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 (THS) 2.2 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 cigarettes. The study reported is part of a global clinical program for THS and was designed to demonstrate sustained exposure reduction to selected HPHCs and to provide first insight on changes in clinical risk endpoints (CRE) in smokers pre-dominantly using tobacco HeatSticks menthol variant (mTHS) for 5 days in confinement followed by an ambulatory period of 85 days, compared to subjects continuing to smoke menthol cigarettes (mCC) and those who abstained from smoking.

Biomarkers of exposure (BoExp) to 16 HPHCs and nicotine were measured to provide an assessment of human uptake of a set of representative toxicants contained in combustible tobacco products. Selected CREs associated with cardiovascular and respiratory diseases and genotoxicity as well as subjective effects to investigate mTHS acceptance compared to mCC were assessed in this study.

Methods

- Open-label, randomized, controlled, 3-arm parallel group study.
- 160 healthy Japanese smokers (23 to 65 years).
- Subjects smoked mCC at baseline prior to being randomized for 5-day confinement and 85-day ambulatory as follows: *ad libitum* mCC use; *ad libitum* mTHS use; or smoking abstinence (SA).
- The BoExp were selected based on a variety of criteria:
  1. specificity to the source of exposure with other sources being minor or non-existent;
  2. detectability using validated methods;
  3. reflecting a specific toxicant exposure;
  4. representing assessment of both gas and particulate phase;
  5. 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 was collected daily from baseline to Day 5 and at Day 30, 60 and 90.
- Subjective effects of smoking were assessed by means of the brief version of the Questionnaire of Smoking Urges (QSU-brief), the revised version of Minnesota Nicotine Withdrawal Symptoms (MNWS-R), and the modified Cigarette Evaluation Questionnaire (mCEQ).
- An analysis of variance (ANOVA), adjusted for baseline values, sex and daily cigarette consumption was applied to 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

Characteristics	Statistic	mTHS (N=78)	mCC (N=42)	SA (N=40)	Overall (N=160)
Females	n (%)	33 (47.3)	17 (40.5)	18 (45.0)	68 (47.5)
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)

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).

Clinical Risk Endpoints

- High density lipoprotein-cholesterol, total white blood cell count, forced expiratory volume in 1 second, soluble intercellular molecule adhesion-1, 8-epi-prostaglandin F2α, and 11-dehydro-thromboxane B2 (11-DTX-B2) were measured as CREs.
- In spite of the variability due to the limited sample size targeting the assessment of BoExp, data showed favorable shifts in the direction of SA for all CREs. A 70% or more preserved effect of SA was observed in the mTHS arm for all CREs except for 11-DTX-B2.

Biomarkers of Exposure

- Reductions in BoExp levels were observed within 5 days of mTHS use and sustained over the 3 months (from 41 to 94% at Day 90).
- Reduction of BoExp in mTHS was close to that observed in SA (preserved SA effect).
- Similar S-BMA levels for mTHS, mCC, and SA indicate that S-BMA is not a sensitive marker to discriminate between smoking and SA (data not shown).

