PHARMACOKINETICS OF NICOTINE FOLLOWING SINGLE USE OF A CANDIDATE MODIFIED RISK TOBACCO PRODUCT: THE TOBACCO HEATING SYSTEM 2.1

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Introduction

To those smokers who are not able or not willing to quit, Philip Morris International (PMI) is investigating alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases. These products are now referred to by the US Food and Drug Administration as modified risk tobacco products (MRTPs).

The challenge in developing and commercializing MRTPs is two-fold, (i.e., developing tobacco products that are shown to reduce risk and that are acceptable to smokers as substitutes for conventional cigarettes (CC). The Tobacco Heating System (THS) 2.1, the MRTP tested in this study is based on the concept that tobacco is heated at significantly lower temperatures than required for CC.
The international Organization on Standardization (ISO) yield per THS Tobacco Sticks were: 7 mg for tar, 0.3 mg for nicotine, and 1 mg for carbon monoxide.

There are a variety of nicotine-containing products on the market ranging from cigarettes, oral snuff, chewing tobacco to nicotine replacement therapy products (NRT) (gum, inhaler, nasal spray, etc.).
There is a large variability of nicotine absorption across this range of products (Molyneux, 2004). For conventional cigarettes, the nicotine is distilled from burning tobacco and carried on liquid droplets which are inhaled and absorbed rapidly across pulmonary membranes. Blood concentrations of nicotine rise very quickly during a smoking session and peak at the completion of smoking (Henningfield,1995). It is important to compare nicotine pharmacokinetics for THS 2.1 against CC.

Objective

The objective of the study was to evaluate the plasma pharmacokinetic (PK) profile of nicotine following single use of the Tobacco heating System 2.1 (THS 2.1) as compared to conventional cigarettes (CC) . Urges-to-smoke after the use THS 2.1 and CC was evaluated and Adverse Events (AE) monitored.

Materials and Methods

- This study was an open-label, randomized, two-period, two-sequence crossover study was conducted in 28 healthy smokers.
- Each period consisted of 3 days, with 1 day of smoking abstinence (nicotine wash-out), 1 day with a single use, and 1 day with *ad libitum* use of THS 2.1 or CC.
- 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 up to 24 hours.
- All bioanalytical assessments in this study will use validated methods.
- Nicotine 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 (QSU-b).
- Safety was monitored throughout the study.
- This study was registered with ClinicalTrials.gov, number NCT01780688. The study was approved by an Independent Ethic Committee and was conducted in Belfast (Northern Ireland) according to ICH GCP guidelines.

Results

Demographics

Characteristics	THS 2.1 - CC (N=14)	CC - THS 2.1 (N=14)	Overall (N=28)
– yr	30.0 ± 4.9	29.1 ± 4.0	29.5 ± 4.4
– no. (%)	6 (42.9%)	8 (57.1%)	14 (50.0%)
-mass index - kg/m²	23.2 ± 2.2	24.3 ± 2.7	23.8 ± 2.5
– no. (%)			
Caucasian/white	14 (100%)	14 (100%)	28 (100%)
– no. (%)			
10 to 19 cpd	11 (78.6%)	14 (100.0%)	25 (89.3%)
20+ cpd	3 (21.4%)	0 (0.0%)	3(10.7%)
– no. (%)			
≥ 3 years	14 (100%)	14 (100%)	28 (100%)
	N=13	N=13	N=26
	5.6 ± 1.8	4.1 ± 2.3	4.8 ± 2.2

FTND = Fagerstroem Test on Nicotine Dependence

Nicotine PK Endpoints Parameters

- Following single use, the extent of the exposure to nicotine was, on average, 23% (90% CI: 15%, 30%) lower for THS 2.1 compared to CC.
- Similarly, maximum nicotine concentrations were, on average, 30% (90% CI: 18%, 40%) lower following single use of THS 2.1 compared to CC.
- For both endpoints, the lower limit of the 90% CI for the geometric means ratio was less than 80.00% and the CIs did not contain 100%.

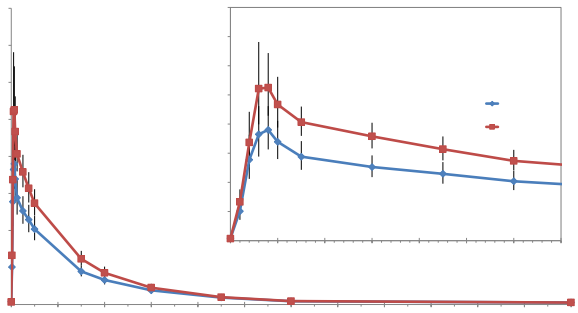
		of	means	Geometric means ratio	90% CIs (%) Upper
0-last .h/mL)	2.1	28 28	17.659 22.813	77.41	70.46 85.04
max	2.1	28 28	8.369 11.914	70.25	60.01 82.23

CI = Confidence Interval
AUC0-last = Area under the Curve
Cmax = Maximum Concentration

Results Continued

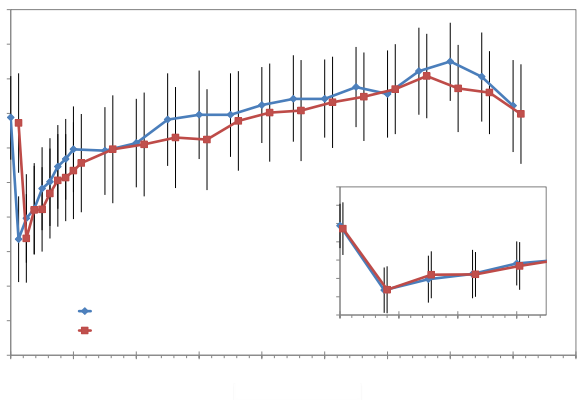
Nicotine PK Profile over 24 hours

The extent of nicotine exposure for THS 2.1, as assessed by both mean $AUC_{0-\infty}$ and AUC_{0-t}, was 19.1 and 0.5 ng.h/mL, respectively. These estimates resulted to be 19% (95% CI: 11%, 27%) and 33% (95% CI: 12%, 48%) lower compared to CC. The overall shape of the average nicotine concentration-time curves appeared similar for the two products, both resulting to have 8 min of median time to maximum nicotine concentration. The figure below reproduces the average nicotine concentration-time curves for the two products.



Urge to smoke Symptoms (QSU-brief) following Single Use

For both THS 2.1 and CC there was an approximately 40% reduction from baseline in the average urge to smoke total score observed 15 minutes after single use. Overall, the average QSU-brief total score was not notably higher for THS 2.1 compared to CC following single use (95%CI: -2.9, 5.3; p=0.552). Consistent results were obtained with the two factors subscales representing the desire and intention to smoke with smoking perceived as rewarding, and the anticipation of relief from negative effect with an urgent desire to smoke



Safety

No serious or severe AEs were reported. Overall, there were 42 AEs reported after randomization in 19 subjects. There were more AEs reported during the first period (30 AEs in 16 subjects) than the second period (9 AEs in 5 subjects). 14 subjects experienced AEs during the THS 2.1 exposure and 10 subjects during CC exposure. The most frequently reported AEs were nausea, headache, and dizziness.

Summary and Conclusion

The PK profiles were similar for both nicotine containing products due to the absorption at the pulmonary level. A transient reduction in urge to smoke was observed with the tobacco heating product, not different to CC after single use. The THS 2.1 was well tolerated.

References

Henningfield, J. E. (1995). "Nicotine medications for smoking cessation." N Engl J Med **333**(18): 1196-203.
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