Module 6 : Research

6.1 Summary of Health Risk Investigations

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1. INTRODUCTION

Philip Morris Products S.A. (PMP S.A.) is providing only new information and data that PMP S.A. has not provided to FDA in earlier submissions. Scientific evidence and information related to the *IQOS* products in the scope of this renewal, as supplied with the initial MRTPA and PMTA for the Authorized *IQOS* 2.4 System Holder and Changer (PM0000479 and MR0000133), *HeatSticks* (PM0000424 - PM0000426 and MR0000059 - MR0000061) and the *IQOS* 3.0 System Holder and Charger (PM0000634 and MR0000192), remains valid and, therefore, is cross-referenced.

2. AEROSOL CHEMISTRY AND PHYSICS

PMP S.A. does not have any new information or data related to the aerosol characterization.

Scientific evidence and information related to the aerosol chemistry and physics that was supplied with the initial MRTPA and PMTA for the Authorized IQOS 2.4 System Holder and Changer (PM0000479 and MR0000133), HeatSticks (PM0000424 - PM0000426 and MR0000059 - MR0000061) and the IQOS 3.0 System Holder and Charger (PM0000634 and MR0000192) remain valid and do not require reanalysis.

3. NON-CLINICAL

PMP S.A. does not have any new information or data related to nonclinical toxicology.

Scientific evidence and information related to the non-clinical toxicology that was supplied with the initial MRTPA and PMTA for the Authorized IQOS 2.4 System Holder and Changer (PM0000479 and MR0000133), HeatSticks (PM0000424 - PM0000426 and MR0000059 - MR0000061) and the IQOS 3.0 System Holder and Charger (PM0000634 and MR0000192) remain valid and do not require reanalysis.

4. CLINICAL INDIVIDUAL HEALTH

4.1. Summary of Health Risk Investigations

In the original MRTPA, the clinical program included multiple studies across countries to characterize the *IQOS* (referred as THS in the scientific documents) risk profile in adult smokers of cigarettes who switched to the product. Those studies were reviewed by the FDA as part of the initial MRTPs (MR0000059-MR0000061 and MR0000133) and their associated amendments[1] and consisted of Table 1:

[1] Amendment to MR0000059-MR0000061 - Additional information – Clinical Study ZRHR-ERS-09-US, submitted on June 8, 2018.

Table 1 Data Submitted in the Original MRTP Application

Study Type	Study Name	Disclosure	Short Description
PK/PD studies	ZRHR-PK-01-EU ZRHR-PK-02-JP ZRHM-PK-05-JP ZRHM-PK-06-US	NCT01967732 [1] NCT01959607 [2] [3] NCT01967706 [3] [4] NCT01967719 [5] Original MRTPA	Demonstrated that the time curve profile of nicotine absorption, as evaluated by pharmacokinetic parameters, is comparable following single use of *IQOS* Heatstick and own cigarette
Reduced exposure studies (REX)	ZRHR-REXC-03-EU ZRHR-REXC-04-JP ZRHM-REXA-07-JP ZRHM-REXA-08-US	NCT01959932 [6] [7] NCT01970982 [8] [9] NCT01970995 [10] [11, 12] NCT01989156 [13] Original MRTPA	Demonstrated that the levels of BoEs representative of the exposure to 15 HPHCs of major toxicity were substantially reduced when smokers completely switched to *ad libitum* use of *IQOS*
Exposure response study	ZRHR-ERS-09-US	NCT02396381 [14][15] Amendment to original MRTPA[2]	Demonstrated statistically significant favorable changes in five out of eight core primary BoPHs (named Clinical Risk Endpoints [CRE] in the original MRTPA) in smokers predominantly switching to *IQOS*, compared to continued cigarette smoking, with all BoPHs showing, at the 6 months time point, modifications in the direction of smoking cessation as reported in the literature

[2] Amendment to MR0000059-MR0000061 - Additional information – Clinical Study ZRHR-ERS-09-US, submitted on June 8, 2018.

Study Type	Study Name	Disclosure	Short Description
Post-hoc analysis	PHAP-22MAR2018 (analysis of the ZRHR-ERS-09-US study)	Amendment to original MRTPA[3] only	Favorable changes of biological and functional in healthy smokers predominantly switching from cigarettes to *IQOS* use by 2-CyEMA quartiles at 6-months

The results of these studies, together with the submission of others scientific evidence, led the FDA to conclude: "*The applicant provided compelling evidence that the IQOS system does not combust tobacco and accompanying aerosol data showing dramatic reductions across a wide range of HPHCs identified by FDA. The applicant also demonstrated that BOEs to many HPHCs dropped significantly and approached the levels seen with complete cessation. Although the use of the IQOS system clearly still exposes users to HPHCs and would be expected to cause harm, such dramatic changes in exposure relative to combusted cigarettes are reasonably likely to, in general, translate to lower risk of tobacco-related morbidity and mortality.*"

Since the submission of the original MRTPA additional clinical studies were completed, and progress with these studies was reported as part of Annual Reports. Since additional results from the ongoing clinical program are available, these are discussed as part of this renewal, as summarized in Table 2.

