## 3.5 Description on how the Consumer Actually Uses the Product

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3.5.1 Data and information regarding whether consumers can and are likely to comply with any instructions for product use.

To determine consumer compliance and understanding of instructions for product use, PMI has conducted a study in the U.S. named "Usability and Comprehension Study of THS 2.2 Instructions for Use within Adult Smokers" (THS-PBA-06-US).

3.5.1.1 "Usability and Comprehension Study of THS 2.2 Instructions for Use within Adult Smokers" (THS-PBA-06-US) study.

This study was a single arm, usability and comprehension study of THS (THD version 2.2) instruction for use (A3.4.3 PBA06User Guide). It consisted of individual interviews with adult smokers conducted at research facilities in 4 US cities. These cities were strategically selected to provide a geographically diverse sample, such that each city was within one of the 4 regions defined by the United States Census Bureau. In total, 258 individuals met study eligibility criteria and completed the interview. A balanced demographic composition of the sample was achieved using 2 recruitment quotas: 1) a minimum of 30% males and 30% females; and 2) a minimum of 30% subjects aged 18 to 40 years and a minimum of 30% subjects ≥40 years. Additionally, the total sample was to include approximately 30% of subjects who had a high school education or less.

In an interview conducted in a private setting, study subjects were asked to read the THS (THD version 2.2) instructions for use. Then, they had to show their ability to correctly comprehend the instructions for use by demonstrating the following 9 use tasks:

1. How to charge the THS 2.2 Holder and the THS 2.2 Pocket Charger simultaneously;
2. How to insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder;
3. How to heat and consume a THS 2.2 Tobacco Stick;
4. How to know when a THS 2.2 Tobacco Stick has been consumed and a session is over;
5. How to remove a THS 2.2 Tobacco Stick from the THS 2.2 Holder;
6. How to 'heat clean' the THS 2.2 Holder;
7. How to clean the THS 2.2. Holder using the THS 2.2 Cleaning Tool;
8. How to remove a THS 2.2 Tobacco Stick that is stuck in the THS 2.2 Holder Cap; and
9. How to re-attach the THS 2.2 Holder Cap to the THS 2.2. Holder Body.

Each of these use tasks were broken down into discrete steps, corresponding to the information in the instructions for use for a particular use task. Performance of these steps were rated (i.e., "correct", "incorrect" or "described") independently and simultaneously by two raters. The Study Summary (Appendix PBA06Sum) and the Study Report (Appendix THS-PBA-06-US) provide detailed descriptions on the 9 use tasks and the task steps that were rated. Subjects were requested to perform each task only one time.

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Following this usability assessment, subjects were also asked to answer open-ended questions about key messages set in the instructions for use. Responses to these comprehension questions were recorded by the interviewer and scored using a predefined answer key contained within the comprehension assessment. More specifically, the comprehension questions assessed if the warnings "never light a *HeatStick*[1] with a match, lighter or other flame source" and "never use the *iQOS*[2] Holder with a conventional cigarette, or other products/objects" were correctly understood.

More information on the study design, methods and procedures are detailed in the study documents available as an appendix 7.3.2 (Appendix THS-PBA-06-US and PBA06Sum).

In general, the study results indicate that the instructions for use are adequate in explaining the various tasks that are required to normally operate the THS. They also show that the adult smokers can comply with the instructions for use and can use the THS properly. In fact, irrespective of the possibility for the subjects to have only one single attempt to demonstrate each use task, most of the tasks were correctly executed or described by the large majority of the subjects (by at least two third of the subjects), with all their respective task steps demonstrated well.

More specifically, 5 main tasks were clearly understood by the large majority of the sample (by at least two third of the subjects, with *all* the respective task steps demonstrated well):

- Use task 1, "How to charge the THS 2.2 Holder and THS 2.2 Pocket Charger simultaneously", including all 5 task steps within this use task, were demonstrated by 68.2% to 95.3% of subjects.
- Use task 3, "How to heat and consume a THS 2.2 Tobacco Stick", including its 2 task steps, were performed by 68.6% to 81.8% of subjects.
- Use task 4, "How to know when a THS 2.2 Tobacco Stick has been consumed and a session is over", including the single task step, was performed by 80.6% of subjects.
- Use task 8, "How to remove a stuck THS 2.2 Tobacco Stick from the THS 2.2 Cap", including the 2 task steps, were performed by 74.4% to 78.3% of subjects.
- Use task 9, "How to properly re-attach the THS 2.2 Holder cap to the THS 2.2 Holder body", including both of its task steps, were performed by 73.3% to 79.5% of subjects.

