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

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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 profile 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 clinical risk endpoints (CRE) 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 (BoExp) to 16 HPHCs were assessed to provide an assessment of human uptake of a variety of representative toxicants contained in combustible tobacco products. Selected CREs associated with cardiovascular, respiratory disease and genotoxicity as well as subjective effects to investigate the acceptance of mTHS compared to mCC 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 randomized for 90 days to the following arms: *ad libitum* mCC use; *ad libitum* mTHS use; or smoking abstinence (SA).
- The BoExp were selected based on a variety of criteria:
  - specificity to the source of exposure with other sources being minor or non-existent;
  - detectability using 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.
- 24h-urine samples were collected daily from Baseline to Day 5 and at Day 30, 60 and 90.
- The Questionnaire of Smoking Urges (QSU) brief to assess urge-to-smoke and the modified Cigarette Evaluation Questionnaire (mCEQ) to assess product evaluation were administered.
- An analysis of variance (ANOVA), adjusted for baseline values, sex and daily CC consumption was applied to the BoExp and CREs levels with the study arm as a factor.
- The study was conducted in Japan in 2013/14 according to ICH GCP, approved by an IRB, and registered at ClinicalTrials.gov (NCT01970995).

Results

Demographics

Variable	Statistic	mTHS (N=80)	mCC (N=40)	SA (N=40)	Overall (N=160)
Females	**n(%)**	33 (42.3)	17 (40.5)	18 (45.0)	68 (42.5)
Age (years)	Mean± SD	37 ± 11	37 ± 11	37 ± 10	37 ± 11
Consumption at screening					
10-19 cig/day	n (%)	40 (51.3)	23 (54.8)	21 (52.5)	84 (52.5)
> 19 cig/day	n (%)	38 (48.7)	19 (45.2)	19 (47.5)	76 (47.5)
ISO Nicotine ≤ 0.6mg	n(%)	63 (80.8)	32 (76.2)	30 (75.0)	125 (78.1)

Biomarkers of Exposure

Exp. reduction
Exp. reduction > 50%

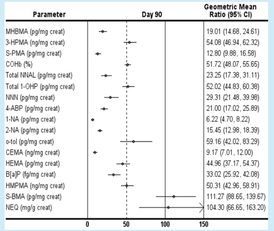


Fig 1: Ratio mTHS vs CC and 95%CI

Exposure Reduction > in:
mTHS SA

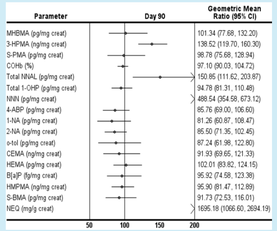


Fig 2: Ratio mTHS vs SA and 95%CI

Clinical Risk Endpoints

Disease Pathway	Marker	SA Effect at 3m	mTHS Effect at 3m
Lipid Metabolism	HDL-C	6.4 mg/dL	4.5 mg/dL
Inflammation	WBC	-0.41 10^9/L	-0.57 10^9/L
Airway Impairment	FEV_1	1.93 %pred	1.91 %pred
Endothelial Dysfunction	sICAM-1	10.9 %reduction	8.7 %reduction
Oxidative Stress	8-epi-$PGF_{2\alpha}$	6.0 %reduction	12.7 %reduction
Clotting	11-DTX-B_2	19.4 %reduction	9.0 %reduction

Participants at Baseline

- Healthy Japanese smokers
- Using at least 10 mCC daily, ≤1 mg nicotine ISO yield, smoking for the last 3 years
- Not using other nicotine containing products (e.g., e-cigarette, nicotine replacement therapy)

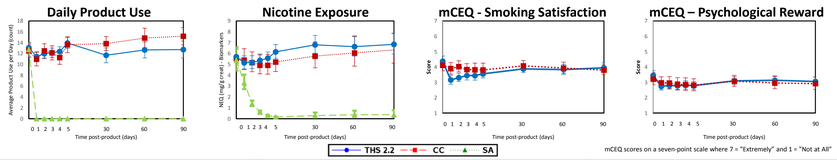
Exposure to HPHCs

- Reductions in BoExp levels were observed within 24 hours of mTHS use and sustained over the entire exposure period.
- After the 90-day exposure period, the levels of BoExp were significantly reduced by 49% up to 94% in the mTHS compared to the mCC arms and were approaching the levels observed in the SA arm.
- Similar levels of S-BMA observed for mTHS, mCC, and SA indicate that S-BMA is not a sensitive marker to discriminate between smoking and smoking abstinence.

Changes in CREs

- CREs started to show favorable changes shifting in the direction of SA.
- Switching for 3 months to mTHS preserved 70% or more of the effect observed in the SA arm except for 11-DTX-B_2.

Daily Product Use, Nicotine Exposure and Subjective Effects



mCEQ scores on a seven-point scale where 7 = "Extremely" and 1 = "Not at All"

- Product adherence, based on self-reporting, in the mTHS arm was high (Day 90), with 87.2% mostly mTHS users, 2.6% dual use (mTHS and mCC), 3.8% of mostly mCC smokers, 5.1% of neither mTHS nor mCC users, and 1.3% of missing product use data. Abstinence rate in the SA arm was >90%.
- Overall, the average daily product use remained comparable between the mTHS and mCC arms with a slight increase in mCC use towards the end of the exposure period.
- Nicotine uptake was comparable between mTHS and mCC with a marginal difference of 4% on Day 90.
- The difference in urge-to-smoke total score for mTHS and mCC at Day 1 was minimal (0.22; 95%CI -0.18:0.62) and remained stable until Day 90 (0.24; 95%CI: -0.25:0.72).
- Although product evaluation showed differences in most of the sub-domains at start of the exposure, similar scores in all sub-domains were reported for mTHS compared to mCC at the end of the exposure period.

Safety

No serious adverse events (SAE)s were reported during this study. Prior to randomization, a total of 22 AEs were reported in 16 subjects (9%) out of 175 subjects enrolled. Following randomization, 49 AEs in 32 (41%) subjects in the mTHS and 22 AEs in 14 subjects for both mCC (33%) and SA (35%) arms were reported with decreased hemoglobin and decreased neutrophils as most frequently reported AEs. All AEs were of mild or moderate severity. Only one mild AE 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-BMA and nicotine) sustained throughout the study period. The kinetics and the magnitude of decrease of the BoExp 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 reduction.

ABBREVIATIONS 1-NA: 1-aminonaphtalene; 1-OHP: 1-hydroxypyrene; 2-NA: 2-aminonaphthalene; 3-HPMA: 3-hydroxypropylmercapturic acid; 4-ABP: 4-aminobiphenyl; CEMA: 2-cyanoethylmercapturic acid; COHb: Carboxyhemoglobin; HEMA: 2-hydroxyethyl mercapturic acid; HMPMA: 3-hydroxy-1-methylpropylmercapturic acid; MHBMA: monohydroxybutenyl mercapturic acid; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN: N-nitrosonornicotine; S-PMA: S-phenylmercapturic acid

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COMPETING FINANCIAL INTERESTS

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