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

A. Donelli, C. Tran, C. Haziza, J. Ancerewicz, G. de La Bourdonnaye, R. Weitkunat, and F. Lüdicke

PMI R&D, Philip Morris Products S.A. Quai Jeanrenaud 5, 2000 Neuchatel, Switzerland (part of Philip Morris International group of companies)

The study was registered at ClinicalTrials.gov (ID: NCT02503254)

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 (HPHC) 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 5-day 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). 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

- Subject 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, based on self-reporting
- Smoking cigarettes during the last 3 years prior to enrollment
- Not planning to quit smoking in the forthcoming 3 months, but ready to switch from cigarettes to CHTP 1.0 use for 5 days

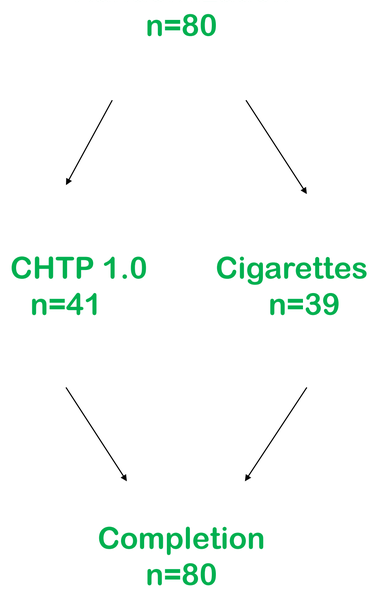
Participants willing to quit smoking after enrolment were encouraged to do so and referred to a smoking cessation counselor.

Sample size estimation

A total of 80 participants randomized at a ratio of 1:1 to CHTP 1.0 or cigarette groups, 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

- Inferential analysis was performed on the endpoints observed on Day 5
- Analysis of covariance on log-transformed Day 5 values to estimate the ratios between the study groups (one sided type I error of 2.5%)
- Adjustment for sex, cigarette use over the 6 weeks before enrollment, and the baseline value of the biomarker



Product

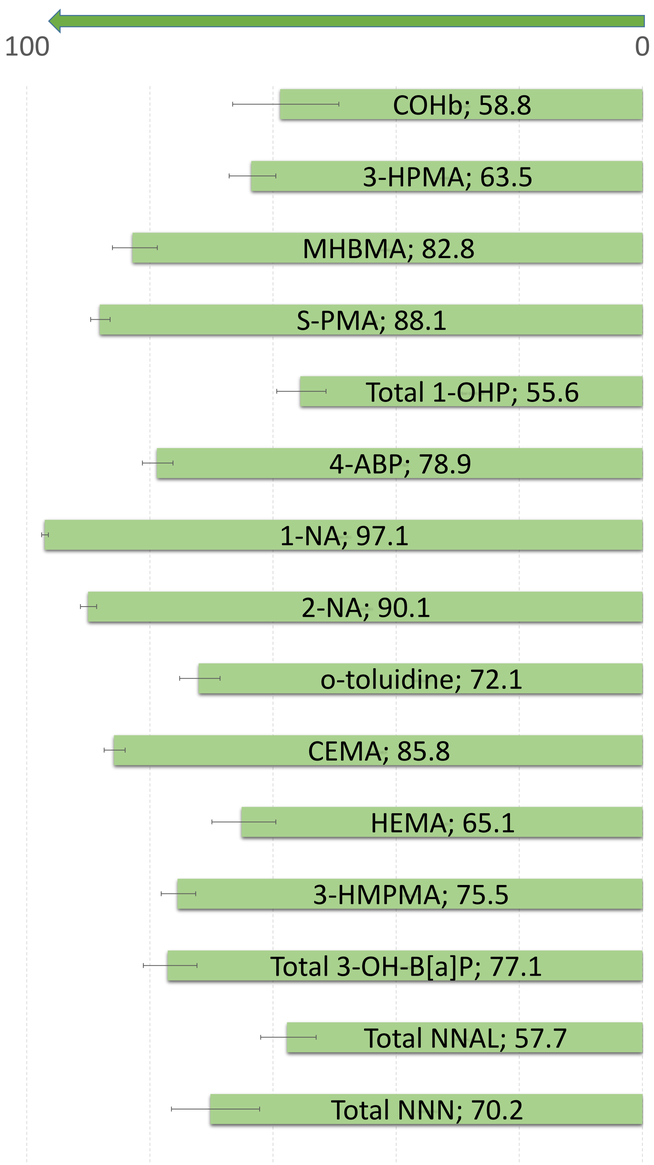
- CHTP 1.0 is a heat-not-burn product that does not involve the combustion of tobacco
- The product generates a nicotine-containing aerosol which has significantly lower levels of harmful and potentially harmful constituents (HPHCs) compared to cigarettes
- CHTP 1.0 has been designed to resemble a cigarette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

Key Points

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

Results

CHTP 1.0 % reduction vs. cigarettes (Day-5)



