Decreased Levels of Biomarkers of Exposure in Smokers Switching to Carbon-Heated Tobacco Product 1.2 compared with those who continued to smoke: A Randomized, Controlled, Open-Label 90-Day Exposure Study

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Introduction and Objectives

Carbon-Heated Tobacco Product (CHTP) 1.2, a heat-not-burn tobacco product.

Figure 1: CHTP Tobacco Stick.

Introduction

In addition to smoking cessation programs, tobacco harm reduction strategies include switching smokers who would otherwise continue to smoke from cigarettes to potentially less harmful alternatives. CHTP 1.2 is similar in appearance to a cigarette, approaching the smoking ritual while generating a nicotine-containing aerosol by heating tobacco instead of burning it. The CHTP 1.2 is currently being assessed for its harm reduction potential compared with cigarettes.

Main Objectives

The study aimed to demonstrate CHTP's exposure reduction to 15 harmful and potentially harmful constituents (HPHC) compared with cigarette smoking and to evaluate its effects on 18 clinical risk endpoints (CRE) indicative of mechanistic pathways underlying the development of smoking-related diseases and the safety profile between smokers switching from cigarettes to CHTP 1.2 compared with smokers continuing to smoke cigarettes.

Table 1: Biomarkers of Exposure (BoExp) to HPHCs Assessed.

• COHb	
• MHBMA	• 4-ABP
• 3-HPMA	• 1-NA
• S-PMA	• 2-NA
• Total NNAL	• o-tol
• Total 3-OH-B[a]P	• CEMA
• Total 1-OHP	• HEMA
• Total NNN	• 3-HMPMA

Table 2: CREs.

Associated with the cardiovascular system:	
Lipid Metabolism:	HDL-C, LDL-C, TG, TC, Apo A1, Apo B
Oxidative stress:	8-epi-$PGF_{2\alpha}$, 8-OHdG, TAC
Endothelial dysfunction:	sICAM-1
Inflammation	WBC, hs-CRP, homocysteine
Platelet function	Platelet cell count, fibrinogen, 11-DTX-B2
Associated with respiratory function:	
Spirometry (post-bronchodilator)	FEV_1
Associated with xenobiotic metabolism:	
CYP1A2	

Methods

Study Conduct

The study was approved by an Institutional Review Board in Warsaw (Poland), initiated in January 2016, conducted according to the International Conference on Harmonisation principles of Good Clinical Practice, registered on ClinicalTrials.gov (NCT02641587), and completed in August 2016.

***HPHCs (Biomarker [Abbreviation])*:**
Nicotine (Nicotine equivalents [NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide]; 1,3-Butadiene (Monohydroxybutenylmercapturic acid [MHBMA]); Acrolein (3-Hydroxypropylmercapturic acid [3-HPMA]); Benzene (S-phenylmercapturic acid [S-PMA]; 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol [Total NNAL]); Benzo[a]pyrene (Total 3-hydroxylbenzo(a)pyrene [Total 3-OH-B[a]P]); Pyrene (Total 1-Hydroxypyrene [Total 1-OHP]); N-nitrosonornicotine (Total N-nitrosonornicotine [Total NNN]; 4-Aminobiphenyl (4-aminobiphenyl [4-ABP]); 1-aminonaphthalene (1-aminonaphthalene [1-NA]); 2-aminonaphthalene (2-aminonaphthalene [2-NA]); o-toluidine (o-toluidine [o-tol]); Acrylonitrile (2-Cyanoethylmercapturic acid [CEMA]); Ethylene oxide (2-hydroxyethylmercapturic acid [HEMA]); Crotonaldehyde (3-Hydroxy-1-methylpropylmercapturic acid [3-HMPMA])

***CREs (Abbreviation)*:**
High-density lipoprotein cholesterol (HDL-C); Low-density lipoprotein cholesterol (LDL-C); Triglycerides (TG); Total cholesterol (TC); Apolipoprotein A1 (Apo A1); Apolipoprotein B (Apo B); 8-epi-prostaglandin F2α (8-epi-$PGF_{2\alpha}$); 8-Hydroxy-2'-deoxyguanosine (8-OHdG); Total anti-oxidant capacity (TAC); Soluble intercellular adhesion molecule-1 (sICAM-1); White blood cell count (WBC); High-sensitivity C-reactive protein (hs-CRP); 11-dehydrothromboxane B2 (11-DTX-B2); Forced expiratory volume in 1 second (FEV_1); Cytochrome P450 1A2 (CYP1A2).

