PMI RESEARCH & DEVELOPMENT

Study Protocol

P1-PMC-01-JP

Study Title:	An observational cohort study in Japan to assess the patterns of product use and changes in health outcomes associated with the use of HeatSticks with the IQOS tobacco heating system
Study Name	LYFE (Lifestyle research for Your Future Environment)
Short Title:	Japanese Post-Market Cohort Study
EUDRACT Number:	eudract_number
Product Name:	IQOS
Study Number:	P1-PMC-01-JP
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchatel
Version Number:	Final Version 6.0
Revision Date:	September 13th, 2017
Authors:	[redacted], PhD, Study Scientist [redacted] MEng, MSc, Study Statistician [redacted] MD, Medical Safety Officer

Summary of changes
Study Protocol
P1-PMC-01-JP

	Protocol Version	Protocol Date
Current protocol	Final Version 6.0	September 13th, 2017
Second amended protocol	Final Version 5.0	March 23rd, 2017
First amended protocol	Final Version 4.0	July 27th, 2016
Original protocol	Final Version 3.0	December 4th, 2015

INTRODUCTION

The main purpose of this summary of changes is:

To summarize the main changes between the study protocol P1-PMC-01-JP (Final Version 5.0) dated March 23rd, 2017 and its updated version (Final Version 6.0) dated September 13th, 2017. The major changes in this amendment are Table 4 Current Behaviors Definitions, Table 5 Event Definition, and percent consumption of tobacco products in section 12.2.1 Product use.

Additionally, clarifications to the protocol Final Version 6.0 are provided.

More precise details on the protocol sections changed are provided. For identification of the changes, the previous and the amended texts are provided. The new text has been highlighted in bold (e.g., **new text**) and deleted text has been crossed out (e.g., ~~deleted text~~).

Section	Changes
Cover Page	Replaced [redacted] with [redacted], as Study Scientist

Section	Changes
	Reason for Change: Changes to the study team
Cover Page	Replaced [redacted] with [redacted] **MEng, MSc** as Study Statistician ***Reason for Change:*** Changes to the study team.
Cover Page	Replace [redacted] with [redacted] as Medical Safety Officer ***Reason for Change:*** Changes to the study team
Synopsis – Participant Identification and Enrollment	***Amended Text:*** **All IQOs participants will fill their baseline questionnaire at time of entry. After baseline CASI, the next CASI is dependent on the exposure time to IQOS. IQOS participants will not complete a CASI if their baseline CASI is within the timeframe (± 4 weeks of the next required CASI).** ~~Since the length of IQOS use drives the timing of the CASI administration, for those IQOS users enrolling into the study with less than 4 weeks between the 'baseline domain" and the next CASI "follow-up domain", the "baseline domain' will correspond to the subsequent CASI "follow-up domain".~~ ***Old Text:*** Since the length of IQOS use drives the timing of the CASI administration, for those IQOS users enrolling into the study with less than 4 weeks between the 'baseline domain" and the next CASI "follow-up domain", the "baseline domain' will correspond to the subsequent CASI "follow-up domain". ***Reason for Change:*** To clarify IQOS participants CASI administration procedure.
Synopsis-Exclusion Criteria	***Amended Text:*** ***<u>Exclusion Criteria:</u>*** • Tobacco industry employees • Employed by the Sponsor, CRO or Clinical Site

Section	Changes
	• For IQOS users: - More than 12 months of IQOS use • For Former Smokers: - Is not currently using CC - Is not currently using IQOS HeatSticks, and - Has used at least 100 CC and/or IQOS HeatSticks in their lifetime • ~~For never-smokers:~~ ~~- Is not currently using CC~~ ~~- Is not currently using IQOS HeatSticks, and~~ ~~- Has not used at least 100 CC and/or IQOS HeatSticks in their lifetime~~ ***Old Text:*** ***<u>Exclusion Criteria:</u>*** • Tobacco industry employees • Employed by the Sponsor, CRO or Clinical Site • For IQOS users: - More than 12 months of IQOS use • For Former Smokers: - Is not currently using CC - Is not currently using IQOS HeatSticks, and - Has used at least 100 CC and/or IQOS HeatSticks in their lifetime • For never-smokers: - Is not currently using CC - Is not currently using IQOS HeatSticks, and - Has not used at least 100 CC and/or IQOS HeatSticks in their lifetime ***Reason for Change:*** The sub-clinical study was discontinued as documented in the previous amendment and no never smokers was

