PHARMACOKINETICS OF NICOTINE AND SUBJECTIVE EFFECTS FOLLOWING THE SINGLE USE OF A MENTHOL VERSION OF TOBACCO HEATING SYSTEM 2.2 IN THE US: A COMPARISON WITH SINGLE USE OF A COMBUSTIBLE CIGARETTE AND NICOTINE NASAL SPRAY

C. Haziza[1], G. Baker[1], G. de La Bourdonnaye[1], N. Lama[1], J. Ancerewicz[1], D. Skiada[1], P. Picavet[1], J. L. Borders[2], and F. Lüdicke[1]

[1] Philip Morris International, Quai Jeanrenaud 5, Neuchâtel, Switzerland, [2] Central Kentucky Research Associates, Lexington, Kentucky, USA

Introduction and Objectives

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 temperatures than required for CC.

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 (mTHS 2.2) as compared to menthol combustible cigarettes (mCC) and nicotine replacement therapy (NRT), respectively. Subjective effects were evaluated to get first insight to which extent adult smokers would find mTHS 2.2 an acceptable substitute for mCC.

Methods

This study was an 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 menthol (mTHS 2.2), menthol CC (mCC) or nicotine nasal spray (NNS) with every subject being exposed to 2 of the 3 study products (mTHS 2.2/mCC and mTHS/NNS). 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.

The International Organization on Standardization (ISO) yield per mTHS 2.2 was 0.5 mg for nicotine yield.

Nicotine concentration was determined in plasma using a validated method (LC-MS/MS; LLOQ: 0.2 mg/mL). Urge to smoke was assessed using the questionnaire of smoking urges-brief (Cox et al., 2001). For product evaluation the modified cigarette evaluation questionnaire (Cappelleri et al., 2007) was used.

The study was registered with ClinicalTrials.gov (NCT01967719). The studies were approved by an Institutional Review Board and were conducted in Kentucky, USA in 2013 in accordance with ICH GCP guidelines.

Results

Demographics

Summary of Demographics and Baseline Characteristics

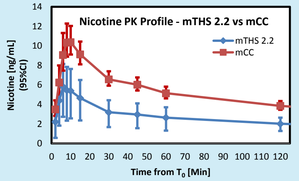
		Group-1-mTHS 2.2/mCC N = 44	Group-2– mTHS 2.2/NNS N = 18	Overall N = 62
Male [%]		24 (54.5%)	9 (50.0%)	33 (53.2%)
Female [%]		20 (45.5%)	9 (50.0%)	29 (46.8%)
Age [yr M ± SD]		37.2 ± 10.2	33.1 ± 7.3	36.0 ± 9.6
ISO nicotine level	<= 1 mg	22 (50.0%)	11 (61.1%)	33 (53.2%)
	> 1 mg	22 (50.0%)	7 (38.9%)	29 (46.8%)
Number of CC/Day [n%]	10-19	28 (63.6%)	12 (66.7%)	40 (64.5%)
	> 19	16 (36.4%)	6 (33.3%)	22 (35.5%)

Nicotine PK Endpoints Parameters

The overall shape of the concentration-time curves appear similar for the mTHS 2.2 and mCC, with the extent of the exposure to nicotine ($AUC_{(0\text{-last})}$) about 44% (95%CI: 29-56%) lower for mTHS 2.2 than for mCC. Similarly, the maximum nicotine concentration was on average 43% (95%CI: 28-56%) lower following single use of mTHS 2.2 compared to mCC. The median t_{max} observed for mTHS 2.2 and mCC was 6.7 minutes and 10.1 minutes, respectively.

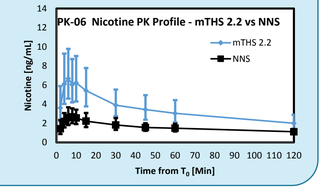
Primary PK Endpoints (Group 1 – mTHS 2.2/mCC)

PK Parameter (unit)	Product Exposure	N	Geometric Means	mTHS2.2/ mCC Ratio	95% CI (%)
$AUC_{(0\text{-last})}$ (ng.h/mL)	mTHS 2.2	41	16.5	55.6	(43.3; 71.5)
	mCC	41	29.7		
C_{max} (ng/mL)	mTHS 2.2	41	7.4	56.6	(44.2; 72.4)
	mCC	41	13.1		



Primary PK Endpoints (Group 2 – mTHS 2.2/NNS)

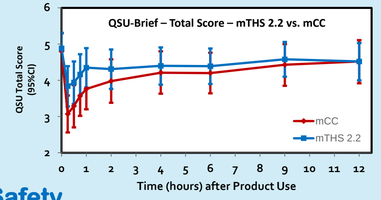
PK Parameter (unit)	Product Exposure	N	Geometric Means	mTHS 2.2/ NNS Ratio	95% CI (%)
$AUC_{(0\text{-last})}$ (ng.h/mL)	mTHS 2.2	17	15.6	178.8	(106.5; 300.3)
	NNS	17	8.7		
C_{max} (ng/mL)	mTHS 2.2	17	8.4	259.8	(168.0; 401.6)
	NNS	17	3.2		

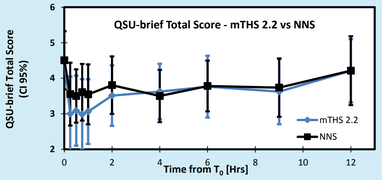


The mean nicotine concentration curves following single use of the mTHS 2.2 and NNS appear similar for the two products, with a higher exposure to nicotine following single use of mTHS 2.2. The median t_{max} was similar for mTHS 2.2 (8.9 minutes) and NNS (8.1 minutes).

Urge to Smoke Symptoms (QSU-brief) Following Single Use

In the mTHS/mCC group, the maximum reduction of the urge-to-smoke total score was reached 15 minutes after product use and was 21% for mTHS 2.2 and 36% for mCC, respectively. In contrast, in the mTHS 2.2/NNS group, the maximum reduction of the urge-to-smoke total score was reached 45 minutes after mTHS 2.2 use and 30 minutes after NNS use with a reduction of 33% and 21%, respectively.





Safety

No serious adverse events (AE) were reported in the study. 28 AEs were reported in 19 of the 62 subjects. Fourteen were mild, 12 were moderate, and 2 were severe in severity. The incidence and frequency of AEs were comparable across all 4 sequences. Five AEs were related to either mTHS 2.2 or mCC and 9 were related to study procedures. One AE was related to NNS. The most frequent AEs were headache, vomiting, and nasal congestion.

Conclusions

The PK profile of mTHS 2.2 appeared to be different compared to mCC and NSS. A transient reduction in urge-to-smoke was observed with mTHS 2.2, less pronounced compared to mCC but to a greater extend than observed after NNS single use. These results might be best explained by subjects switching to a new product which requires an adaptation of product use behavior.

REFERENCES

Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res. 2001;3:7-16.

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007;32:912–23.

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