REDUCED EXPOSURE TO HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS AFTER 90 DAYS OF USE OF TOBACCO HEATING SYSTEM 2.2 MENTHOL IN JAPAN: A COMPARISON WITH CONTINUED CIGARETTE USE OR SMOKING ABSTINENCE

C. Haziza1, N. Lama1, A. Donelli1, P. Picavet1, G. Baker1, J. Ancerewicz1, M. Benzimra1, M. Franzon1, M. Endo2, and F. Lüdicke1
1 Philip Morris International R&D, Neuchâtel, Switzerland. 2 Osaka Hospital Tokyo Heart Center, Tokyo, Japan

Introduction and Objectives

The Tobacco Heating System 2.2 menthol (mTHS) was developed to reduce or eliminate the formation of harmful and potentially harmful smoke constituents (HPHCs) in the aerosol through heating and not burning tobacco, while preserving as much as possible taste, sensory experience, nicotine delivery and psychoactive and ritual characteristics of menthol cigarettes (mCC). The study reported is part of a global clinical program for THS and was designed to demonstrate sustained exposure reduction to selected HPHCs in smokers pre-dominantly using mTHS and to provide first insight on changes in usual risk endpoints (CREs) when switching from mCC to mTHS use for 5 days in confinement followed by an ambulatory period of 85 days, compared to subjects continuing to smoke mCC and those who abstained from smoking. Biomarkers of exposure (Bcep) to 15 HPHCs were assessed to provide an assessment of human uptake of a variety of representative toscains contained in combustible tobacco products. Selected CREs were associated with cardiovascular, respiratory disease and genotoxicity as well as subjective effects to investigate the acceptance of mTHS compared to mCC which were also assessed in this study.

Methods

• Open-label, randomized, controlled, 3-arm parallel group study in confined and ambulatory conditions.
• 160 healthy Japanese smokers aged between 23 and 65 years.
• Subjects smoked mCC during 2 baseline days prior to being randomly allocated to the following arms: ad libitum mCC use; ad libitum mTHS use; or smoking abstinence (SA).
• The Bcep were selected based on a variety of criteria:
  - specificity to the source of exposure with other sources being minor or non-existent;
  - detectability by validated methods;
  - reflecting a specific toxic exposure;
  - representing assessment of both gas and particulate phase;
  - covering a broad range of chemical and organ toxicity classes (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential).
• CREs were selected based on their association to smoking-related disease, an existing dose-response relationship to smoking and reversibility upon smoking cessation.
• Biochemical and biological markers included baseline and day 30, day 60, and day 90.
• The Questionnaire of Smoking Urges (USQ) brief to assess urge-to-smoke and the modified Cigarette Evaluation Questionnaire (MEQ) to assess product evaluation were administered.

An analysis of variance (ANOVA), adjusted for baseline values, sex and daily CC consumption was applied to the Bcep and CREs levels with the study arm as a factor. The study was conducted in Japan in 2015 according to ICH GCP, approved by an IRB, and registered at ClinicalTrials.gov (NCT01979095).

Results

Demographics

Variable | Statistic | mTHS (n=32) | mCC (n=37) | Overall (n=69) | p-value
--- | --- | --- | --- | --- | ---
Sex | | | | | |
Female | % | 15.6 | 16.2 | 15.9 | 0.946
Age (years) | Mean | 37.8 | 37.1 | 37.4 | 0.924
Consumption at screening | | | | | |
10-19 cig/day | % | 46.9 | 45.1 | 45.9 | 0.928
10-19 cig/day | % | 34.4 | 39.1 | 36.9 | 0.411
ISO Nicotine ≤0.6 mg | % | 63.6 | 66.0 | 64.8 | 0.835