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

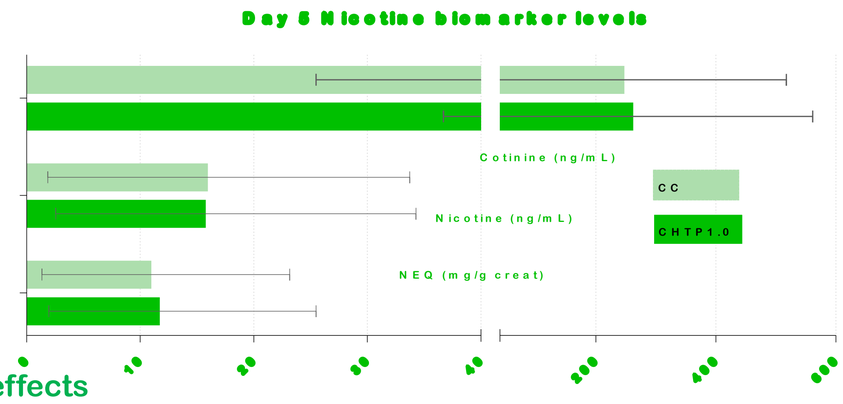
- Day 5 levels were reduced, relative to cigarettes, by 58.8% to 88.1% in primary biomarkers COHb, MHBMA, 3-HPMA and S-PMA
- Other biomarkers were reduced by 55.5% to 97.0%

Safety

- No serious adverse events were reported during the study
- 31/41 CHTP subjects (75.6%) and 20/39 Cigarettes subjects (51.3%) experienced adverse events (AE)
- 27.1% of AEs were mild and 38.8% were moderate
- Occurrence of subjects having cough and headache were higher in the CHTP 1.0 group (32% vs. 0% for cough and 46% vs. 23% for headache)

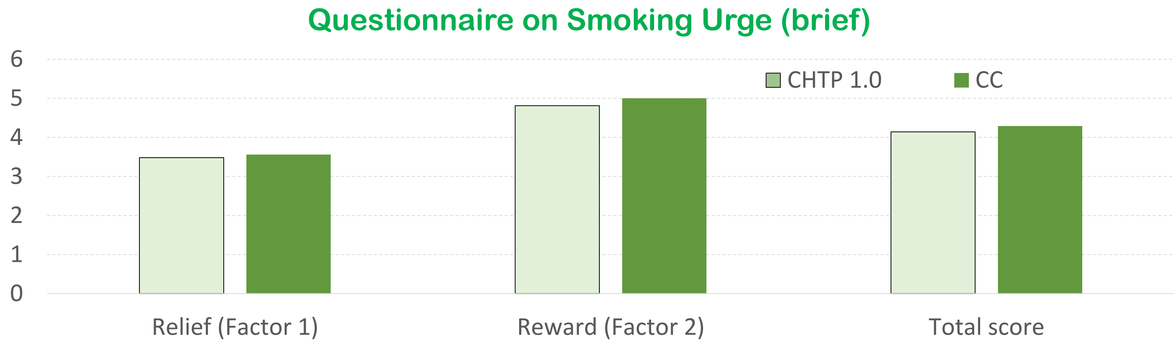
Nicotine Uptake

- NEQ level was 3.0% lower in the CHTP 1.0 compared to the cigarette group over all time points.
- On day 5 plasma nicotine and cotinine levels were respectively 3.0% lower and 2.6% higher in CHTP 1.0 group as compared to the cigarettes group



Subjective effects

- Cigarettes and CHTP 1.0 users scored similarly in the urge-to-smoke assessment questionnaire of relief, reward and total scores
- The scoring scales of CHTP 1.0 were close to those of cigarettes over the whole study period



Conclusions

At the end of the 5 day 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. Smoking urge questionnaire scores indicate similar responses for CHTP 1.0 as for CC, which is encouraging for CHTP adoption as an alternative to CC.

Smoke Constituent (Abbreviation : Biomarker)
1-aminonaphtalene (1-NA : 1-aminonaphtalene); Pyrene (1-OHP: 1-hydroxypyrene); 2-aminonaphthalene (2-NA: 2-aminonaphthalene); Acrolein (3-HPMA: 3-hydroxypropylmercapturic acid); 4-aminobiphenyl (4-ABP: 4-aminobiphenyl); Acrylonitrile (CEMA: 2-cyanoethylmercapturic acid); Carbon Monoxide (COHb: Carboxyhemoglobin); o-toluidine (o-toluidine : o-toluidine); Ethylene Oxide (HEMA: 2-hydroxyethyl mercapturic acid; Crotonaldehyde (3-HMPMA: 3-hydroxy-1-methylpropylmercapturic acid); 1,3-Butadiene (MHBMA: monohydroxybutenyl mercapturic acid); NNK (Total NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone); NNN (Total NNN: N-nitrosonornicotine); Benzene (S-PMA: S-phenylmercapturic acid).

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

SRNT – Annual Meeting, Florence, Italy

8-11 March 2017

Competing Financial Interest

The research described in this poster was sponsored by Philip Morris International

The research described in this poster was sponsored by Philip Morris Products & Manufacturing SA