Section	Changes
	enrolled in the study anymore, this section was not updated by error.
Synopsis – Sample Size	***Amended Text:*** ~~The sample size and the study duration is sufficient to detect with more than 80% power an incidence of cardiovascular disease at the year 4 analysis based on an occurrence of 882 cases in 220965 person years in smokers and at the year 5 analysis based on an occurrence of 251 cases in 86383 person years in never smokers as reported in Iso et al (5). The CC smokers will serve as a benchmark for the background incidence in smokers.~~ ~~This incidence will be calculated at the final analysis with a precision of 0.239% based on the latter assumed incidence in smokers and using a Clopper-Pearson confidence interval.~~ This sample size is ~~also~~ sufficient to detect for the trajectories analysis, using the assumption of 20% participants switching to another group, an incidence of 1% of participants switching with a precision of less than 1.32% after one year using the first wave at the first analysis and up to 0.62% the final analysis. ***Old Text:*** The sample size and the study duration is sufficient to detect with more than 80% power an incidence of cardiovascular disease at the year 4 analysis based on an occurrence of 882 cases in 220965 person-years in smokers and at the year 5 analysis based on an occurrence of 251 cases in 86383 person-years in never-smokers as reported in Iso et al (5). The CC smokers will serve as a benchmark for the background incidence in smokers. This incidence will be calculated at the final analysis with a precision of 0.239% based on the latter assumed incidence in smokers and using a Clopper-Pearson confidence interval. This sample size is also sufficient to detect for the trajectories analysis, using the assumption of 20% participants switching to another group, an incidence of 1% of participants switching with a precision of less than 1.32% after one year using the first wave at the first analysis and up to 0.62% the final analysis.

<table>
<tr><th>Section</th><th>Changes</th></tr>
<tr><td></td><td>Reason for Change: To base the sample size only on measuring the transitions</td></tr>
<tr><td>List of Abbreviations and Definitions of Terms</td><td>Replace the old list with the new one

Reason for Change: To align the analysis strategy as described in the SAP version 2.0 (31 August 2017)</td></tr>
<tr><td>4.1.2 Enrollment</td><td>Amended Text:

All IQOs participants will fill their baseline questionnaire at time of entry. After baseline CASI, the next CASI is dependent on the exposure time to IQOS. IQOS participants will not complete a CASI if their baseline CASI is within the timeframe (± 4 weeks of the next required CASI). ~~Since the length of IQOS use drives the timing of the CASI administration, for those IQOS users enrolling into the study with less than 4 weeks between the 'baseline domain" and the next CASI "follow-up domain", the "baseline domain' will correspond to the subsequent CASI "follow-up domain".~~

Old Text:
Since the length of IQOS use drives the timing of the CASI administration, for those IQOS users enrolling into the study with less than 4 weeks between the 'baseline domain" and the next CASI "follow-up domain", the "baseline domain' will correspond to the subsequent CASI "follow-up domain".

Reason for Change: To clarify IQOS participants CASI administration procedure.</td></tr>
<tr><td>5.1.1 Inclusion Criteria</td><td>Amended Text:

Table 1 Inclusion Criteria
<table><tr><th>Inclusion Criteria</th><th>~~Rationale~~</th></tr><tr><td>1. Adults legally authorized to buy tobacco products in Japan (20 years of age)</td><td>~~Legal~~</td></tr><tr><td>2. Japanese</td><td>~~Effect~~</td></tr></table></td></tr>
</table>