Methods

Design

Randomized, controlled, open-label, two-arm parallel group, single center study in healthy adult European smokers who either switched from cigarette smoking to CHTP 1.2 or continued to smoke cigarettes for five days in a confined setting followed by 85 days in an ambulatory setting.

Participants

- Participants understood the information provided for the study and signed the Informed Consent Form.
- Healthy male and female smoking participants were ≥ 28 years old and smoked ≥10 commercially available non-menthol cigarettes per day for the last six weeks and had been smoking for ≥10 years.
- Subjects had negative alcohol and drug tests.
- Female subjects were not pregnant or breastfeeding.

Table 3: Randomized Population Characteristics.	CHTP 1.2 (N=80)	CC (N=40)	Overall (N=120)
Males – n (%)	44 (55.0)	20 (50.0)	64 (53.3)
Females – n (%)	36 (45.0)	20 (50.0)	56 (46.7)
Age (years) – Mean ± SD	38.9 ± 8.8	39.0 ± 8.0	38.9 ± 8.6
BMI – Mean ± SD	25.7 ± 3.5	25.7 ± 3.0	25.7 ± 3.3
Daily CC consumption prior to study – n (%)			
10–19 cig/day	36 (45.0)	18 (45.0)	54 (45.0)
> 19 cig/day	44 (55.0)	22 (55.0)	66 (55.0)

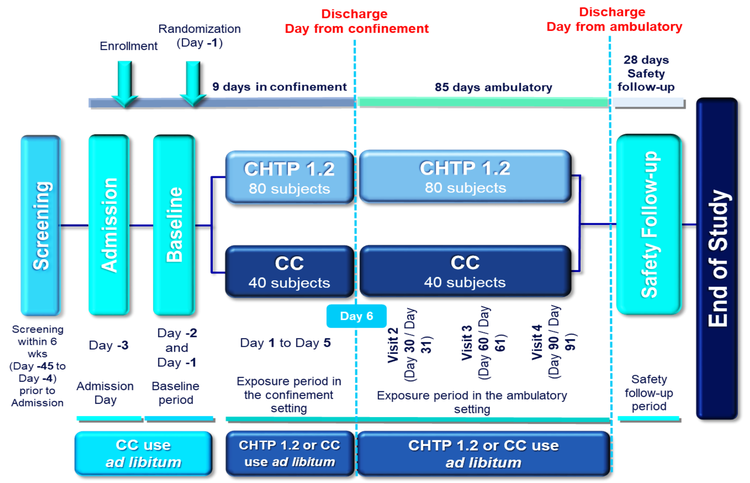


Figure 2: Study Design.

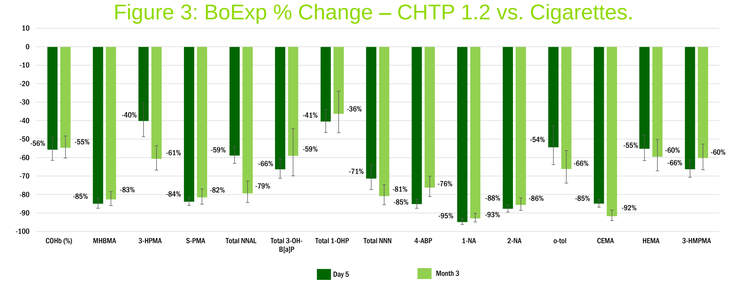
Safety

- One serious adverse event (AE) led to discontinuation of one randomized participant in the CHTP 1.2 group; however, this was considered unrelated to CHTP 1.2.
- Two non-serious AEs in one randomized participant in the cigarette group led to his discontinuation; however, they were considered unrelated to cigarettes.
- The incidence of AEs was comparable in the CHTP 1.2 (80.0%) and cigarette (77.5%) groups .
- The majority of AEs reported during the study were mild or moderate in severity.
- The most frequently reported AE during the study was headache (25.0% of the participants in the CHTP 1.2 group and 27.5% in the cigarette group).
- The most frequently reported AE considered to be related to CHTP 1.2 was cough (four subjects in the CHTP 1.2 group).
- The proportion of participants reporting a cough was lower in the CHTP 1.2 arm than in the cigarette arm (odds ratio CHTP 1.2/cigarette = 0.458) during the entire Ambulatory Period.

