0%)	5 (12.8%)
FTND Total Score		
Mean± SD	5.4±1.78	5.8± 2.00

Biomarkers of Exposure

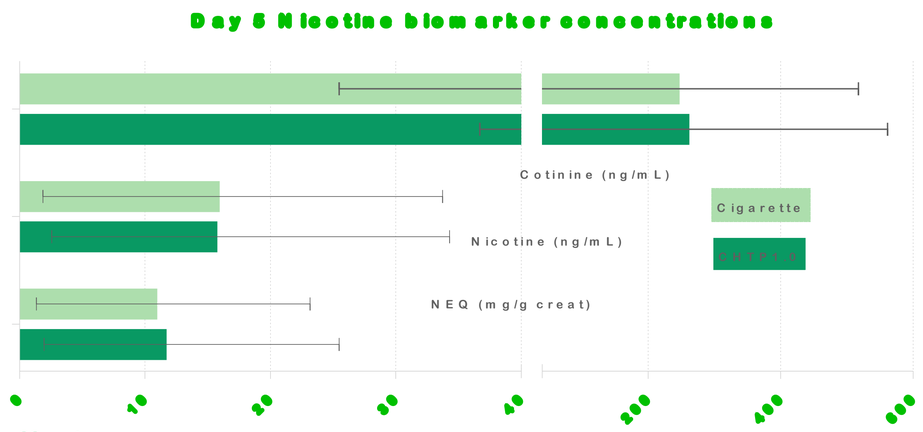
- Day 5 levels were reduced, relative to cigarettes, by 58.8% to 88.1% in primary biomarkers of exposure COHb, MHBMA, 3-HPMA and S-PMA.
- Other biomarkers were reduced by 55.6% to 97.1%

Safety

- No serious adverse events were reported in both study arms.
- 31/41 CHTP 1.0 subjects (75.6%) and 20/39 cigarette subjects (51.3%) experienced adverse events (AE).
- All AEs were assessed as mild or moderate.
- Cough and headache were more frequent in the CHTP 1.0 group (32% vs. 0% for cough and 46% vs. 23% for headache) than in the cigarette group.

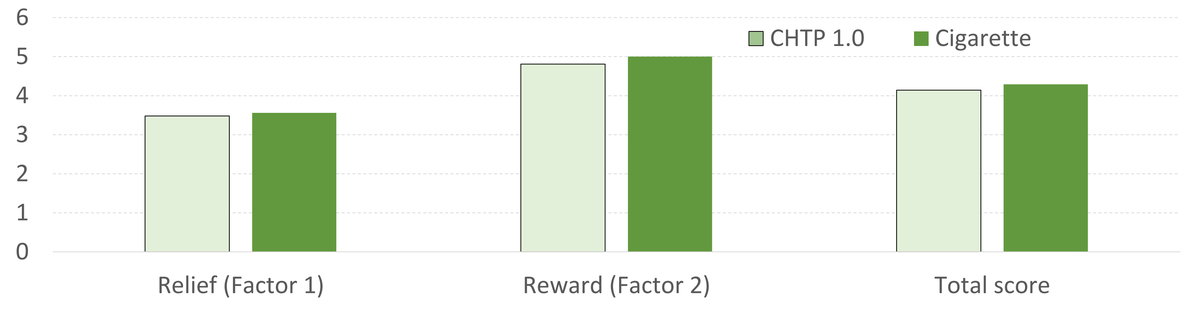
Nicotine Uptake

- NEQ conc. was 3.0% lower in the CHTP 1.0 compared to the cigarette group over 5 days.
- On Day 5, plasma nicotine and cotinine levels were 3.0% lower and 2.6% higher, respectively, in the CHTP 1.0 group compared to the cigarettes group.



Subjective effects

- Cigarette smokers and CHTP 1.0 users scored similarly in the urge-to-smoke assessment questionnaire in terms of relief and reward as well as in total scores.
- CHTP 1.0 scores were close to those of cigarettes over 5 days.



Conclusions

At the end of the 5-days-exposure period, biomarkers of exposure to HPHCs were markedly reduced upon switching to CHTP 1.0 use, whereas nicotine levels were similar to cigarette smoking. The urge-to-smoke was similar between CHTP 1.0 and cigarettes, which is encouraging for CHTP 1.0 adoption as an alternative to cigarettes.

Harmful and potentially harmful constituents (Biomarker (Abbreviation)):
1,3-Butadiene (Monohydroxybutenylmercapturic acid (MHBMA)); 1-Aminonaphtalene (1-Aminonaphtalene (1-NA)); 2-Aminonaphthalene (2-Aminonaphthalene (2-NA)); 4-Aminobiphenyl (4-Aminobiphenyl (4-ABP)); 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL)); Acrolein (3-Hydroxypropylmercapturic acid (3-HPMA)); Acrylonitrile (2-Cyanoethylmercapturic acid (CEMA)); Benzene (S-Phenylmercapturic acid (S-PMA)); Benzo[a]pyrene (Total 3-hydroxybenzo(a)pyrene (Total 3-OH-B[a]P)); Carbon Monoxide (Carboxyhemoglobin (COHb)); Pyrene (Total 1-Hydroxypyrene (Total 1-OHP)); Crotonaldehyde (3-Hydroxy-1-methylpropylmercapturic acid (3-HMPMA)); Ethylene Oxide (2-Hydroxyethylmercapturic acid (HEMA)); NNN (Total N-nitrosonornicotine (Total NNN)); o-toluidine (o-toluidine (o-tol)); Nicotine equivalents (NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide).

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Competing Financial Interest

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