Section	Changes	
	3. Participant is able to understand the information provided in the informed consent form (ICF).	~~Administrative~~
	4. Signed informed consent form	~~Administrative~~
	5. Willing to participate in the study and has access to the internet	~~Administrative~~
	6. For IQOS users: o Is currently using IQOS HeatSticks o Has used at least 100 IQOS HeatSticks in their lifetime; and o Has used IQOS HeatSticks for at least 2 months NOTE: The use of IQOS HeatSticks defines the user as an IQOS user, regardless of other tobacco or nicotine product use	~~Effect~~
	7. For CC smokers: o Is currently using CC o Is not currently using IQOS HeatSticks, and o Has used at least 100 CC in their lifetime	~~Effect~~
	Old Text:	
	Table 2 Inclusion Criteria	
	Inclusion Criteria	**Rationale**
	1. Adults legally authorized to buy tobacco products in Japan (20 years of age)	Legal
	2. Japanese	Effect
	3. Participant is able to understand the information provided in the informed consent form (ICF).	Administrative
	4. Signed informed consent form	Administrative
	5. Willing to participate in the study and has access to the internet	Administrative
	6. For IQOS users: o Is currently using IQOS HeatSticks	Effect

<table>
<tr><th>Section</th><th>Changes</th></tr>
<tr><td></td><td>

Has used at least 100 IQOS HeatSticks in their lifetime; and
Has used IQOS HeatSticks for at least 2 months

NOTE: The use of IQOS HeatSticks defines the user as an IQOS user, regardless of other tobacco or nicotine product use
7. For CC smokers:

Is currently using CC
Is not currently using IQOS HeatSticks, and
Has used at least 100 CC in their lifetime

Effect

Reason for Change: To remove the rational, as it is not relevant for the study
</td></tr>
<tr><td>5.1.2 Exclusion Criteria</td><td>
Amended Text:

Table 3 Exclusion Criteria
<table>
<tr><th>Exclusion Criteria</th><th><s>Rationale</s></th></tr>
<tr><td>8. Tobacco industry employees</td><td><s>Legal</s></td></tr>
<tr><td>9. Employed by the Sponsor, CRO or Clinical Site</td><td><s>Legal</s></td></tr>
<tr><td>10. For IQOS users:
o More than 12 months of IQOS use</td><td><s>Effect</s></td></tr>
<tr><td>11. For former smokers:
o Is not currently using CC
o Is not currently using IQOS HeatSticks, and
o Has used at least 100 CC and/or IQOS HeatSticks in their lifetime</td><td><s>Effect</s></td></tr>
<tr><td><s>12. For never smokers:
o Is not currently using CC
o Is not currently using IQOS HeatSticks, and
o Has not used more than 100 CC and/or</s></td><td><s>Effect</s></td></tr>
</table>
</td></tr>
</table>

Section	Changes
	~~IQOS HeatSticks in their lifetime~~ **Table 4 Exclusion Criteria** **Exclusion Criteria** / **Rationale** 13. Tobacco industry employees — Legal 14. Employed by the Sponsor, CRO or Clinical Site — Legal 15. For IQOS users: o More than 12 months of IQOS use — Effect 16. For former smokers: o Is not currently using CC o Is not currently using IQOS HeatSticks, and o Has used at least 100 CC and/or IQOS HeatSticks in their lifetime — Effect 17. For never-smokers: o Is not currently using CC o Is not currently using IQOS HeatSticks, and o Has not used more than 100 CC and/or IQOS HeatSticks in their lifetime — Effect ***Reason for Change:*** The sub-clinical study was discontinued as documented in the previous amendment and no never smokers was enrolled in the study anymore, this section was not updated by error. The rational was removed, as it is not relevant for the study.
5.3 Discontinuation of Participants from the Study	***Amended Text:*** • The Sponsor terminates the study. If the Sponsor decides to prematurely terminate the study, the participants **and the IRB** will be promptly informed. ~~The head of the medical institution will report this fact and the reason in writing to the IRB.~~ • ***Amended Text:***

<table>
<tr><th>Section</th><th>Changes</th></tr>
<tr><td></td><td>

- The Sponsor terminates the study. If the Sponsor decides to prematurely terminate the study, the participant will be promptly informed. The head of the medical institution will report this fact and the reason in writing to the IRB.