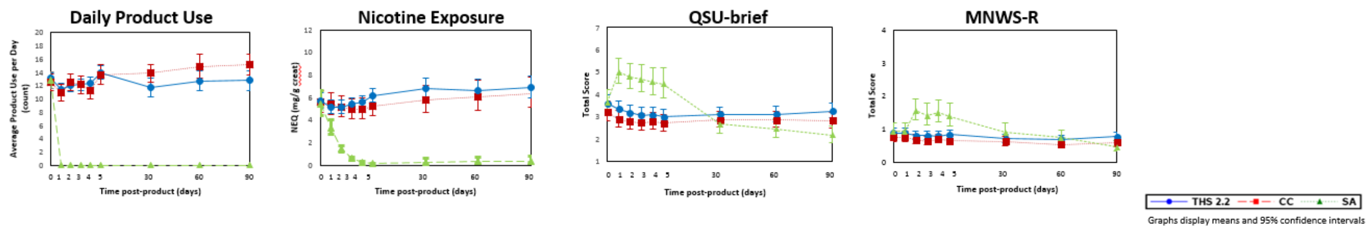
Marker	Day 5 (Confinement) expressed as %			Day 90 (Ambulatory) expressed as %		
	mTHS (n=76) Reduction from mCC (n=42)	SA (n=39) Reduction from mCC (n=42)	Preserved SA Effect	mTHS (n=70) Reduction from mCC (n=41)	SA (n=37) Reduction from mCC (n=41)	Preserved SA Effect
MHBMA	87	86	100	81	81	100
3-HPMA	49	69	71	46	61	75
S-PMA	89	90	99	87	87	100
COHB	55	55	100*	48	47	100*
Total NNAL	56	63	89	77	85	91
Total 1-OHP	61	64	95	48	45	100*
Total NNN	73	97	76	71	94	75
4-ABP	80	77	100*	79	78	100*
1-NA	94	95	100	94	92	100*
2-NA	86	85	100*	85	82	100*
o-tol	58	57	98	41	32	100*
CEMA	62	83	99	91	90	100*
B[a]P	73	75	97	67	66	100*
HMPMA	57	61	94	50	48	100*
HEMA	50	51	98	55	56	98

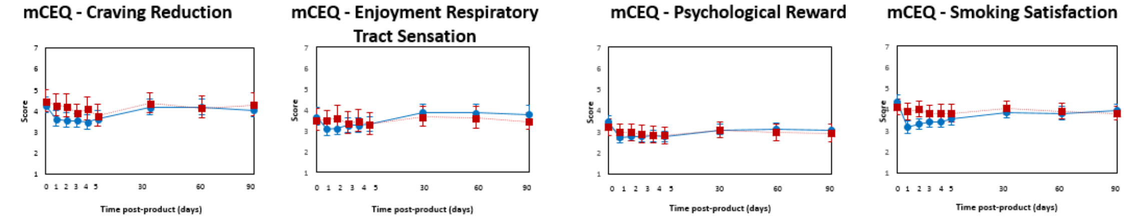
*>100%. Considering that mTHS effect can not be greater than for SA, values are set to 100%.

Product Adherence

- Product adherence to mTHS, based on self-reporting, was high (Day 90), with 87.2% mostly mTHS users (≥70% THS use), 2.6% dual use (30%<THS use<70%), 3.8% of mostly mCC smokers (≤30% THS use), 5.1% of neither mTHS nor mCC users, and 1.3% of missing product use data. Abstinence rate in the SA arm was >90%.

Daily Product Use, Nicotine Exposure, Subjective Effects





mCEQ scores on a seven-point scale where 7 = "Extremely" and 1 = "Not at All".
mCEQ Aversion subscale not shown; no notable differences were observed.
QSU-brief scores reported on a 7-point scale. Higher values indicate greater intensity of urge.
MNWS-R score is reported on a scale of 0 to 4. Higher scores indicate greater intensity on the scale.

Safety

No serious adverse events were reported during this study. Prior to randomization, 22 adverse events (AE)s were reported in 16 (9%) out of 175 subjects enarolled. Post randomization, 49 AEs in 32 subjects (41%) in mTHS, 22 AEs in 14 subjects for both mCC (33%) and SA (35%) were reported with decreased hemoglobin and decreased neutrophils as most frequently reported AEs. All AEs were of mild or moderate severity. One mild AE was judged related to mTHS (diarrhea).

Conclusions

- Switching from mCC to mTHS resulted in substantial reductions in exposure to selected HPHCs (except S-BMA) sustained throughout the 3 month exposure period. The kinetics and the magnitude of decrease of the BoExp levels in mTHS were close to those observed in SA.
- Similar exposure to nicotine between mTHS and mCC and comparable reduction in urge-to-smoke and satisfaction show that users adapted quickly to the new product, indicating that mTHS could be an acceptable substitute for mCC.
- The directional favorable shift of CREs towards SA supports the clinical relevance of the reduction to exposure.

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; S-BMA: S-benzylmercapturic acid.

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