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6.2 Effect on Tobacco Use Behavior among Current Tobacco Users

6.2.4 Overall Conclusions on Tobacco Use Behavior among Current Tobacco Users

Product appeal and consumer perception of an MRTP (sensorial experience, intended use) as well as potential for abuse (extent to which the product is pharmacologically reinforcing and may produce addiction) are important for assessing the potential impact of an MRTP on the population health (Hatsukami 2012). The scientific data reported in this application demonstrate that switching completely to THS has the potential to present less risk of harm than continuing to smoke (Section 6.1). Pre-market clinical studies and PBA studies presented in Section 6.2 constitute the two main sources of information to build the evidence against which to gauge the potential of THS being an acceptable substitute of CC for adult smokers.

6.2.4.1 Likelihood that Current Smokers Start Using THS

Product Acceptance

THS has been designed to approximate as closely as possible the taste, satisfaction, nicotine PK profile, and ritual of cigarettes in order to facilitate switching of current adult smokers. Four PK/PD studies (i.e., [ZRHR-PK-01-EU], [ZRHR-PK-02-JP], [ZRHM-PK-05-JP], and [ZRHM-PK-06-US]) showed that the nicotine uptake by THS users is comparable to that of cigarette smokers (time to maximal nicotine concentration (t_{max}), maximum nicotine plasma concentrations (C_{max}) and exposure (AUC) are comparable to CC) (Section 6.2.1.3). This is the case for THS Regular and high Menthol variants. The results also indicate that THS is able to reduce smoking urges as effectively as CC and at least as well, if not better, than NRTs (Section 6.2.1.3.3). The population PK model showed that menthol has no relevant effect on two parameters that are the determinants of plasma exposure (AUC) at a given nicotine ISO yield (Frel and Cl/F) (Section 6.2.1.3.2). The model supports the similarity in PK between THS with CC, as the relative bioavailability (Frel) of CC was only 2% higher than that of THS.

Nicotine uptake was measured in reduced exposure clinical studies during 5-days in confinement in [ZRHR-REXC-03-EU], [ZRHR-REXC-04-JP], [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US] and for additional 85 days in ambulatory settings in [ZRHM-REXA-07-JP] and [ZRHM-REXA-08-US]. These studies showed that urinary NEQ, plasma nicotine and cotinine are comparable between THS and CC, indicating that THS, when consumed *ad libitum*, allows the users to reach similar levels than those delivered by CC (Section 6.2.2.4.1.2.1). Measures of subjective effects e.g., urge-to smoke, withdrawal symptoms, and product evaluation as collected in these reduced exposure studies demonstrate that THS offers an experience close to what is observed in smokers when smoking CC (Section 6.2.2.4.1.2.4). Overall, the nicotine PK profiles and parameters from the PK studies as well as the levels of exposure to nicotine from the reduced exposure studies do not indicate a higher risk of abuse liability in smokers switching to THS compared to CC (Section 6.2.3.4).

Human puffing topography results from the 4 reduced exposure studies showed that smokers switching to THS are able to adapt their puffing behavior at both puff and product use level, with a trend to longer and more frequent puffs with a shorter total puff duration for THS compared to CC (Section 6.2.2.4.1.2.3).

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Overall, the findings on product acceptance (based on nicotine uptake, subjective effects and puffing behavior), are consistent with adult smokers likely finding THS an acceptable alternative to cigarettes.

Product Adoption

Data from observational studies (6-week and 4-week observational periods in [THS-PBA-07-US] and WOTs, respectively), where consumers interacted freely with the product in near to real-world conditions, provide substantial evidence on the potential of THS being a viable substitute of CC. As a strong indicator of product adoption, the proportion of participants who switched predominantly or exclusively to THS at the end of the observational period represented 10 to 37% of the study participants (Section 6.2.2.4.1.3.3). These studies indicate, consistently across the 6 countries, that smokers who switched rapidly to THS were more likely to adopt a continued use of THS long-term. Findings from the US actual use study show in addition that satisfaction with the product (easiness to use, taste, smell and aftertaste experienced with the product) clearly played a role in switching to THS (Section 6.2.2.4.1.3.1.2). These results, in combination with the aforementioned evidence on product acceptance, support the conclusion that THS offers an experience sufficiently close to cigarettes to provide an overall satisfying experience, thus enabling adult smokers to convert predominantly or exclusively to THS use.

Level of Consumption

Variations in product consumption, in particular during the first days of experimenting with a new product with characteristics different from CC, are expected and are part of the adaptation process to a new product. This was in fact observed in 4 clinical studies (either in confinement or incorporating a confinement period), with consumption of THS being lower compared to baseline CC consumption during the first days. These variations disappeared mostly, as observed in the ambulatory setting, when followed up for a period of more than 30 days. The final levels of consumption were comparable to what was observed at baseline and to the consumption levels reported in the CC arms (Section 6.2.2.4.1.2.2). Furthermore, product use data collected in close to real-world conditions (THS-PBA-07-US and WOTs) provide evidence that adult daily smokers who consumed THS freely with other tobacco and nicotine containing products did not increase their overall tobacco product consumption, whether they used THS predominantly or in combination with CC (Section 6.2.2.4.1.3.3). Given that the THS tobacco sticks were provided for free in these observational studies, whilst participants had to pay for their own CC, the findings indicate that it is unlikely to observe increased consumption when smokers would have to pay for both products.

