PHARMACOKINETICS OF NICOTINE AND SUBJECTIVE EFFECTS FOLLOWING THE SINGLE USE OF A NON-MENTHOL AND MENTHOL VERSION OF TOBACCO HEATING SYSTEM 2.2 IN TWO STUDIES IN JAPAN: A COMPARISON WITH SINGLE USE OF A COMBUSTIBLE CIGARETTE AND NICOTINE GUM

Philip Morris International is currently developing potentially reduced risk products (RRPs) with the intention to reduce the risk of tobacco-related diseases. The challenge in developing RRPs is two-fold, i.e., developing tobacco products that are shown to reduce risk and that are acceptable to smokers as substitutes for combustible cigarettes (CC). The candidate RRP, the Tobacco Heating System (THS) 2.2, tested in this study is heated at significantly lower points was lower following THS use.

The study reported here is part of a global clinical program and the objective of the study was to evaluate the plasma pharmacokinetic (PK) profile of nicotine following single use of THS 2.2 menthol and non-menthol compared to menthol and non-menthol combustible cigarettes (CC) and nicotine replacement therapy (NRT), respectively. Subjective effects were evaluated to get first insight to which extent adult smokers would find THS 2.2 an acceptable substitute for CC.

**Methods**

The two studies were open-label, randomized, two-period, four-sequence crossover studies in 62 healthy smokers. Each period consisted of 2 days, with 1 day of smoking abstinence (nicotine wash-out) and 1 day of single use THS 2.2, CC or nicotine gum with every subject exposed to 2 of the 3 study products (THS 2.2/CC and THS 2.2/nicotine gum [NRT]). During the single use day, a total of 16 venous blood samples were collected including 1 sample prior to product use and at various time points for up to 24 hours.

One study (Study PK-02) tested the THS 2.2 non-menthol (THS 2.2), the two studies (Study PK-05) tested the THS 2.2 menthol (mTHS 2.2) product. The International Organization on Standardization (ISO) yield for THS 2.2 was 0.5 mg nicotine. (The ISO yield for mTHS 2.2 was 0.5 mg nicotine. Nicotine concentration was determined in plasma using a validated method (LC-MS/MS; LOD, 0.2 mg/mL). Urate to smoke was assessed using the questionnaire of smoking urges (Cox et al., 2001). The studies were registered with ClinicalTrials.gov (NCT01959607/NCT01967706). The studies were approved by institutional Review Board and were conducted in Tokyo, Japan in 2013 in accordance with ICH GCP guidelines.

**Results**

**Nicotine PK Endpoints Parameters**

The overall shape of the nicotine concentration-time curves for THS and CC were similar in both studies and differed for THS and NRT gum. The values for AUC(0→last) and Cmax were comparable for THS and CC in both studies. The tmax was similar for CC and THS (about 6 min) in both studies.

**Safety**

No serious or severe adverse events (AEs) were reported in the studies. The pooled incidence and frequency of AEs were low with 18 AEs reported in 15 subjects after randomization. Three AEs were related to the THS 2.2 or CC, and 5 AEs were related to study procedures. No AEs were related to NRT gum. The most frequent AEs were hemoglobin decreased, bilateral increased, blood triglycerides increased, and dysphoria.

**Conclusions**

The PK profiles for both THS 2.2 variants evaluated were comparable to CC and different from nicotine gum in both studies. A transient reduction in urge-to-smoke was observed with THS 2.2, comparable to CC and higher than nicotine gum after single use.

**References**


**COMPETING FINANCIAL INTERESTS**

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