Table 2 New Data Presented in this MRTP Application Renewal[4]

Study Type	Study Name	Disclosure	Short Description
Exposure response study	ZRHR-ERS-09-EXT-US	NCT02649556 [16]	A 6-month extension of the 6-month Exposure Response Study (ZRHR-ERS-09-US); describes the impact of a 12 month use period of *IQOS* on the eight selected core BoPHs and BoEs
Smoking cessation study	SA-SCR-01 Study	NCT02432729 [17]	A 12-month ambulatory Smoking Cessation Response study, where the eight core BoPH evaluated in the main

[3] Amendment to MR0000059-MR0000061 - Additional information – Clinical Study ZRHR-ERS-09-US, submitted on June 8, 2018

[4] Also see Appendix 7-a07-clin-ind-health-additional-studies

Study Type	Study Name	Disclosure	Short Description
			objective of the Exposure Response Study were assessed in smokers abstaining from smoking for 12 months. Provides a "benchmark" study with the profiles of changes of the selected BoPH upon smoking cessation that can help contextualizing changes after switching to *IQOS* in the frame of cessation
Post-hoc analysis	P1-ERS-EXT-SCR-PH-SHP	NA	A cross study analysis between the ZRHR-ERS-09-EXT-US and SA-SCR-01 studies conducted to contextualize the changes in BoPHs and BoEs when switching predominantly to *IQOS* use or cigarette quitting over 12 months
Post-hoc analysis	P1-ERS-EXT-SCR-PH-RESP	NA	A cross study analysis between the ZRHR-ERS-09-EXT-US and SA-SCR-01 studies ERS and SCR studies conducted to contextualize the changes in lung function and cough when switching predominantly to *IQOS* to cigarette quitting over 12 months
Oral health study	P1-OHS-01-JP	NCT03364751 [18] [19, 20]	A 6-month ambulatory oral health study, conducted in Japan, that investigated the potential benefit of predominantly switching from cigarette smoking to *IQOS* use on the healing of periodontal pockets in subjects with chronic generalized periodontitis following the standard of care i.e., a mechanical treatment called scaling and root planing (SRP).

Study Type	Study Name	Disclosure	Short Description
Exercise capacity study	P1-EXC-01-EU	NCT03887117 [21]	A 12-week exploratory ambulatory study on exercise capacity conducted in Germany to assess whether switching from cigarette smoking to using *IQOS* would influence the following exercise capacity-related parameters (e.g., VO_2max) subsequently to a training program

4.2. Overall Summary of Clinical Evidence

Additional findings are presented in Appendix 7-a07-clin-ind-health-additional-studies (paragraph 1.1.5 and 1.1.6) to further support the original MRTP application, including reductions of exposure in clinical studies. These additional findings provide further evidence that, as per the data submitted in the original MRTPA application, there is a substantial reduction in exposure to HPHCs when users of *IQOS* switch completely from combusted cigarettes to *IQOS*, and to support the renewal of the modified risk claim: "*Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals*"[5]. These data therefore further support the FDA's decision to issue the MRGO.

Furthermore, some of these clinical studies demonstrated that reduction of exposure to HPHCs upon switching from cigarettes to *IQOS* is associated with favorable changes in key relevant BoPH in *IQOS* users (vs CC smokers), in line of the smoking cessation data reported both in the literature and observed in our own smoking cessation study. Considering that smoking cessation is well established to decrease the risk of the main diseases attributable to smoking (*e.g.*, CVD, COPD, cancer), the findings on *IQOS* likely translate further into a reduced risk for these diseases compared to continued smoking. Some epidemiological data, published recently by independent scientists corroborate these statements. The selection of BoPH was previously presented to the FDA. It is in line with the main findings from the 2016 FDA-sponsored workshop on BoPH, which highlighted the applicability of BoPH to tobacco regulatory science, and is further summarized in Appendix 7-a07-clin-ind-health-additional-studies (paragraph 1.1.5 and 1.1.6) and in [22].