Together with the nicotine exposure results, the transient variations in THS use and the subsequent puffing behavior adaptations indicate that smokers switching to THS (fully or partially) self-titrate their nicotine intake, i.e. seeking nicotine levels similar to what they are used to with regard to their CC consumption. Thus, the product use behaviors observed in clinical and observational settings do not raise an abuse liability concern beyond that for CC and suggest instead a partial transfer from CC to THS, without promoting an increase in total tobacco product use (Section 6.2.3.6).

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Effects of THS Communication

Accurate scientifically substantiated information about the modified risk of THS needs to be communicated to consumers. Risk/benefit communication plays a crucial role in helping adult smokers to switch to THS. Data on the effect of THS communication consistently showed that the way potential risks and benefits of THS are communicated to adult smokers generate substantial intent to use THS among this population (Section 6.2.2.4.2.5). At the same time, the findings demonstrate that adult smokers have an accurate understanding of the potential risks of THS, and that THS is not free of risk (see Section 6.4.1 for more details).

Considering the growing interest in smokers to use potentially less harmful alternatives to CC, as evidenced by the current trends observed for e-cigarettes and smokeless tobacco (see Section 6.3.2 for more details), it can be expected that, with a scientifically substantiated and non-misleading communication on the potential reduced risk of using the product, THS could substantially move smokers away from CC.

Yet, these results need to be put into perspective with impacts on non-smokers to assess the population health impact (Hatsukami 2012). Results from PBA studies consistently showed that, while THS communication is effective to engage adult smokers in using THS, it deters non-smokers to initiate or re-initiate tobacco use with THS (see Section 6.3.1 for more details). These results support the conclusion that THS label, labeling and marketing materials as submitted in this MRTPA are likely to promote the correct understanding and intent to use among current adult smokers, and are unlikely to have unintended effects in adult non-smokers, including in young adult never smokers.

6.2.4.2 Likelihood that THS Users Switch Back to CC

The aforementioned evidence on THS use patterns and consumption is based on exposure studies with a duration deemed appropriate to assess primarily (i) the reduced exposure to HPHCs (clinical confinement and ambulatory studies) and (ii) the likely adoption of the product in near to real-world conditions (observational studies), including potential use in conjunction with other products and potential misuse. Thus, the evidence available to date on the likelihood that THS users may switch back to CC is based on the exposure periods as actually implemented.

The PMI clinical studies were supportive for understanding product self-administration, as product use was *ad libitum*, with concomitant or intermittent use of other tobacco products (dual use) not being prohibited in the ambulatory 3-month periods. Patterns of product use were different between Japan and the US (Section 6.2.2.4.1.2.2.2). High compliance to THS allocation was observed in study [ZRHM-REXA-07-JP] during the 3-month ambulatory period, with switching back from *THS use* to mainly *CC use* occurring in 3.8% of the subjects. In contrast, in [ZRHM-REXA08-US], product use patterns were different, with a higher level of mainly *CC use* during the ambulatory period (up to 7.5% of subjects).

Observational studies provide more realistic insights on how THS is likely to be used by consumers when introduced on the market. WOTs conducted in Europe and Asia and [THS-PBA-07-US] conducted in the US showed that between 26% and 63% of the study participants were CC smokers at the end of the observational period. This proportion

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tended to increase over the course of the usage period. These results, in combination with results on the rates of THS adoption, suggest that it is unlikely that those who switch to THS early on will then switch back to CC. Overall higher levels of THS predominant or exclusive use in Japan and South Korea, compared to the US, may be indicative of higher product acceptance, likely due to sensory properties and higher propensity to adopt new product in Japan and South Korea compared to the US.

In conclusion, PMI's clinical and PBA studies provide consistent evidence pointing toward a low likelihood that smokers who adopt THS will switch back to cigarette smoking.

6.2.4.3 Likelihood that Consumers Use THS in Conjunction with Other Tobacco Products

Concomitant use of two or more tobacco products is an increasing public health concern, even though there is not much data on the implications of such behaviors (e.g., higher levels of nicotine exposure, lower likelihood to stop tobacco use). Clinical endpoint results, presented by various levels of dual use, will only be available as the PMI clinical assessment program progresses, but are not, and cannot be, available to date (Section 6.1.6.4).

Data from the 6 observational studies ([THS-PBA-07-US] and 5 WOTs) show that, though THS was used in combination with CC by a certain proportion of adult daily smokers (between 22% and 39% of the participants across the 6 countries), the overall level of tobacco consumption (THS+CC) did not increase in any of the studies. In addition, the transient decrease in *Combined use* observed consistently across the 6 observational studies over time, indicates that smokers who started with *Combined use* in the first week or so returned to *CC use* or, to a lesser extent, transitioned towards *THS Tobacco Stick use* (Section 6.2.2.4.1.3.3).