[1] *HeatStick* is the commercial name for Tobacco Stick.

[2] *iQOS* is the commercial name for Tobacco Heating System.

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However, subjects found that a few tasks presented some difficulties in terms of demonstration and comprehension. More precisely, the remaining 4 main tasks had some task steps well understood by the large majority of the sample (by at least two thirds of the subjects), while other task steps of the 4 main tasks were not as equally well understood (by less than two third of the subjects):

- Use task 2, "How to insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder", where 3 of the 4 task steps were performed well by over 90.3% of subjects. (b) (4)
- Use task 5, "How to remove a THS 2.2 Tobacco Stick from the THS 2.2 Holder after consuming using the pull-pull technique", where 2 task steps were performed well by 96.9% of subjects (b) (4) .
- Use task 6, "How to heat clean the THS 2.2 Holder", where 1 task step (namely "knowing when it is time to perform the heat clean") was performed well by 88.4% of subjects. (b) (4)
- Use task 7, "How to clean the THS 2.2 Holder with the cleaning tool", where the 2 step tasks related to cleaning the THS Holder body with the long brush of the cleaning tool was carried out correctly by at least 75.2% of subjects (b) (4) .

The THS-PBA-06-US Study Summary (PBA06Sum) provides a detailed and comprehensive overview of all 9 use tasks with their respective step tasks and their results.

Finally, concerning the comprehension questions on the key messages included in the instructions for use, the results indicated that these messages were well understood. 94.6% of the participants provided either a correct (87.2%) or an acceptable (7.4%) answer about the fact that it is improper to "light up a *HeatStick* with a lighter to smoke it". The level of comprehension of the instruction of "never use conventional cigarettes using *iQOS*" reached 85.3%.

#### 3.5.1.2 THS (THD version 2.4) instructions for use modifications and improvements versus THS (THD version 2.2) instructions for use

As stated above, the instructions for use tested in the THS-PBA-06-US study were related to the THD version 2.2 (A3.4.3 PBA06User Guide). Based on the study results, the instructions for use and, to some extent, the device, have been significantly improved. The resulting User Guide (A3.4.1 Userguide), which is part of this application, is provided in section 3.4 and relates to the THD version 2.4. This User Guide has benefited from the results of the THS-PBA-06-US study.

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(b) (4)

(b) (4)

In addition, as the THD version 2.4 User Guide is very detailed, a Quick Start Guide (A3.4.2 Quickstartguide) has been created. The Quick Start Guide presents instructions for use in a simplified manner, using more images rather than text, and focuses on those actions that are most commonly needed with the iQOS System: charging the different components of the *iQOS* System, and how to use and remove a *HeatStick*.

Further details on the results of this study are available in the Study Summary (PBA06Sum) and in the Study Report (THS-PBA-06-US).

3.5.2 Data and information regarding consumer use in both controlled and natural environments, including the number of units of the product consumed per day and the way in which individuals consume each unit of the product.

Data and information regarding consumer use in both controlled and natural environments were gathered in a series of clinical and consumer studies. Table 1 summarizes those studies: 4 clinical studies from the premarket clinical assessment program; 1 observational study from the premarket PBA program conducted in the US; and market research "Whole Offer Test" (WOT) conducted in 5 different countries.

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**Table 1 Overview of Studies Regarding Consumer Use in Both Controlled and Natural Environments**

| Study Code | Country | Design | Setting | Exposure Duration | Population | Sample size | Outcome Measure |
|---|---|---|---|---|---|---|---|
| ZRHR-REXC-03-EU | Poland | 3-arm parallel | Confinement | 5 days | S-NITQ | 80 THS, 40 CC, 40 SA | Level of consumption, nicotine uptake, subjective effects, puffing topography |
| ZRHR-REXC-04-JP | Japan | 3-arm parallel | Confinement | 5 days | S-NITQ | 80 THS, 40 CC, 40 SA | Level of consumption, nicotine uptake, subjective effects, puffing topography |
| ZRHM-REXA-07-JP | Japan | 3-arm parallel | Confinement and ambulatory | 3 months | S-NITQ | 80 THS, 40 CC, 40 SA | Level of consumption, patterns of use, nicotine uptake, subjective effects, puffing topography |
| ZRHM-REXA-08-US | USA | 3-arm parallel | Confinement and ambulatory | 3 months | S-NITQ | 80 THS, 40 CC, 40 SA | Level of consumption, patterns of use, nicotine uptake, subjective effects, puffing topography, intention to quit smoking |
| THS-PBA-07-US | USA | 1-arm actual use study | Observational | 6 weeks | S-NITQ | 1106 | Patterns of use, level of consumption, sensorial experience, misuse |
| Whole Offer Test (WOT) Study | Italy, Germany, Switzerland, Japan, South Korea | 1-arm | Observational | 4 weeks | AS | 2809 | Patterns of use, level of consumption |

