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 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 (CREs) 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 days of 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.
- 24-h 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 (MNWSS-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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>104(65)</td>
</tr>
<tr>
<td>Male</td>
<td>56(35)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>37 ± 11</td>
</tr>
<tr>
<td>Range</td>
<td>27-59</td>
</tr>
<tr>
<td>Nicotine Exposure</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>58(36)</td>
</tr>
<tr>
<td>n (%)</td>
<td>102(64)</td>
</tr>
<tr>
<td>n (%)</td>
<td>30(19)</td>
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</tbody>
</table>

Clinical Risk Endpoints

- High density lipoproteins (HDL), total blood low density lipoprotein (LDL), and triglycerides (Trig) were measured as BoExp.
- In spite of the variability due to the limited sample size targeting the assessment of BoExp, data showed statistically significant differences in the direction of SA for all BoExp. A 20% or more reduced effect of SA was observed in the mTHS arm for all CREs except for COHb.

Daily Product Use, Nicotine Exposure, Subjective Effects

- Daily Product Use
- Nicotine Exposure
- QSU-brief
- MNWSS-R

mCEQ - Craving Reduction
mCEQ - Enjoyment Respiratory Tract Sensation
mCEQ - Psychological Reward
mCEQ - Smoking Satisfaction

Safety

No serious adverse events were reported during this study. Prior to randomization, 22 adverse events (AEs) were reported in 16 (9%) out of 175 subjects enrolled. 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 5-BMA) sustained throughout the 3 month exposure period. The kinetics and magnitude of the 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 were observed in mTHS.
- The directional favorable shift of CREs towards SA supports the clinical relevance of the reduction to exposure.