Reason for Change: To clarify that reporting is not the responsibility of the head of institution
</td></tr>
<tr><td>12.1.1 Definitions</td><td>

Amended Text:

Current behavior at MT_i (i being ST in months), will be denoted CB_i and will be defined as described in Table 4. **Additional CB_i or sub-category CB_i may be added during data analysis which will be specified in the SAP.**

Table 5 Current Behaviors Definitions (percentages defined in 12.2)

CB(i)	Notation at MT(i)	Definition
Daily THS	Daily THS_i	• THS ≥ 1/day, • each OTP <1/day, • CC < 1/day
Daily CC Smoker	Daily CC_i	• THS = 0/day, • CC ≥ 1/day, • each OTP < 1/day
Daily OTP user	Daily OTP_i	• THS = 0/day, • 0 ≤ CC < 1/day, • At least one OTP ≥ 1/day
Dual THS – CC	DU_THS_CC_i	• THS ≥ 1/day, • CC ≥ 1/day, • each OTP <1/day
Dual THS – OTP	DU_THS_OTP_i	• THS ≥ 1/day, • At least one OTP≥ 1/day,

</td></tr>
</table>

Section	Changes

THS – CC-OTP	PU_THS_CC_OTP$_i$	• CC < 1/day • THS ≥ 1/day, • at least one OTP ≥ 1/day, • CC≥ 1/day
Occ THS	Occ_ THS$_i$	• THS < 1/day, • all OTP <1/day, • CC < 1/day
Occ THS-CC-OTP	Occ_THS_CC-OTP$_i$	• THS < 1/day, • CC ≥ 1/day • at least one OTP ≥ 1/day
Occ THS-CC	Occ_THS_ CC$_i$	• THS < 1/day, • CC ≥ 1/day • all OTP < 1/day
Occ THS-OTP	Occ_THS_ OTP$_i$	• THS < 1/day, • at least one OTP ≥ 1/day • CC < 1/day
Non User/Smoker	Non_Smoker$_i$	• THS = 0/day, • CC = 0/day, • each OTP = 0/day,
Occ User/Smoker	Occ_Smoker$_i$	• THS = 0/day, • 0 ≤ CC < 1/day, • each OTP must be: 0 ≤ OTP <1/day • not (CC=0 and OTPs=0)

Note: OTP includes other Heat-not-Burn products (HnB) except THS
Note: ePD is considered as one of the other tobacco product (OTP) when we determine the CB.

~~Table 6 Current Behaviors Definitions (percentages~~

Section	Changes

~~defined in 12.2)~~

~~CB(i)~~	~~Notation at MT(i)~~	~~Definition~~	~~Use Subcategory~~
~~Exclusive IQOS~~	~~Excl_IQOS~~	~~• IQOS ≥ 1/day, • each OTP <1/day, • CC < 1/day~~	~~%IQOS =100% %IQOS < 100%~~
~~Dual IQOS – CC~~	~~DU_IQOS_CC~~	~~• IQOS ≥ 1/day, • CC ≥ 1/day, • each OTP <1/day~~	~~%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%~~
~~Dual IQOS – OTP~~	~~DU_IQOS_OTP~~	~~• IQOS ≥ 1/day, • one OTP≥ 1/day, • CC < 1/day • each other OTP < 1/day~~	~~%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%~~
~~Poly IQOS – CC OTP~~	~~PU_IQOS_CC~~	~~• IQOS ≥ 1/day, • at least one OTP ≥ 1/day, • CC≥ 1/day~~	~~%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%~~
~~Poly IQOS – OTP~~	~~PU_IQOS_OTP~~	~~• IQOS ≥ 1/day, • at least two OTP ≥ 1/day, • CC < 1/day~~	~~%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%~~
~~Infrequent IQOS only~~	~~Inf_IQOS~~	~~• IQOS < 1/day, • each OTP <1/day, • CC < 1/day~~	~~None (percentiles will be examined and definitions may be added)~~
~~Infrequent IQOS CC~~	~~Inf_IQOS_CC~~	~~• IQOS < 1/day, • CC ≥ 1/day~~	~~none~~
~~Infrequent IQOS OTP~~	~~Inf_IQOS_OTP~~	~~• IQOS < 1/day, • at least one OTP ≥ 1/day, • CC < 1/day~~	~~none~~
~~Non User/Smoker~~	~~Non_Smoker~~	~~• IQOS = 0/day, • CC = 0/day,~~	