Abbreviations: AS: Adult Smokers; CC: Conventional cigarettes; S-NITQ: Adult Smoker with No Intention to Quit CC; SA: Smoking abstinence; THS: Tobacco Heating System

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These studies focused on various parameters underlying product usage. The corresponding outcome measures were defined to gather information on product use behavior including (i) level of consumption (providing information on the "*number of units of the product consumed per day*") and (ii) human puffing topography (offering information on "*the way in which individuals consume each unit of the product"*).

Comparisons across studies are based on summary statistics of individual studies. The verbal qualifiers "comparable" and "similar" are used to qualitatively describe findings in a comprehensive rather than exclusively statistical manner; although CIs were considered for the assessment of findings, they mainly informed about the precision of parameter estimates rather than on effects in an inferential manner.

#### 3.5.2.1 Level of Consumption

Level of consumption was measured by counting the number of CC and THS Tobacco Sticks used per day by subjects during the conduct of the studies. Consumption was recorded by the study site staff when subjects were confined, or was otherwise self-reported by subjects in a diary (paper or electronic) on a stick-by stick basis when in ambulatory or "home-use" setting.

*Level of Consumption - Summary of Results of Clinical Studies*

Four reduced-exposure clinical studies assessed daily product consumption. Graphical presentation of daily product use is presented in Figure 1.

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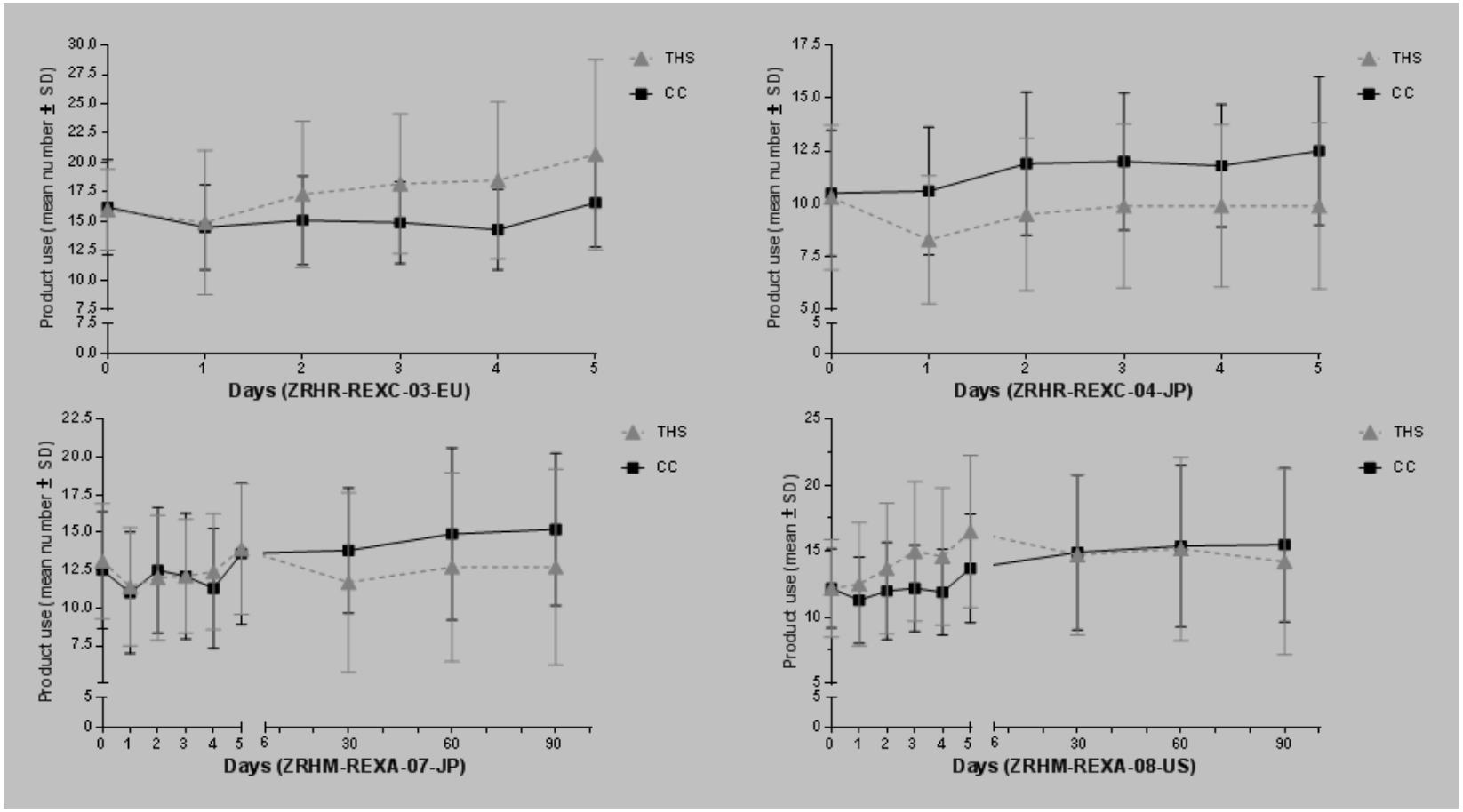