Biomarkers of Exposure

Variable | Statistic | mTHS | mCC | Overall | p-value
--- | --- | --- | --- | --- | ---
Nicotine | ng/mL | 13 (4.3) | 17 (5.0) | 15 (4.5) | 0.180
Methacholine | ng/mL | 24.0 (11.5) | 22.8 (10.5) | 23.4 (10.4) | 0.350
Oxidative stress | | | | | |
DPPH | μmol/mL | 7.9 (7.0) | 7.2 (4.8) | 7.6 (5.9) | 0.450
Methylnitrosamino (mmol/mL) | | | | | |
Total | | | | | |
SBMA | | | | | |
Total | 3 - | | | | |
Moderate | 2 - | | | | |
Moderate | 1 - | | | | |
Small | 0 - | | | | |
Other | | | | | |
Risk factors at baseline | | | | | |
Cigarette | Lower | 65.6 | 65.2 | 65.4 | 0.938
Smoker | Higher | 34.4 | 34.8 | 34.6 | 0.938

Clinical Risk Endpoints

Lipid Metabolism | | | | | |
HDL-C | mg/dL | 64.6 (9.4) | 64.5 (9.4) | 64.5 (9.4) | 0.974
LDL-C | mg/dL | 132.5 (37.5) | 134.1 (37.2) | 133.3 (37.2) | 0.974
Triglycerides | mg/dL | 131.7 (91.6) | 130.1 (90.7) | 130.9 (90.7) | 0.974
Diabetes | | | | | |
Glucose | mg/dL | 99 (9) | 100 (9) | 99.5 (9) | 0.974
HbA1c | % | 5.7 (0.5) | 5.7 (0.5) | 5.7 (0.5) | 0.974
Airway Impairment | FEV1 | 1.31 ± 0.34 | 1.31 ± 0.34 | 1.31 ± 0.34 | 0.974
Endothelial Dysfunction | ELF-ECAT | 0.9 ± 0.06 | 1.0 ± 0.07 | 0.97 ± 0.07 | 0.974
Dorsal Dilation | BDI-PgD2 | 6.3 ± 0.7 | 6.3 ± 0.7 | 6.3 ± 0.7 | 0.974
Climbing | | | | | |
20-40 sec | 12.0 ± 4.3 | 12.0 ± 4.3 | 12.0 ± 4.3 | 0.974
Daily Product Use, Nicotine Exposure and Subjective Effects

Variable | Statistic | mTHS | mCC | Overall | p-value
--- | --- | --- | --- | --- | ---
Nicotine Exposure | mg/dL | 6.9 (1.9) | 6.6 (1.9) | 6.7 (1.9) | 0.268
Safety

• No serious adverse events (SAEs) were reported during this study. Prior to randomization, a total of 124 SAEs were reported in 16 subjects (9%) out of 175 subjects enrolled. Following randomization, 49 SAEs in 32 (41%) subjects in the mTHS and 22 SAEs in 14 subjects for both mCC (33%) and SA (10%) arms were reported with decreased hemoglobin and decreased neutrophils as most frequently reported SAEs. All SAEs were of mild or moderate severity. Only one mild AF was judged related to mTHS (diarrhea).

Conclusions

The study demonstrated that switching from mCC to mTHS resulted in substantial reductions in exposure to selected HPHCs (except S-8MA and nicotine) sustained throughout the study period. The kinetics and the magnitude of decrease of the Bcep levels observed in the mTHS arm were approaching the levels observed in the SA arm. Similar exposure to nicotine between the mTHS and mCC arms, comparable reduction in urge-to-smoke and comparable satisfaction show that users adapted quickly to the new product, indicating that mTHS could be an acceptable substitute for mCC.

The directional shift towards SA was also seen in the CREs and add to the clinical relevance of the observed exposure reductions.

ABREVIATIONS: CC: Cigarette; CRE: Clinical Risk Endpoint; HPHC: Harmful and Potentially Harmful Constituent; mCC: Menthol Cigarette; mTHS: Tobacco Heating System; mTHS 2.2: Tobacco Heating System 2.2; mTHS 2.2 Menthol: Tobacco Heating System 2.2 Menthol; NCC: Nicotine Content; NTR: Nicotine Tartrate; PMA: S-8-pyridyl phenylmercapturic acid; S-8MA: S-8-pyridyl methylnitrosamino; S-NNK: S-NNK: S-nitrosonornicotine; S-NNAL: S-N-nitrosonornicotine; SA: Smoking Abstinence; Tobacco Heating System; THS: Tobacco Heating System.