Results*

* In the Per-Protocol population

Figure 3: BoExp % Change – CHTP 1.2 vs. Cigarettes.



Following switching to CHTP 1.2 vs. continuing smoking cigarettes, BoExp levels were reduced by 40%–95% after five days and by 36%–94% after three months.

CREs – CHTP 1.2 vs. Cigarettes

Figure 4: Platelet Function – Cigarettes vs. CHTP 1.2 at Month 3.

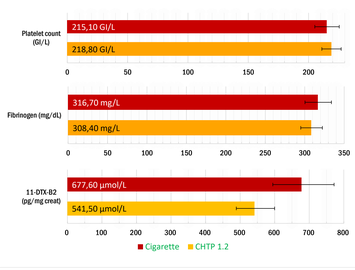


Figure 8: Inflammation – Cigarettes vs. CHTP 1.2 at Month 3.

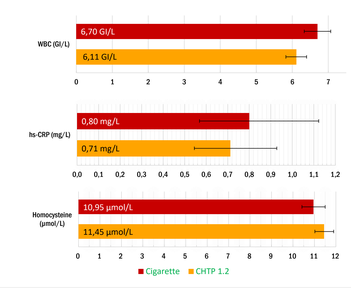


Figure 5: Lipid Metabolism – Cigarettes vs. CHTP 1.2 at Month 3.

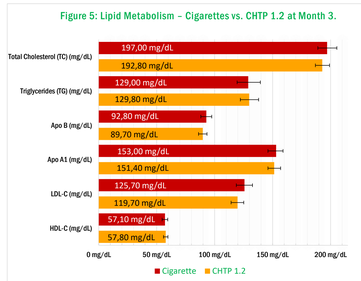


Figure 9: Respiratory Function – Cigarettes vs. CHTP 1.2 at Month 3.

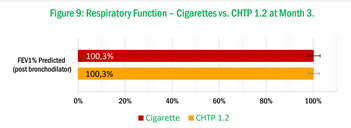


Figure 10: Xenobiotic Metabolism – Cigarettes vs. CHTP 1.2 at Month 3.

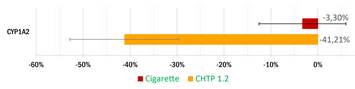


Figure 6: Oxidative Stress % Change – CHTP 1.2 vs. Cigarette at Month 3.

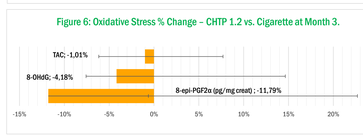


Figure 7: Endothelial Dysfunction – Cigarettes vs. CHTP 1.2 at Month 3.

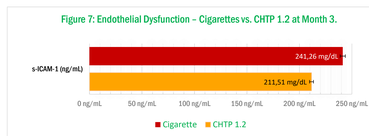


Table 4: Mechanistic Pathway.	Endpoint	CHTP 1.2 vs. cigarette effect at three months		Change toward smoking cessation (literature) using CHTP
		Mean	95% CI	
Lipid Metabolism	HDL-C	0.7 mg/dL	–2.3, 3.8	✓
Inflammation	WBC	–0.59 10^9/L	–1.06, –0.12	✓
Respiratory Function	FEV_1	0.0 %pred	–3.4, 3.4	No change
Endothelial Dysfunction	sICAM-1	12.3 %reduction	7.3, 17.1%	✓
Oxidative Stress	8-epi-$PGF_{2\alpha}$	11.8 %reduction	–0.6, 22.7%	✓
Clotting	11-DTX-B2	20.1 %reduction	5.7, 32.3%	✓

- Exposure to nicotine at the end of the confinement period (on Day 5) was higher in the CHTP 1.2 arm than in the cigarette arm.
- However, during the Ambulatory Period, levels of NEQ, nicotine, and cotinine returned to levels similar to baseline.

Conclusions

Switching from cigarettes to CHTP 1.2 resulted in significant reductions in BoExp levels that were associated with favorable changes in some CREs in the direction of smoking cessation. These results confirm the potential to present less risk of harm than continuing smoking and suggest that CHTP 1.2, while not risk-free, might reduce the risk of developing smoking-related diseases when compared with cigarettes.

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