**Figure 1 Product Consumption (Number of products used) between Baseline and at Day 5 (ZRHR-REXC03-EU and ZRHR-REXC04-JP) and Baseline and Day 90 (ZRHM-REXA07-JP and ZRHM-REXA08-US)**

Abbreviations: THS = Tobacco Heating System, CC= Conventional cigarette, SD = standard deviation
Note: Day 0 = Baseline
Data Source: Clinical Study Report [ZRHR-REXC03-EU] Appendix 15, Table 15.2.2.1., [ZRHR-REXC04-JP] Appendix 15, Table 15.2.2.1., [ZRHM-REXA07-JP] Appendix 15, Table 15.2.2.1.2 and Table 15.2.2.3.2 and [ZRHM-REXA08-US] Appendix 15, Table 15.2.2.3.2

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At Baseline, product consumption in the THS arm, when subjects used their own preferred brand of CC, ranged from 10.3 cigarettes/day in study [ZRHR-REXC-04-JP] to 16.0 cigarettes/day in study [ZRHR-REXC-03-EU]. Comparable levels of product consumption were reported in the CC arms across all studies (from 10.5 to 16.2 cigarettes/day).

During the confinement period, an initial decrease in product consumption in the THS arms from Baseline to Day 1 was observed in all studies, except study [ZRHM-REXA-08-US] where product consumption increased from Day 1 onwards. From Day 2 onwards, THS Tobacco Sticks product consumption increased in the two Japanese studies reaching levels comparable to Baseline between Day 3 and Day 5. In studies [ZRHR-REXC-03-EU] and [ZRHM-REXA-08-US], THS Tobacco Stick use was higher from Day 2 and Day 3 onwards compared to product consumption at Baseline with an about 30% and 35% increase of product consumption observed at Day 5 (20.7 THS Tobacco Sticks/day and 16.5 THS Tobacco Sticks/day in [ZRHR-REXC-03-EU] and [ZRHM-REXA-08-US], respectively). In the CC arm, a similar decrease of product consumption from Baseline to Day 1 was observed in most of the studies, except [ZRHR-REXC-04-JP] where product consumption remained at levels comparable to Baseline. CC consumption increased afterwards in all studies exceeding Baseline levels, except in [ZRHR-REXC-03-EU] where CC use was comparable to Baseline (Figure 1).

During the Ambulatory Period, THS Tobacco Stick consumption decreased in both studies between Day 5 (13.9 THS Tobacco Sticks/day for [ZRHM-REXA-07-JP] and 16.9 THS Tobacco Sticks/day for [ZRHM-REXA-08-US]) and Day 30 (11.7 THS Tobacco Sticks/day for [ZRHM-REXA-07-JP] and 14.7 THS Tobacco Sticks/day for [ZRHM-REXA-08-US]). THS Tobacco Stick consumption returned to levels comparable to Baseline in study [ZRHM-REXA-07-JP] from Day 60 onwards (Day 60: 12.7 THS Tobacco stick consumption/day) with no changes afterwards. In study [ZRHM-REXA-08-US], levels remained only slightly above Baseline on Day 90 (14.2 THS Tobacco stick/day or 16% difference compared to Baseline).

Consumption of CC in the mCC arms during the Ambulatory Period further increased in both studies during the ambulatory period, remained higher as compared to Baseline, and higher than the number of THS Menthol Tobacco Sticks consumed at Day 30, Day 60 and Day 90 (Figure 1).

*Level of Consumption - Summary of Results of Observational Studies*

One of the characteristics of the observational studies, unlike the clinical studies, was that participants were free to use THS Tobacco Sticks and CC *ad libitum* and with no restriction (i.e., concomitantly).