Section	Changes

~~• each OTP = 0/day,~~

~~**Infrequent User/Smoker**~~	~~Inf_Smoker_i~~	~~• IQOS = 0/day,~~ ~~• 0 ≤ CC < 1/day,~~ ~~• each OTP must be: 0 ≤ OTP <1/day~~ ~~• not CC=0 and OTPs=0~~
~~**CC Smoker**~~	~~CC_i~~	~~• IQOS = 0/day,~~ ~~• CC ≥ 1,~~ ~~• each OTP < 1/day~~
~~**CC OTP**~~	~~CC_OTP_i~~	~~• IQOS = 0/day,~~ ~~• CC ≥ 1,~~ ~~• one OTP ≥ 1~~
~~**OTP user**~~	~~OTP_i~~	~~• IQOS = 0/day,~~ ~~• 0 ≤ CC < 1/day,~~ ~~• one OTP ≥ 1/day~~

Old Text:

Current behavior at MT_i (i being ST in months), will be denoted CB_i and will be defined as described in Table 4:

Table 7 Current Behaviors Definitions (percentages defined in 12.2)

CB(i)	Notation at MT(i)	Definition	Use Subcategory
Exclusive IQOS	$Excl\_IQOS_i$	• IQOS ≥ 1/day, • each OTP <1/day, • CC < 1/day	%IQOS =100% %IQOS < 100%
Dual IQOS - CC	$DU\_IQOS\_CC_i$	• IQOS ≥ 1/day, • CC ≥ 1/day, • each OTP <1/day	%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%

Section	Changes			
	Dual IQOS - OTP	DU_IQOS_ OTP_i	• IQOS ≥ 1/day, • one OTP≥ 1/day, • CC < 1/day • each other OTP < 1/day	%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%
	Poly IQOS – CC-OTP	PU_IQOS_C C_i	• IQOS ≥ 1/day, • at least one OTP ≥ 1/day, • CC≥ 1/day	%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%
	Poly IQOS - OTP	PU_IQOS_O TP_i	• IQOS ≥ 1/day, • at least two OTP ≥ 1/day, • CC < 1/day	%IQOS ≥ 70% 30% < %IQOS < 70% %IQOS ≤ 30%
	Infrequent IQOS only	Inf_ $IQOS_i$	• IQOS < 1/day, • each OTP <1/day, • CC < 1/day	None (percentiles will be examined and definitions may be added)
	Infrequent IQOS-CC	Inf_IQOS_ CC_i	• IQOS < 1/day, • CC ≥ 1/day	none
	Infrequent IQOS-OTP	Inf_IQOS_ OTP_i	• IQOS < 1/day, • at least one OTP ≥ 1/day, • CC < 1/day	none
	Non User/Smoker	Non_Smoker $_i$	• IQOS = 0/day, • CC = 0/day, • each OTP = 0/day,	
	Infrequent User/Smoker	Inf_ $Smoker_i$	• IQOS = 0/day, • 0 ≤ CC < 1/day, • each OTP must be: 0 ≤ OTP <1/day • not CC=0 and OTPs=0	
	CC Smoker	CC_i	• IQOS = 0/day, • CC ≥ 1, • each OTP < 1/day	

<table>
<tr><th>Section</th><th>Changes</th></tr>
<tr><td></td><td>
<table>
<tr><td>CC-OTP</td><td>CC_OTP_i</td><td>• IQOS = 0/day,
• CC ≥ 1,
• one OTP ≥ 1</td></tr>
<tr><td>OTP user</td><td>OTP_i</td><td>• IQOS = 0/day,
• 0 ≤ CC < 1/day,
• one OTP ≥ 1/day</td></tr>
</table>

Reason for Change: To clarify product use category and to align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
</td></tr>
<tr><td>12.1.1 Definitions</td><td>
Amended Text:

Events assessed at MT_i (i being ST in months), will be denoted Current Events (CE_i) and will be defined as described in Table 5. Additional CE_i may be added during data analysis which will be specified in the SAP.

