Appendix 26 – THS-PBA-07-US Study Summary

PMI RESEARCH & DEVELOPMENT

Study Report

THS-PBA-07-US

Study Title:	Actual Use Study of THS 2.2 – THS-PBA-07-US
Study Number:	THS-PBA-07-US
Product Name:	THS 2.2 (Tobacco Heating System Version 2.2)
Study Initiated (first subject enrolled):	21 September 2015
Study Completed (last subject completed):	07 January 2016
Principal Investigator and Affiliation:	Kantar Health LLC Ariella Dugan, Senior Director Health Outcomes 11 Madison Avenue, 12th Floor New York, NY 10010, USA +1 212-706-4267 ariella.dugan@kantarhealth.com
Sponsor:	Philip Morris International Management S.A. Avenue de Rhodanie, 50 1007 Lausanne Switzerland
Sponsor Signatories:	Pierpaolo Magnani, *PBA Program Manager* Gerd Kallischnigg, *Study Biostatistician* Steve Roulet, *Study Manager*
Version:	1.0
Date:	11 August 2016

This study was conducted in accordance with Good Epidemiological Practice.

SYNOPSIS

Sponsor: Philip Morris International (PMI)	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: THS 2.2 (Tobacco Heating System Version 2.2)[1]	**Volume:**	
Name of Active Ingredient: Not applicable	**Page:**	

Study Title: Actual Use Study of THS 2.2 – THS-PBA-07-US

Investigator and Study Centre:

Principal Investigator: Ariella Dugan, Senior Director Health Outcomes, Kantar Health LLC

The study was conducted in 8 limited geographic areas of the United States (US). The study sites were located in research facilities in the following malls:

1. Asheville, NC - Asheville Mall
2. Charlotte, NC - Eastridge Shopping Centre
3. Denver, CO – Aurora Mall
4. Detroit, MI - Laurel Park Place
5. Las Vegas, NV - Galleria Mall
6. Miami/Fort Lauderdale, FL - Westfield Broward Mall
7. Oklahoma City, OK - Quail Springs Mall
8. Tampa, FL - Westfield Countryside Mall

Publication (reference):

Not applicable as the findings of the study have not been published before the study report was prepared.

Period of Study:

First Subject In: 21 September 2015
Last Subject Out: 07 January 2016

Overall Aim:

The purpose of this study was to investigate how U.S. adult daily smokers of Conventional Cigarettes (CC) actually used the *iQOS* system in a near to real-world conditions environment.

Primary Objectives and Endpoints:

The primary study objectives of this study were to describe,

1. The proportion of participants that "start using" *HeatSticks*
   Endpoints (over the observational period):
   - Number of *HeatSticks* consumed; where "start using" is defined as ≥ 100 *HeatSticks* consumed during the observational period as reported by the study participant on a stick-by-stick basis in an electronic diary
2. The proportion of participants who "start using" *HeatSticks* that "switch" from CC to *HeatSticks.*
   Endpoints (expressed based on weekly reporting):
   - Number of *HeatSticks* and CC consumed; where "switch" is defined as ≥ 70% of tobacco

[1] Tobacco Heating System (THS) 2.2 is comprised of a device commercialized under the brand name "*iQOS*", and Tobacco Sticks branded as "*HeatSticks*" designed to be exclusively used with the *iQOS* device. In the context of this study, the terminology of "the *iQOS* system" will be used to describe "THS 2.2", and "*HeatSticks*" will be used to describe "Tobacco Sticks".

products used are *HeatSticks* after participant "start using" of *HeatSticks* as reported by the study participant on a stick-by-stick basis in an electronic diary

3. The proportion of participants who "start using" *HeatSticks* that have "combined use" of CC and *HeatSticks*.
   Endpoints (expressed based on weekly reporting):
   - Number of *HeatSticks* and CC consumed; where "combined use" is defined as >30% and <70% of tobacco products used are *HeatSticks* after participant "start using" of *HeatSticks* as reported by the study participant on a stick-by-stick basis in an electronic diary
4. The proportion of participants who "start using" *HeatSticks* that "switch back" to CC after "switch" to *HeatSticks*.
   Endpoints (expressed based on weekly reporting):
   - Number of *HeatSticks* and CC consumed; where "switch back" is defined as ≤ 30% of tobacco products used are *HeatSticks* after participant "start using" and "switch" to *HeatSticks* as reported by the study participant on a stick-by-stick basis in an electronic diary
5. How *HeatSticks* are consumed during continued use (≥ 100 *HeatSticks,* i.e. "start using") according to "usage categories" (e.g., "CC use", "Combined use", "*HeatSticks* use")
   Endpoints (expressed based on weekly reporting):
   - Number of *HeatSticks* and CC consumed as reported by the study participant on a stick-by-stick basis in an electronic diary.