The aim of THS-PBA-07-US Study was to investigate how US adult current daily smokers of CC use the THS system under near to real-world conditions. The market research WOT had a similar purpose but it was conducted in five other countries (Japan, Italy, Germany, Switzerland and South Korea). In particular, the THS-PBA-07-US and the WOT studies assessed the quantities of THS Tobacco Sticks and of CC consumed by individual participants, over a six-week and a four-week observational period respectively. More

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details can be found in the summary and full report of the studies [Section 7.3.2 and Section 7.3.3].

In the THS-PBA-07-US study, the average daily *total tobacco consumption* (i.e., THS Tobacco Sticks + CC) measured at the end of the observational period (9.3 Sticks/day) was slightly lower than the Baseline consumption (CC only) measured before the start of the observational period (10.2 Sticks/day). This was true for the overall Full Analysis Set (FAS) and the stratified groups by usage category at week 6. A summary of tobacco consumption during the Baseline period and the observational period for the FAS and the stratified groups by usage category at week 6 is presented in Table 2.

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**Table 2 THS Tobacco Sticks and/or CC consumed daily (mean±SD) at Baseline and during the Observational Period (average across the 6 weeks) in THS-PBA-07-US – Overall (FAS) and Stratified by Usage Category at Week 6**

| | Baseline (1 week) | Observational Period (6 weeks) | | |
|---|---|---|---|---|
| | CC | All tobacco (THS Tobacco Sticks +CC) | CC | THS Tobacco Sticks |
| **Stratified by Usage Category at Week 6** | | | | |
| Participants with *THS Tobacco Sticks use* at week 6 (n=141) | 9.0 ±5.89 | 8.1±5.37 | 1.4±1.57 | 6.7±4.82 |
| Participants with *Combined use* at week 6 (n=217) | 9.3 ±6.34 | 8.9±6.21 | 4.8±3.72 | 4.1±3.06 |
| Participants with *CC use* at week 6 (n=607) | 10.9 ±7.69 | 9.9±6.75 | 8.3±6.32 | 1.7±1.99 |
| **Overall (FAS)** (n=1106) | 10.2 ±7.22 | 9.3±6.56 | 6.3±5.78 | 3.0±3.57 |

Abbreviations: n= number of values reported, CC= conventional cigarette; SD= Standard Deviation, FAS= Full Analysis Set.
Data Source: Study report THS-PBA-07-US, Appendix 15.2; FAS, Table 15.2.3.11, Table 15.2.4.1, 15.2.4.2; Appendix 15.2; FAS By usage week6, Table 15.2.3.11, Table 15.2.4.1, 15.2.4.2

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In the WOT studies, the average daily *total tobacco consumption* (i.e., THS Tobacco Sticks + CC) during the observational period ranged from 10.1 Sticks/day (Italy) to 14.6 Sticks/day (Japan). This was approximately 2 Sticks/day lower than the self-reported consumption of CCs prior to the observational period. This was consistent across all countries and study weeks. A summary of tobacco consumption during the observational period and the difference between consumption/day during and prior to the observational period is provided in Table 3.

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**Table 3 Average Daily Consumption of THS Tobacco Sticks and CC in Week 4 and Difference to Average Daily CC Consumption at Screening for WOTs**

| | | JP | IT | DE | CH | KR |
|---|---|---|---|---|---|---|
| | | **Study Week 4** | **Study Week 4** | **Study Week 4** | **Study Week 4** | **Study Week 4** |
| Daily average Tobacco Consumption (CC+THS Tobacco Sticks) | *n* | 638 | 535 | 377 | 416 | 843 |
| | Mean ±SD | 14.57±7.76 | 10.13±5.56 | 12.64±7.35 | 14.31±7.77 | 14.00±6.98 |
| | 95% CI | [13.97, 15.17] | [9.66, 10.60] | [11.89, 13.38] | [13.56, 15.05] | [13.53, 14.48] |
| Difference: (CC+THS Tobacco Sticks) in week 4 – (self-reported CC daily consumption prior starting the observational period) | Mean ±SD | -1.95±4.42 | -2.57±5.42 | -4.72±6.84 | -2.95±6.54 | -1.17±6.02 |
| | 95% CI | [-2.30, -1.61] | [-3.03, -2.11] | [-5.41, -4.03] | [-3.58, -2.32] | [-1.57, -0.76] |

Abbreviations: CH = Switzerland; DE = Germany; IT = Italy; JP = Japan; KR = South Korea
Note: In each cell, the mean is the average number of the sum of THS Tobacco Sticks and CC consumed per day in week 4.
Note: Difference with a negative value indicates that daily average combined CC+THS Tobacco Sticks consumption in week 4 is lower than self-reported CC daily consumption prior to starting the observational period.
Data Source: WOTSTUDYREPORT, Table 11-8, Table 11-16, Table 11-24, Table 11-32, Table 11-40.