Table 8. Events Definition

<table>
<tr><th>CE_i</th><th>Notation at MT(i)</th><th>Definition</th></tr>
<tr><td><u>Switching</u></td><td></td><td></td></tr>
<tr><td>First Switch from Initial Behavior to another Behavior</td><td>S_i</td><td>CBi≠CBi-1 | for any j<i CBj=IB</td></tr>
<tr><td><u>Initiation</u></td><td></td><td></td></tr>
<tr><td>CC Initiation</td><td>I_{CCi}</td><td>CPD_i≥1| for any j<i CPDj<1
Has not used 100 CC in their lifetime</td></tr>
<tr><td>THS Initiation</td><td>I_{THSi}</td><td>$THSPD_i$≥1| for any j<i THSPDj<1
Has not used 100 THS (heatsticks) products in their lifetime</td></tr>
<tr><td>THS Initiation by brand</td><td>$I_{THSi\_brand\ name}$</td><td>$THSPD_i$≥1(stratified by brand)
Has not used 100 THS (HeatSticks) products in their lifetime</td></tr>
</table>
</td></tr>
</table>

Section	Changes		
	OTP Initiation	I_{OTPi}	$OTPD_i \geq 1$ Has used OTP less than daily used or not used (wave 1) Has not ever used OTP or not used regularly (wave 2 and following waves) Has not used 100 Ploom capsules in their lifetime (Wave2 and following waves) Has not used 100 Glo Neostiks® in their life (Wave2 and following waves)
	CC Re-Initiation	$Re\text{-}I_{CCi}$	$CPD_i \neq 0 \mid CPD_k = 0$, for any k in [j; i-1] where i and j differ by more than 12 months.
	THS Re-Initiation	$Re\text{-}I_{THSi}$	$THSPD_i \neq 0 \mid THSPD_k = 0$, for any k in [j; i-1] where i and j differ by more than 12 months.
	Quitting attempt/cessation/relapse		
	Quit Attempt	QA_i	A quit attempt is defined according to the participant's answer to the intention to stop and quit attempt questionnaire at MT(i)
	CC Cessation	$CC\text{-}Cess_i$	$CPD_k = 0 \mid CPD_j \neq 0$, for any k in (j; i] where i and j differ by more than 12 months. Has used at least 100 CCs in their lifetime
	THS Cessation	$THS\text{-}Cess_i$	$THSPD_k = 0 \mid THSPD_j \neq 0$, for any k in (j; i] where i and j differ by more than 12 months. Has used at least 100 THS (heatsticks) in their lifetime
	OTP Cessation	$OTP\text{-}Cess_j$	$OTPD_k = 0 \mid OTPD_j \neq 0$, for any k in (j; i] where i and j differ by more than 12 months. Has used OTP daily (wave 1) Has used at least 100 heatsticks in their lifetime (wave 1) Has used regularly OTP (wave 2 and following waves) Has used at least 100 other HnB

Section	Changes		
			products (except THS) in their lifetime (wave 2 and following waves)
	CC Relapse	$CCrel_i$	$CPD_i \neq 0 \mid CPD_k=0$, for any k in [j; i-1] where i and j differ by strictly less than 12 months.
	THS Relapse	$THSrel_i$	$THSPD_i \neq 0 \mid THSPD_k=0$, for any k in [j; i-1] where i and j differ by strictly less than 12 months.
	OTP Relapse	$OTPrel_i$	$OTPD_i \neq 0 \mid OTPD_k=0$, for any k in [j; i-1] where i and j differ by strictly less than 12 months.
	Consumption changes		
	CC Increase	$CCinc_i$	$(CPD_i-CPD_{i-1})/ CPD_{i-1} \geq 10\%$
	CC Decrease	$CCdec_i$	$(CPD_{i-1}-CPD_i)/ CPD_{i-1} \geq 10\%$
	THS Increase	$THSinc_i$	$(THSPD_i-THSPD_{i-1})/ THSPD_{i-1} \geq 10\%$
	THS Decrease	$THSdec_i$	$(THSPD_{i-1}-THSPD_i)/ THSPD_{i-1} \geq 10\%$
	Product uptake		
	THS uptake	$THSuptake_i$	The new THS product one participant uses at specific timepoint and was not used in the previous timepoint based on product use questionnaire $THSPD_i \neq 0$, $THSPD_{i-1}=0$
	HnB uptake	$HnBuptake_i$	The new HnB products one participant uses at specific timepoint and was not used in the previous timepoint based on product use questionnaire $HnBPD_i \neq 0$, $HnBPD_{i-1}=0$
	Note: CPD_i, $THSPD_i$, $HnBPD_i$ and $OTPD_i$ are defined in section 12.2.1 **Note: The CC Initiation is defined for THS user cohort participants; the THS Initiation is defined for CC smoker cohort participants.** ~~Table 9. Events Definition~~		