Secondary Objectives and Endpoints:

The secondary objectives of this study were to describe:

1. How *HeatSticks* are consumed during the early stages of use (1-99 *HeatSticks*) according to "usage categories" (e.g., "CC use", "Combined use", "*HeatSticks* use")
   Endpoints (expressed based on weekly reporting):
   - Number of *HeatSticks* and CC consumed as reported by the study participant on a stick-by-stick basis in an electronic diary
2. The "effect" of *HeatSticks* on the consumption of tobacco products (*HeatSticks* and CC).
   Endpoints (expressed as change from baseline reported CC consumption and weekly reporting of CC+*HeatSticks* during the observational period):
   - Number of *HeatSticks* and CC consumed as reported by the study participant on a stick-by-stick basis in an electronic diary
3. The proportion of participants that report "misuse" of the *iQOS* system.
   Endpoints (expressed based on last follow-up interview):
   - Number of participants that report either use of the *iQOS* device with product other than *HeatSticks* and/or consuming *HeatSticks* without the *iQOS* device provided by the study participant
   - Number of misuse events reported by the study participant
4. The "product assessment" among participants
   Endpoints (expressed based on bi-weekly reporting and average over the observational period):
   - Ease of use the *iQOS* system (using 7-point scale) reported by the study participant in bi-weekly follow-up interviews
   - Sensorial experience, including taste, smell and after-taste of *HeatSticks* (using 7-point scales) reported by the study participant in bi-weekly follow-up interviews
5. The "occasions of use" of the *iQOS* system (pre-determined categories) among participants
   Endpoints (expressed based on bi-weekly reporting and average over the observational period):
   - Settings of the *iQOS* system use (e.g., at home, at work, in public area) provided by the study participant in bi-weekly follow-up interviews.

Methodology

Study design:

This Actual Use Study of the *iQOS* system is a single group, prospective observational study, implying an assessment of subject-reported stick-by-stick consumption of *HeatSticks* and of CC and other products containing nicotine (i.e. e-cigarettes, nicotine replacement therapy products and other tobacco products such as cigars, cigarillos and smokeless tobacco products). Participants received *HeatSticks* free of charge and were able to consume *HeatSticks,* CC and other products containing nicotine *ad libitum*.

The study consisted of a 1-week baseline period, a subsequent 6-week observational period, and a 1-week close out period. Participants were requested to make an entry into an electronic diary (e-diary) every time they consumed a CC during the 1-week baseline period and every time they consumed a *HeatStick* or a CC during the 6-week observational period of the study. Participants were also requested to indicate on a daily basis using the e-diary whether or not they had used other products containing nicotine. Participants were not required to record any data during the 1-week close out period. Participants were interviewed 5 times. The first interview occurred at rescreening (before the 1-week baseline period). The first follow-up interview occurred after the 1-week baseline period. Subsequent follow-up interviews occurred every 2 weeks during the 6-week observational period. Participants were able to call the toll-free telephone hotline to raise queries related to the study, resolve issues related to the e-diary or the *iQOS* system and report product quality complaints, including adverse health events associated with the use of the *iQOS* system.

Procedures:

All data used to analyze the endpoints were obtained from participants via the computer-assisted web-based interview (CAWI) at enrollment, via electronic diary (e-diary), and via follow-up interviews using CAWI or computer assisted telephone interviews (CATI). All data collection (e-diary, CAWI, CATI) was performed electronically using 21 Code of Federal Regulations (CFR) Part 11 compliant EDC systems.

Candidate participants were pre-recruited from C&C Market Research's consumer-based databases. The candidate participants were identified based on their smoking status, and their socio-demographic characteristics related to sex, age, race and income. The study did not restrict enrollment using quotas, however, the sampling approximated the adult smoker distribution contained in a report published by the Centers for Disease Control and Prevention in 2012. Subject to eligibility determination, candidate participants were invited to the study site for rescreening and enrollment into the study.