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*Level of Consumption - Conclusions*

Changing patterns of product consumption, during the first days of experience with a new product with different characteristics compared to consumers own brand of CC, are expected and part of the adaptation process to a new product such as THS. In observational studies, there was no increase in the total tobacco consumption (THS Tobacco Sticks and CC) between the Baseline and the observational period, when participants were able to use both THS Tobacco Sticks and CC *ad libitum*. More detailed information are included in the relating section included in Module 6 (see Section 6.2.2).

### 3.5.2.2 Human Puffing Topography

Human Puffing Topography (HPT) assesses each user's unique way of using a product and constitutes an established research tool in smoking behavior research to assess individual product use patterns on a per single-use basis. A total of 7 parameters were considered, 3 at the puff level (Average Puff Volume, Average Puff Duration and Average Pressure Drop) and 4 at the product use level (Total Puff Volume, Total Number of Puffs, Total Smoking Duration and Puff Frequency). These reflected how the user changed or adapted his/her puffing at an average puff level (i.e., by changing the length of the puffing duration and volume inhaled), as well as during a full tobacco stick use experience (i.e., at the product use level, by changing the puffing frequency).

*Human Puffing Topography - Summary of Results*

Human Puffing Topography was assessed in four studies [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US].

At the puff level, (i) decreased Average Puff Volume from Baseline onwards for THS in the studies in Japan, (ii) comparable Average Puff Volume values to Baseline and CC were observed for THS in Europe in the Polish study, and (iii) higher Average Puff Volume values for THS compared to Baseline and CC were observed during most of the study in the US. Similarly, Average Puffing Duration varied between the different populations with a comparable Average Puffing Duration to Baseline and CC in the Japanese studies [ZRHR-REXC-04-JP] and [ZRHM-REXA-07-JP], while the puffing duration increased in the Polish study [ZRHR-REXC-03-EU] and was variable in the US study with THS values remaining higher than CC. Average Pressure Drop was stable and comparable during the confinement period for THS and CC within studies, with the exception of a relative decrease of THS compared to CC in [ZRHM-REXA-08-US], whereas Average Pressure Drop continuously and markedly increased during the ambulatory period in both studies ([ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]) for THS compared to Baseline and CC.

In the CC arms, values were stable over time, with the exception of [ZRHM-REXA-08-US] where the HPT parameters at the Puff Level (Average Puff Volume, Average Puffing Duration and Average Pressure Drop) varied over time.

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Overall, these results suggest a different pattern of adaptation when switching from CC to THS across populations at the puff level, with a reduction in average puff volumes in Japan and stable puff volumes in the non-Japanese countries. Average Puffing Duration was stable in Japan compared to an increase observed in the European ([ZRHR-REXC03-EU]) and US ([ZRHM-REXA-08-US]) studies.

At the product use level, Total Puff Volume for THS decreased in the Japanese studies ([ZRHR-REXC04-JP] and [ZRHM-REXA-07-JP]) from the beginning of the confinement period but increased afterwards and reached levels comparable to CC, remaining however generally lower than Baseline levels throughout the studies. In contrast, Total Puff Volume remained stable in the study in Europe ([ZRHR-REXC03-EU]) and increased in the US [ZRHM-REXA08-US] from Day 1 onwards, remaining consistently at higher levels compared to Baseline and CC.

No regional differences were observed for the Total Number of Puffs drawn, which increased in all studies when the smokers switched from CC to THS. Users seemed to adapt their puffing behavior by using a multipuff technique (i.e. one puff with multiple peaks caused by a modulating inhalation). This is supported by the evaluation of individual profiles showing the presence of multiple peaks in some individual puffs. Similarly, Puff Frequency increased in all studies from Day 1 until Day 30 when subjects switched to THS, before reaching stabilization in all studies. Total Smoking Duration was shorter with THS compared to CC in all studies, with the most pronounced reduction from Baseline in the non-Japanese studies ([ZRHM-REXA-08-US] and [ZRHR-REXC-03-EU]). This reduction in duration with THS might be due to the intrinsic limitation of the THS system (a maximum of 14 puffs or 6 minutes product use, whichever comes first). To note, Total smoking duration at Baseline was markedly higher in study [ZRHM-REXA-08-US] than in the other studies and remained higher compared to all other studies at all-time points and across all study arms.

