REDUCED EXPOSURE TO HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS AFTER 90 DAYS OF USE OF TOBACCO HEATING SYSTEM 2.2 MENTHOL IN THE U.S.: 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 smokers aged minimum 22 years.
- Subjects smoked *m*CC during 2 baseline days prior to being randomized for 90 days to the following arms: *ad libitum m*CC use; *ad libitum m*THS 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 of the mTHS aerosol;
  - 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, 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 urges-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 CRE levels with the study arm as a factor.
- The study was conducted in U.S. in 2013/14 according to ICH GCP, approved by an Internal IRB, and registered at ClinicalTrials.gov (NCT01989156).

Results

Demographics

Variable	Statistic	mTHS (N=80)	mCC (N=41)	SA (N=39)	Overall (N=160)
Females	n (%)	32 (40.0)	17 (41.5)	15 (38.5)	64 (40.0)
Age (years)	Mean ± SD	39.2 ± 11.7	33.7 ± 10.2	38.8 ± 11.4	37.7 ± 11.5
Consumption at screening					
10-19 cig/day	n (%)	43 (53.8)	21 (51.2)	18 (46.2)	82 (51.3)
> 19 cig/day	n (%)	36 (45.0)	20 (48.8)	21 (53.8)	77 (48.1)

Biomarkers of Exposure

Exp. reduction
Exp. reduction > 50%

Reduction > in: mTHS SA

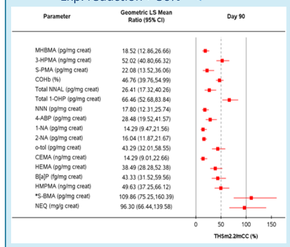


Fig 1: Ratio mTHS 2.2 vs CC and 95%CI

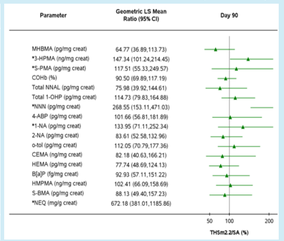


Fig 2: Ratio mTHS 2.2 vs SA and 95%CI

Clinical Risk Endpoints

Disease Pathway	Marker	SA Effect at 3m	mTHS Effect at 3m
Lipid Metabolism	HDL-C	0.0 mg/dL	1.4 mg/dL
Inflammation	WBC	-0.94 10^9/L	0.17 10^9/L
Airway Impairment	FEV_1	1.95 %pred	0.49 %pred
Endothelial Dysfunction	sICAM-1	9.9 %reduction	10.6 %reduction
Oxidative Stress	8-epi-$PGF_{2\alpha}$	8.5 %reduction	13.5 %reduction
Clotting	11-DTX-B_2	7.2 %reduction	3.6 %reduction

Participants at Baseline

- White (62%), African-American (32%), and other races (6%) healthy smokers
- Using at least 10 mCC daily, smoking for the last 3 years
- Not using other nicotine containing products (e.g., e-cigarette, nicotine replacement therapy)

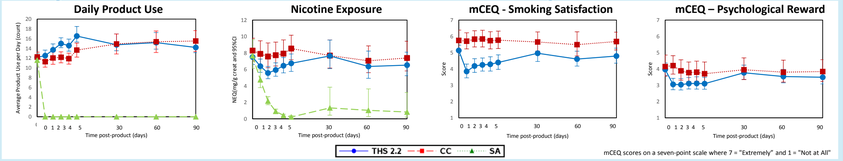
Exposure to HPHCs

- Reductions in BoExp levels were observed within 24 hours of initiating mTHS use and sustained over the exposure period.
- After 90 days of exposure, the levels of BoExp were reduced by 34% up to 86% in the mTHS arm as compared to mCC 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

- After switching for 3 months to mTHS some of the monitored CREs started to show favorable changes shifting in the direction of SA.

Daily Product Use, Nicotine Exposure and Subjective Effects



- Product adherence, based on self-reporting, in the mTHS arm was moderate (Day 90), with 72.5% mostly mTHS users, 15.0% dual users (mTHS and mCC), 6.3% mostly mCC smokers, 1.3% neither mTHS nor mCC users and 5.0% of missing product use data. Abstinence rate in the SA arm was 18.0%.
- The average daily product use increased by 16.4% for mTHS and by 27.0% in the mCC arm over the exposure period.
- Nicotine uptake was comparable between mTHS and mCC with a difference of -4% on Day 90.
- The difference in urge-to-smoke total score for mTHS and mCC at Day 1 was minimal (0.10 [95% CI -0.78, 0.58]; and remained comparable until the end of the exposure period (Day 90: 0.25 [95%CI -0.87, 0.37]).
- Differences for product evaluation were observed in most sub-domains at Day 1 for mTHS compared to mCC, whereas comparable scores in all sub-domains were reported at the end of the exposure period.

Safety

Prior to randomization, 84 adverse events (AEs) were observed in 62 (37.6%) of 165 subjects enrolled. One subject reported 2 serious adverse events (SAE) (sinusitis and diabetic ketoacidosis) and was not randomized. Following randomization, 114 AEs in 52 (65.0%) subjects in the mTHS, 32 AEs in 20 (48.8%) subjects in the mCC and 49 AEs in 23 (59.0%) subjects in the SA study groups were reported with decreased hemoglobin and increased lymphocyte count as most frequently reported AEs. 7 Mild AEs in the THS arm were reported as related to mTHS. No SAE was reported after randomization.

Conclusions

- The study demonstrated that switching from mCC smoking to mTHS use 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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