At the study site, candidate participants were invited to consent (Part 1 of the informed consent form [ICF]) to being exposed to the *iQOS* system label, labeling and marketing material. Once signed, candidate participants were rescreened according to inclusion/exclusion criteria, and in particular, to confirm their actual age per identity document (ID; government issued ID). Following exposure to the *iQOS* system material, candidate participants' "Intention to Use" the *iQOS* system was assessed. Participants who did not respond positively (i.e. responded either "definitely not", "very unlikely" or "somewhat unlikely" on a 6-pt rating scale to the question "If you try this product and like it, how likely or unlikely are you to use this product regularly?") were not able to enroll into the study. Participants who indicated positive intention to use the *iQOS* system were invited to participate in an 8-week Actual Use Study and received ICF Part 2 for their review. Participants who signed Part 2 of the ICF were enrolled in the 8-week study.

Once enrolled, every participant received an e-diary. After the 1week baseline period, participants returned to the study site to receive the *iQOS* system kit and all other study materials necessary for participation including a maximum of 100 *HeatSticks* (either regular or menthol or a mix of both types of *HeatSticks)*, according to the participant's stated preferences. Additional *HeatSticks* were available to participants from the study site directly or by calling the hotline.

Follow-up CAWI interviews were conducted with participants at the study site after the 1-week baseline period and at the end of the 6-week observational period. Moreover, interim follow-up CATI interviews took place every other week during the observational period.

Upon exit from the study, all enrolled study participants underwent a debriefing to address potential misperceptions about the *iQOS* system that could have arisen from participation in the study.

Type of blinding: not applicable

Type of control: not applicable

Number of Subjects (Planned and Analyzed):

Planned:	1,300 subjects
Enrolled:	1,336 subjects
Full Analysis Set (FAS):	1,106 subjects
Per Protocol (PPROT):	465 subjects

Definition of the FAS:

- Fulfillment of all inclusion / exclusion criteria as stated below
- At least 1 documented consumption of a CC during the 1-week baseline period
- At least 1 documented consumption of a *HeatStick* during the 6-week observational period

Definition of the PPROT:

- Fulfillment of all inclusion / exclusion criteria as stated below
- Documentation of CC consumption for at least 6 days of the 1-week baseline period
- At least 1 documented consumption of a *HeatStick* during the 6-week observational period
- Documentation of CC and / or *HeatStick* consumption for at least 39 days of the 6-week observational period
- A participant was invalid for the PPROT if his / her cumulated *HeatStick* consumption as self-reported in the e-diary exceeded the number of available *HeatSticks* by more than 5 percent (Ratio documented *HeatSticks* versus available *HeatSticks*) and by more than 20 *HeatSticks* in absolute numbers (Difference documented *HeatSticks* minus available *HeatSticks*)[2]

The FAS was the primary analysis set for all analyses. Results of the PPROT were considered as supportive.

Main Criteria for Inclusion:

Participants meeting the following criteria were eligible for enrollment into the study:

- 18 years of age or above or the minimum local or State legal smoking age (LA) and above, whichever was higher.
- Current daily smokers of regular and/or menthol CC with no intention of quitting within the next 30 days (current daily smoker was defined as an individual who had smoked at least 100 cigarettes in his/her lifetime and was currently smoking at least 1 regular or menthol CC (no brand restrictions) per day, disregarding religious fasting).
- Individuals who signed ICF and were able to understand the information provided in the ICF.
- Individuals available and interested in participating in an 8-week study about tobacco.
- Individuals with positive intention to use the *iQOS* system.
- Individuals currently living in the US.

Main Criteria for Exclusion:

Participants meeting the following criteria were <u>not</u> eligible for recruitment:

- Pregnant or breastfeeding women (based on self-reported status).
- Women of childbearing potential who were not using adequate means of contraception (self-reported)
- Individuals with no proof of age (photo ID, such as passport, driver's license).
- Individuals who had started smoking within the last 30 days.
- Individuals who were not able to read and speak English.

[2] Note: This additional rule was defined after observational period and before database lock leading to a new version of the SAP (version Final 3.0, dated 01 March 2016)

- Individuals who were employed in the fields of market research, marketing, advertising, media or journalism, law, manufacturers or distributors of tobacco products, or who were health care providers.
- Individuals who had taken part in a consumer or clinical study within the past 3 months.