In summary, THS users took more puffs from THS compared to CC, at a higher frequency and for shorter total duration of use. Total Puff Volume was variable, with an increase observed in the US, a stable volume in the EU and an initial decrease in the Japanese studies. No relevant changes were observed in subjects who continued to use their CC.

*Human Puffing Topography - Conclusions*

Taken together, the results from the “at the puff level” and “at the product use level” indicate that smokers switching from CC to THS adapt their puffing behaviors. Changes in Average and Total Puff Volume were different between the studies, as well as the effect on the other parameters, but a general trend for longer and more frequent puffs with a shorter Total Puff Duration was observed for THS compared to CC.

More detailed information is included in the related section in Module 6 (see Section 6.2.2).

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### 3.5.3 Data and information regarding concurrent use of multiple products containing nicotine or tobacco

*Combined Use*

Data on the use of a candidate MRTP alone and in combination with other tobacco products are important to determine the extent to which adult smokers find a novel tobacco product acceptable as a cigarette substitute. To describe patterns of product use across the different studies, product use categories were defined based on the percentage of THS Tobacco Sticks used in a predefined period of time compared to the number of total tobacco products used (i.e. THS Tobacco Sticks + CC). In particular, *Combined use* of THS and CC was defined as the proportion of THS Tobacco Sticks used representing (or accounting for) between ]30-70[% of the total number of tobacco products used.

PMI observational and clinical studies provide first insight on how THS might be concurrently used with other products containing nicotine or tobacco after introduction in the market. Table 1 aforementioned at the beginning of Section 3.5.2 summarizes those studies.

*Combined Use – Observational Studies*

Valuable data about the combined use of THS and other tobacco or nicotine-containing products can be derived from the THS-PBA-07-US Study. In this study, the quantities of THS Tobacco Sticks and CC consumed by US adult current daily smokers over time, under near to real-world conditions, were assessed. More details can be found in the summary [PBA07Sum] and full report of the study [THS-PBA-07-US]. A summary of the *combined use* rates is presented in Table 4 for each of the 6 weeks observational period.

Among the 1106 participants who were offered THS and included in the FAS, 459 (41.5%) participants used THS Tobacco Sticks and CC in a combined way (i.e., ]30-70[% THS) during the first week. In week 6, the number of participants with *Combined use* was reduced to 217 participants (22.4%). Analysis of usage categories over different time points via transition tables, created for each week to any other posterior weeks during the observational period, support this indication. Out of the 459 participants who reported *Combined use* in week 1, 50 (10.9%) transitioned to *THS Tobacco Stick use,* 223 (48.6%) transitioned to *CC use* and 133 (29.0%) continued *Combined use* in week 6 [3].

In addition, there was no increase in the total use of tobacco products (THS Tobacco Sticks and CC) between the Baseline and the observational period. For participants in *combined use*, as illustrated in Table 2, the combination of average daily THS Tobacco Sticks and CC consumption at week 6, was slightly lower (8.9 Sticks/day) than at Baseline (9.3 Sticks/day). This indicates that *combined use* was not associated with an increase of the total tobacco consumption.

[3] 52 Participants were no longer in the study in week 6 and 1 participant had zero consumption of THS Tobacco Stick and CC in week 6.

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The market research WOT had a similar purpose to the THS-PBA-07-US study and it was conducted in five countries (Japan, Italy, Germany, Switzerland and South Korea). More details can be found in the summary report [WOTSTUDYREPORT]. Across the 5 countries, the number of participants with a *combined use* at the end of the observational period (i.e. week 4) ranged from 27.3% in Germany to 39.4% in Switzerland. Similarly to what was observed in the THS-PBA-07-US study, *Combined use* was decreasing over time. An overview of *combined use* rates is tabulated in Table 5 for each of the 5 countries during the 4 weeks observational period. An analysis of the usage categories over different time points via transition tables, created for each week to any other posterior week in the observational period, provide additional information. Among the participants reporting *combined use* in week 1, between 46.0% (Germany) and 58.5% (Switzerland) remained with *combined use*, between 9.4% (Italy) and 27.4% (Japan) transitioned to *THS Tobacco Stick use* and between 22.7% (Japan) and 39.8% (Germany) went back to *CC use* in week 4.

More detailed information is included in the related section in Module 6 (see Section 6.2.2).