Findings from our pre-market studies are overall in line with some of the published literature, which shows that dual use may be considered as an experimentation phase rather than establishing a long-term behavior. For instance, a study by Gilreath et al. (Gilreath 2016) showed that the prevalence of poly-tobacco use is almost 3 times higher for non-daily poly-tobacco users compared to daily poly-tobacco users (13.9% and 5.6%, respectively). Along the same lines, Klesges et al. (Klesges 2011) showed that, due to varying definitions of dual use of smokeless tobacco and CC, mainly linked to frequency of use, prevalence estimates of dual use vary by a factor of 50 (0.5%–25.3%). Furthermore, available data on dual or poly-tobacco use does not provide clear evidence that this use pattern deter smokers to quit smoking (Frost-Pineda 2010, Kalkhoran 2015, McRobbie 2014).

Overall, results from our observational studies indicate relatively high rates of combined use (between 22% and 39%) compared to what has been reported in the published literature on dual and poly-tobacco use for tobacco products currently commercialized in the US (between 1% and 18% across 13 publications assessing the prevalence of dual or poly-tobacco use among daily CC smokers, see Section 6.3.2.3.3). One possible factor to explain the higher rates in our studies may be attributed to our study duration (4 to 6

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weeks) which probably did not allow for a full investigation of complete switch to THS or switching back to CC.

In combination with evidence from published literature on dual or poly-tobacco use, results from our clinical and PBA studies support the conclusion that combined use is likely to occur in some smokers over the first few months of exposure to THS. The long-term patterns of product use and adoption will be studied in post-market surveillance but based on the results from our clinical and observational studies, it is unlikely that dual users will experience an increase in their overall nicotine exposure or tobacco product use.

6.2.4.4 Likelihood that Smokers who may have Otherwise Quit Using Tobacco Products will instead Use THS

It can be very difficult to quit smoking cigarettes or using other tobacco products, but millions of people have successfully done so.

Nonetheless, though many smokers are interested in and attempt to quit, the rates of long-term smoking cessation remain low. For example, according to the United States Surgeon General, (U.S. Department of Health and Human Services 2014), although about 45% of smokers quit for a day, only approximately 5% succeed in achieving long-term abstinence for one year or more.

Overall, our PBA studies assessing the effect of the THS communications (i.e., [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], and [THS-PBA-05-REC-US]) showed that intent to use THS was broadly similar in smokers with and with no intention to quit CC. At the same time, the impact of THS communication on the intention to quit among adult smokers with intention to quit CC was relatively small (between 1.0% and 11.8% of the participants delayed their intention to quit CC or all Tobacco following exposure to any of the THS label, labeling and marketing material). Overall, these findings indicate that exposure to THS communications including either reduced risk or reduced exposure claim did not substantially alter the subsequent intentions of smokers who intended to quit smoking. This was further supported by qualitative data from THS-PBA-02-US, which found that some adult smokers with the intention to quit CC viewed THS as a potentially less harmful alternative that could be used as a ‘step down’ product to help them on their way to quitting smoking but understood that THS is not an alternative to cessation (section 6.2.2.4.2.1.2).

In sum, the PBA results based on the stated intentions of adult smokers point consistently toward a low likelihood that smokers who may have otherwise quit using tobacco products will instead use THS.

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6.2.4.5 Likelihood that THS is used as Intended

The ability of consumers to use THS as intended is a crucial aspect of the overall product assessment, as it will ascertain that harm reduction can be achieved under intended use as assumed when THS was developed.

Findings from [THS-PBA-06-US] showed that adult smokers were able to execute the majority of tasks described in the THS instructions for use (charging the THS Holder, how to consume the stick, end of stick use, how to remove a stick from the THS Holder), with the exception of a few tasks related to the cleaning process (how to remove the stick with the pull-pull technique, how to heat clean the holder, how to use the THS Cleaning Tool) (Section 6.2.2.4.3). The results of [THS-PBA-06-US] led to the development of an improved version of the instructions for use, and to some extent, the device (THD version 2.4, see Section 3.5.1.2).

Comprehension levels of key messages such as "*not using the device with a CC*" or "*not to smoke the THS tobacco stick as a CC*" were high in [THS-PBA-06-US] (85% and 95% of users, respectively). These results are in line with the rarity of misuse observations from study [THS-PBA-07-US] (4.8% of participants reported to have smoked at least once the THS stick as a CC, by lighting it) which is likely due to negligence or curiosity rather than indicative of alternative ways to use THS sticks (Section 6.2.2.4.3).

Overall, based on the available evidence on potential misuse, THS is likely to be used as intended by adult smokers. Once commercialized, appropriate customer support will be provided to ensure that customers can use the product properly. It can thus be expected that some of the technicalities associated with the use of the THS (e.g., cleaning process, removal of sticks with the pull-pull technique), will be more rapidly adopted by consumers, and that the proper use of the THS would become clear after repeated attempts.

In conclusion, the available information suggests that THS meets the IOM recommendation for a desirable MRTP being sufficiently reinforcing so as to attract smokers away from cigarettes, but not to encourage the use of the product by non-smokers, including those who have quit smoking. The pre-market results require confirmation in post-market settings.

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