[5] Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911(d) of the FD&C Act – Technical Project Lead, FDA, 06 July 2020

4.3. Literature Review on *IQOS* Use and Disease Risk

4.3.1. Introduction

Clinical studies have demonstrated that the reduction of exposure to HPHC, upon switching from cigarettes to *IQOS*, is associated with favorable changes in key relevant BoPH in *IQOS* users (*vs*. CC smokers), in line with the smoking cessation data reported both in the literature and observed in our own smoking cessation study. Considering that smoking cessation is well established to decrease the risk of the main diseases attributable to smoking (*e.g.*, CVD, COPD, cancer), the findings on *IQOS* likely translate further into a reduced risk for these diseases compared to continued smoking. Some epidemiological data, published recently by independent scientists, corroborate these statements. A literature review was conducted to summarize published data on the associations between HTP use and risk of CVD, stroke, COPD, cancer, and diabetes.

4.3.2. Methods

PMP S.A. searched Embase, PubMed, and Scopus for observational studies published from 2020 to February 2023 and comparing the risk of smoking-related diseases between THS users and cigarette smokers and non-smokers. Since epidemiological studies rarely distinguish between HTP types, all relevant studies evaluating HTP in general were included. The quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools [23]. Evidence from the included studies was categorized as weak (cross-sectional studies scoring 0-6 points), moderate (cross-sectional studies scoring 7-8 points or cohort studies scoring 0-5 points), strong (cohort studies scoring 6-8 points), and very strong level of evidence (cohort studies scoring 9-11 points). To minimize the impact of major study limitations, conclusions in this report were based on studies with at least moderate level of evidence. The review followed the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [24].

4.3.3. Results

Results are presented in Appendix 7-a08-ind-health-lit-review-results.

4.3.4. Conclusion

None of the included studies was conducted in the US, as the prevalence of HTP use is very low in the US (<0.5%). However, while prevalence estimates may not be generalizable to the U.S. population, results from association studies should be generalizable. Thus, the findings of the review can be contextualized to the general U.S. adult population.

The findings of this review, mainly based on a large cohort study from South Korea, demonstrated that switching from CC to NNTP (THS and electronic cigarettes vs continuous CC smoking) is associated with a lower risk of CVD and stroke. The health benefits of switching from CC to NNTP

regarding COPD risk appeared to wane over time. However, among COPD patients, switching from CC to THS was associated with substantial improvement in health outcomes, including decreased COPD exacerbations and COPD assessment test scores, irrespective of years since switching. The follow-up period of the available data on NNTP use and lung cancer risk was too short to enable a thorough assessment of the benefits of switching from CC to NNTP in the population.

5. CLINICAL POPULATION HEALTH – LITERATURE REVIEW

5.1. Introduction

Data from individual participant studies have demonstrated a lower risk of smoking-related diseases (SRDs), including CVD and COPD, in CC smokers who switch to THS as compared to those who continue to smoke CC (see section 4.3). However, there is a need to also evaluate whether the improvements in health outcomes associated with THS use at the individual level extend to the population level. Since PMP S.A. does not have internal data on THS use and population-level health outcomes in the US, a literature review was conducted to summarize published data on the population health impacts of THS use in comparison to CC smoking. Given that studies assessing the impact of HTP use on population health outcomes do not distinguish between HTP variants (*e.g.*, *IQOS*, PLOOM), relevant studies evaluating HTPs in general were included in the review.

5.2. Methods

PMP S.A. searched the Embase, PubMed, and Scopus databases for studies published from 2020 to February 2023 and assessing the impacts of HTP use on health outcomes at the population level. Given the low prevalence of HTP use in the US (<0.5%), data from non-US-based studies were also included. Outcomes assessed included (i) initiation and prevalence of CC in the population, (ii) CC consumption, quit attempts, and cessation, (iii) incidence of SRDs (*e.g.*, CVD, stroke, COPD, cancer) and smoking-attributable deaths (SADs), (iv) life-years (*e.g.*, life-years lost [LYL] due to SRDs, life-years saved, and quality-adjusted life-years), and (v) healthcare cost and hospitalizations due to SRDs. PMP S.A. used the updated Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [25] to assess the quality of the included studies. Level of evidence was classified as weak (scores < 5), moderate (scores 5-6), and strong (scores 7-8) based on the CHEERS scores. The review followed the updated PRISMA guideline [24].

5.3. Results

Results are presented in Appendix 7-a09-pop-health-lit-review-results.

5.4. Conclusion

Even though none of the included studies were conducted in the United States, the results of the included studies are consistent with those from the U.S.-based studies published before the literature search period, which showed that THS use would result in significant decline in CC prevalence, all-cause mortality, and SADs and improved life expectancy [26-28].

The findings of the review thus suggest that THS use (*vs*. CC smoking only) would result in significant reduction in the prevalence of CC smoking and SADs and improvement in life expectancy. These findings indicate that the improvements in health outcomes reported by individual-level characteristic data extend to the population level.

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