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## Table 4 Combined Use Rates by Week for the FAS Population in THS-PBA-07-US

| *n (% column)*<br>*95% CI (%,%)* | Week 1<br>(n=1106) | Week 2<br>(n=1061) | Week 3<br>(n=1038) | Week 4<br>(n=1009) | Week 5<br>(n=997) | Week 6<br>(n=968) |
|---|---|---|---|---|---|---|
| **Combined use** | 459 (41.5%)<br>(38.5% , 44.5%) | 360 (33.9%)<br>(31.0% , 36.9%) | 326 (31.4%)<br>(28.5% , 34.4%) | 267 (26.5%)<br>(23.7% , 29.3%) | 243 (24.4%)<br>(21.7% , 27.2%) | 217 (22.4%)<br>(19.8% , 25.2%) |

Abbreviations: n= number of values reported, CI= Confidence Interval, FAS= Full Analysis Set.
Data Source: Study report THS-PBA-07-US, Appendix 15.2; FAS, Table 15.2.6.1.2,

## Table 5 Combined Use Rates by Week for the FAS Population in WOTs

| *n (% column)*<br>*95% CI (%,%)* | **Week 1** | **Week 2** | **Week 3** | **Week 4** |
|---|---|---|---|---|
| ***Japan (n=638)*** | | | | |
| **Combined use** | 277 (43.42%)<br>(39.53%, 47.36%) | 229 (35.89%)<br>(32.17%, 39.75%) | 209 (32.76%)<br>(29.13%, 36.55%) | 206 (32.29%)<br>(28.67%, 36.07%) |
| ***Italy (n=535)*** | | | | |
| **Combined use** | 256 (47.85%)<br>(43.55%, 52.18%) | 229 (42.80%)<br>(38.57%, 47.12%) | 204 (38.13%)<br>(34.00%, 42.4%) | 203 (37.94%)<br>(33.82%, 42.21%) |
| ***Germany (n=377)*** | | | | |
| **Combined use** | 176 (46.68%)<br>(41.56%, 51.86%) | 141 (37.40%)<br>(32.50%, 42.5%) | 131 (34.75%)<br>(29.95%, 39.79%) | 103 (27.32%)<br>(22.88%, 32.12%) |
| ***Switzerland (n=416)*** | | | | |
| **Combined use** | 200 (48.08%)<br>(43.18%, 53.00%) | 179 (43.03%)<br>(38.22%, 47.94%) | 165 (39.66%)<br>(34.93%, 44.54%) | 164 (39.42%)<br>(34.70%, 44.30%) |
| ***South Korea (n=843)*** | | | | |
| **Combined use** | 408 (48.40%)<br>(44.98%, 51.83%) | 336 (39.86%)<br>(36.53%, 43.25%) | 318 (37.72%)<br>(34.44%, 41.09%) | 306 (36.30%)<br>(33.05%, 39.65%) |

Abbreviations: n= number of values reported, CI= Confidence Interval, FAS = Full Analysis Set.
Data Source: WOTSTUDYREPORT, Table 11-6, Table 11-7, Table 11-14, Table 11-15, Table 11-22, Table 11-23, Table 11-30, Table 11-31, Table 11-38, Table 11-39.

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*Combined Use – Clinical Studies*

Data on combined use of THS and other tobacco or nicotine-containing products derived from the actual use studies were further supported by clinical studies data. In studies [ZRHM-REXA-07-JP], [ZRHM-REXA-08-US], [ZRHR-REXC-04-JP] and [ZRHR-REXC-03-EU], product use was strictly controlled during the Confinement Period ensuring that all subjects in each study arm (i.e., THS, CC, and Smoking Abstinence) were compliant with their assigned product. During the 3-month Ambulatory Period, subjects were instructed to exclusively use their allocated product but due to the ambulatory setting, they had the possibility to use other nicotine-containing products. During this period, compliance to the assigned product was assessed based on self-reported product consumption.

Patterns of product use were comparable between the Confinement and Ambulatory periods with high compliance to product allocation in study [ZRHM-REXA-07-JP]. During the Ambulatory Period in the THS study arm, dual-use of THS and CC occurred in under 2.6% of the subjects. In [ZRHM-REXA08-US], product use patterns were different, with a higher level of dual-use (up to 15% of subjects) in the THS arm.

*Combined Use – Conclusions*

Data from the observational and clinical studies indicate that it is likely that a certain proportion of adult smokers will use THS in combination with other tobacco or nicotine-containing products. However, data also indicates that (i) this proportion will decrease over time, with more consumers likely to return to *CC use* and a smaller proportion transitioning towards *THS Tobacco Stick use*; (ii) the c*ombined use* does not indicate an increase in the total use of tobacco products.

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