Section	Changes

~~CE_i~~	~~Notation at MT(i)~~	~~Definition~~
~~CC Increase~~	~~$Cinc_i$~~	~~$(CPD_i - CPD_{i-1})/ CPD_{i-1} \geq 10\%$~~
~~CC Decrease~~	~~$Cdec_i$~~	~~$(CPD_{i-1} - CPD_i)/ CPD_{i-1} \geq 10\%$~~
~~IQOS Increase~~	~~$Iinc_i$~~	~~$(iPD_i - iPD_{i-1})/ iPD_{i-1} \geq 10\%$~~
~~IQOS Decrease~~	~~$Idec_i$~~	~~$(iPD_{i-1} - iPD_i)/ iPD_{i-1} \geq 10\%$~~
~~e-cigarettes Increase~~	~~$Einc_i$~~	~~$(ePD_i - ePD_{i-1})/ ePD_{i-1} \geq 10\%$~~
~~e-cigarettes Decrease~~	~~$Edec_i$~~	~~$(ePD_{i-1} - ePD_i)/ ePD_{i-1} \geq 10\%$~~
~~Other Products Increase~~	~~$Oinc_i$~~	~~$(oPD_i - oPD_{i-1})/ oPD_{i-1} \geq 10\%$~~
~~Other Products Decrease~~	~~$Odec_i$~~	~~$(oPD_{i-1} - oPD_i)/ oPD_{i-1} \geq 10\%$~~
~~Quit Attempt~~	~~QA_j~~	~~A quit attempt is defined according to the participant's answer to the intention to quit and quit attempt questions at MT(i)~~
~~Cessation~~	~~$Cess_j$~~	~~$0_{j-i}|0'_{i-j}$, where i and j are two different records of measurement time.~~ ~~Person who meets 1 or more of the following cessation types:~~ ~~1) Cessation from smoking cigarettes (CC)~~ ~~• Has used at least 100 cigarettes (CC) in their lifetime~~ ~~• Is not currently using combustible cigarette (CC) and stopped using CC since the previous visit~~ ~~• Has ≥ 12 months with no CC product use~~ ~~2) Cessation from Tobacco Products~~ ~~• Has used at least 100 cigarettes (CC) or 100 IQOS HeatSticks in their lifetime~~ ~~•Is not currently using any tobacco products and stopped using tobacco products since the previous visit~~

Section	Changes

~~• Has ≥ 12 months with no tobacco product use~~

~~3) Cessation from IQOS HeatSticks~~

~~• Has used at least 100 IQOS HeatSticks in their lifetime~~

~~• Is not currently using IQOS HeatSticks and stopped using IQOS since the previous visit~~

~~• Has ≥ 12 months with no IQOS product use~~

~~**CC Relapse**~~	~~$Crel_j$~~	~~$C_{j-i}\|C'_{i-j}$, where i and j are two different records of measurement time.~~
~~**IQOS Relapse**~~	~~$Irel_j$~~	~~$I_{j-i}\|I'_{i-j}$, where i and j are two different records of measurement time.~~

~~Note: CPDi iPDi are defined in section 12.2.1~~

Old Text:

Events assessed at MT_i (i being ST in months), will be denoted Current Events (CE_i) and will be defined as described in Table 5:

Table 10. Events Definition

CE_i	Notation at MT(i)	Definition
CC Increase	$Cinc_i$	$(CPD_i\text{-}CPD_{i-1})/ CPD_{i-1}\geq 10\%$
CC Decrease	$Cdec_i$	$(CPD_{i-1}\text{-}CPD_i)/ CPD_{i-1}\geq 10\%$
IQOS Increase	$Iinc_i$	$(iPD_i\text{-}iPD_{i-1})/ iPD_{i-1}\geq 10\%$
IQOS Decrease	$Idec_i$	$(iPD_{i-1}\text{-}iPD_i)/ iPD_{i-1}\geq 10\%$
e-cigarettes Increase	$Einc_i$	$(ePD_i\text{-}ePD_{i-1})/ ePD_{i-1}\geq 10\%$
e-cigarettes Decrease	$Edec_i$	$(ePD_{i-1}\text{-}ePD_i)/ ePD_{i-1}\geq 10\%$
Other Products	$Oinc_i$	$(oPD_i\text{-}oPD_{i-1})/ oPD_{i-1}\geq 10\%$