Test Product and Lot Numbers:

iQOS system kit (2 holders, pocket charger, USB power adaptor and USB cable, cleaner and a booklet of instructions for use) and *HeatSticks.*

Batch 1: *HeatSticks* (menthol) lot number: B-21025;

Batch 2: *HeatSticks* (regular) lot number: B-21526.

Duration of Exposure Period:

The duration of the exposure to the investigational product corresponds to the 6-week observational period of the study, during which participants recorded their stick-by-stick consumption of both *HeatSticks* and CC.

Reference Products:

Not applicable

Statistical Methods:

All analyses undertaken were descriptive. The study was not aimed to confirm or reject pre-defined hypotheses. Instead, measures for precision of estimates for the primary and secondary outcome variables were given (i.e. 95% confidence intervals (CIs)).

Sample size calculation was based on attaining ±5% precision in the measures associated with primary study objectives. Approximately 1,300 eligible participants were planned to be enrolled into this Actual Use Study. This sample size was based on an expected proportion of 50% "starters" (≥ 100 *HeatSticks*) and 40% attrition during the observational period with a 95% confidence level.

Continuous data were described by the total n, the number of non-missing and missing values, mean, standard deviation (SD), median, minimum (Min), maximum (Max) as well as lower and upper quartiles.

Categorical data including categories of continuous data were presented in frequency tables containing absolute and relative frequencies. Frequency tables included the total number of observations and the number of missing values as additional categories. Multiple response data were presented as distribution of single entries.

All primary objectives as well as the secondary objectives "how *HeatSticks* are consumed during early stages of use" and "the "effect" of *HeatSticks* on the consumption of tobacco products (*HeatSticks* and CC)" were assessesd based on data gathered through the e-diary. The secondary objectives "misuse", "product assessment" and "occasions of use" were assessed based on data gathered through CAWI/CATI interviews.

For primary and secondary objectives 95% CIs were displayed for the mean of continuous data or frequencies, respectively. For continuous data the normal approximation was used to calculate CIs. CIs for frequencies were calculated using the Clopper-Pearson formula.

Where appropriate, data were presented for subsamples of interest such as 18-24 years old (young adult) smokers, Black or African American adult smokers and adult smokers with low socioeconomic status.

The study data were analyzed using SAS 9.3 or 9.4.

Summary of Results

Demographics and Other Baseline Characteristics

Analysis of the **demographic characteristics** for the screened subjects indicates that sex and race were closely in line with the distribution in the CDC report (2012). Concerning age, slightly fewer subjects aged 18-24 years than in the CDC report were screened and concerning income, slightly more subjects with a low income (annual household ≤ $44,999) than in the CDC report were screened.

The distribution of the subjects screened and of the subjects enrolled was similar to the distribution of participants in the FAS. Similarly, there were no major differences between the FAS and the PPROT, with

the exception that participants in the PPROT were more often females and older (above 44 years old).

The only two reasons for non-enrollment in this study were not signing the two-part ICF (i.e., did not sign ICF Part 2, 22 of 1,368 subjects screened) or not stating a positive intention to use the *iQOS* system (10 of 1,368 subjects screened).

Primary endpoints:

Overall the study results were broadly similar between the FAS and the PPROT, indicating the robustness of the findings. In the rest of the synopsis, study results refer to the FAS only.

About a third of the participants (33.8%) "**started using"** *HeatSticks* during the observational period, meaning that they were no longer experimenting with *HeatSticks*, but rather using the product on a continuous basis.

About a third of them (32.7%) "**switched"** from CC to *HeatSticks* at the end of the observational period. This proportion remained overall constant during the observational period of the study. This is further confirmed by the fact that 62.9% of participants who "switched" from CC to *HeatSticks* at the end of the observational period had already "switched" from CC to *HeatSticks* in the first week of the observational period. A total of 16.3% of the participants who "started using" *HeatSticks* were using the product exclusively at the end of the observational period.

The study data shows that 15.5% of participants, who "started using *HeatSticks* and switched" to *HeatSticks*, **"switched back" to CC** at the end of the observational period, which also means that a larger proportion of the participants who "switched" from CC to *HeatSticks* **did not "switch back"** to CC.

The study data shows that about a third of the participants (34.6%) who "started using" *HeatSticks* had a **"combined use"** of CC and *HeatSticks* at the end of the observational period.

Another third of the participants who "started using" *HeatSticks* had a **"CC use"** at the end of the observational period (32.7%). While the proportion of **"combined use"** decreased over time, the proportion of **"CC use"** increased during the course of the study.

Secondary endpoints:

With respect to participants who remained in the "**early stages of use**", at the end of the observational period 80.1% had"CC use". The proportion of "CC use" increased over time.

There was no increase in the **use of tobacco products** between the baseline and the observational period (per week between 5.9 and 8.8 less *HeatSticks* and CC compared to baseline (CC only)). This was observed regardless of whether participants were in "*HeatSticks* use", "combined use" or "CC use" at the end of the observational period. Between the baseline and the end of the observational period, the usage of nicotine replacement therapy products remained stable, while the usage of e-cigarettes increased and the usage of other tobacco products such as cigars, cigarillos and smokeless tobacco products decreased.

The levels of **misuse** of the *iQOS* system were overall low. During the last follow-up interview, 47 of 985 participants (4.8%) reported using *HeatSticks* without the *iQOS* device and 2 of 985 participants (0.2%) reported using the *iQOS* device without *HeatSticks*.

Participants used the *iQOS* system in a broad range of **locations** (e.g. at home, at work)**, situations** (e.g. alone, with friends) **and times of the day** (e.g. morning, afternoon, evening).

Participants who adopted a "*HeatSticks* use" usage pattern at the end of the observational period liked the **taste** (60.9%)**, smell** (47.8%) and **aftertaste** (46.4%)[3] and found the product **easy to use** (81.9%[4]). Moreover, about half of them claimed they would definitely (15.9%) or probably (31.2%) **buy** *HeatSticks* if "the *iQOS* device were available for $79.99 and a pack of *Marlboro HeatSticks* were available at a price comparable to a pack of *Marlboro* cigarettes".

[3] The taste, smell, and aftertaste of the product were assessed using a 7-point rating scale ranging from "1=I don't like it at all" to "7=I like it very much". Rating of 5-7 response categories provided in the text.
[4] Ease of use of the *iQOS* system was assessed using a 7-point rating scale ranging from "1=not easy to use at all" to "7=very easy to use". Rating of 5-7 response categories provided in the text.

Additional Analysis

Comparing the profile of participants who adopted a "*HeatSticks* use" usage pattern at the end of the observational period with the total FAS, data shows that ***HeatSticks*** **may be slightly more attractive** to adult smokers who were males, above 25 years old, Black or African Americans, Hispanic or Latino, who consume between 1 and 10 CC per day and whose favorite brand of CC was menthol as stated at rescreening.

Safety:

The study surveillance population included the 1,336 participants enrolled in the study. The safety population exposed to product use included the 1,158 participants who used at least one *HeatStick*. A total of 121 AEs in 48 cases were spontaneously reported during the study (reporting rate of 4.14%). Eight cases were assessed as serious and 40 cases were assessed as non-serious. During the conduct of the study, no safety concerns about the safety profile of the investigational product emerged.

CONCLUSIONS

Based on the results of this actual use study, several key conclusions can be drawn regarding the behavior of adult daily smokers:

1. A sizeable proportion of adult daily smokers is likely to "start using" *HeatSticks*.
2. A sizeable proportion of adult daily smokers is likely to "switch" from CC to *HeatSticks* and is likely to use them exclusively or predominantly as a substitute for CC.
3. Once adult daily smokers "switch" from CC to *HeatSticks*, their likelihood of switching back to CC is relatively low.
4. It is likely that a certain proportion of adult daily smokers will use *HeatSticks* and CC in a combined way. The data also indicates that a substantial proportion of them is likely to return to CC over time unless they adopt a usage behavior involving either exclusive or predominant use of *HeatSticks*.
5. There is no evidence that suggests that the availability of *HeatSticks* would lead to an increase in total tobacco product consumption (*HeatSticks* and CC).
6. Finally, the low level of misuse is a strong indicator that the *iQOS* system will be used as intended or designed.

Although the study results are not generalizable to the U.S. adult smoker population, the study data suggests that a sizeable proportion of the U.S. daily smokers is likely to "switch" from CC to the *iQOS* system, when available in the U.S. market.

Final Report Date: Version 1.0 / 11 August 2016

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