Section	Changes		
	Increase		
	Other Products Decrease	$Odec_i$	$(oPD_{i-1}-oPD_i)/ oPD_{i-1}\geq 10\%$
	Quit Attempt	QA_j	A quit attempt is defined according to the participant's answer to the intention to quit and quit attempt questions at MT(i)
	Cessation	$Cess_j$	$0_{j<i}\|0'_{k<j}$, where i and j are two different records of measurement time. Person who meets 1 or more of the following cessation types: 1) Cessation from smoking cigarettes (CC) • Has used at least 100 cigarettes (CC) in their lifetime • Is not currently using combustible cigarette (CC) and stopped using CC since the previous visit • Has ≥ 12 months with no CC product use 2) Cessation from Tobacco Products • Has used at least 100 cigarettes (CC) or 100 IQOS HeatSticks in their lifetime •Is not currently using any tobacco products and stopped using tobacco products since the previous visit •Has ≥ 12 months with no tobacco product use 3) Cessation from IQOS HeatSticks • Has used at least 100 IQOS HeatSticks in their lifetime • Is not currently using IQOS HeatSticks and stopped using IQOS since the previous visit • Has ≥ 12 months with no IQOS product use
	CC Relapse	$Crel_j$	$C_{j<i}\|C'_{k<j}$, where i and j are two different records of measurement time.
	IQOS Relapse	$Irel_j$	$I_{j<i}\|I'_{k<j}$, where i and j are two different records of measurement time.
	Note: CPDi iPDi are defined in section 12.2.1		
	Reason for Change: To clarify event definition and to align the analysis strategy as described in the SAP version 2.0 (31 August 2017)		

Section	Changes
12.1.3 Handling of Missing Values and of Values outside the Detection Limits	***Amended Text:*** **Product use at MT(i) if missing, can be interpolated by averaging across neighboring product use at MT(i-1) and MT(i+1). There will be no imputation for missing CE(i). Only the reported CE(i) will be used in the analysis.** ~~CB_i may, in the case of intermediate missing data, be derived by averaging across neighboring ie non missing MT_i's ie $CB_{j<i}$ and $CB_{j>i}$.~~ ***Old Text:*** CB_i may, in the case of intermediate missing data, be derived by averaging across neighboring ie non missing MT_i's ie $CB_{j<i}$ and $CB_{j>i}$. ***Reason for Change:*** To clarify procedures for handling missing product use data and CE(i) and to align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
12.2.1 Product use	***Amended Text:*** **Percent consumption of THS, CC, OTP, e-cig and HnB, respectively, with respect to THSPD, CPD, ePD and OTPD will be calculated at MT_i based on THS Tobacco Sticks, CC, e-cigarettes and OTP reported in Product use questionnaire as:** $$\%THS_i = 100 * \frac{\mathrm{THSPD_i}}{THSPD_i + CPD_i + OTPD_i}$$ $$\%CC_i = 100 * \frac{\mathrm{CPD_i}}{THSPD_i + CPD_i + OTPD_i}$$ $$\%OTP_i = 100 * \frac{\mathrm{OTPD_i}}{THSPD_i + CPD_i + OTPD_i}$$ $$\%e-cig_i = 100 * \frac{\mathrm{ePD_i}}{THSPD_i + CPD_i + OTPD_i}$$ $$\%HnB_i = 100 * \frac{\mathrm{HnBD_i}}{THSPD_i + CPD_i + OTPD_i}$$

Section	Changes
	where CPD_i is the average daily Cigarettes consumption at MT_i, $THSPD_i$ is the average daily THS consumption (Marlboro Heatsticks with iQOS device), $OTPD_i$ is the average daily other tobacco products consumption, $HnBPD_i$ is the average daily HnB products consumption and ePD_i is the average daily e-cigarette products consumption, which is part of the other tobacco products consumption will also be calculated. **Additional percent consumption of tobacco products may be added and will specified in the SAP.** ~~Percent consumption of IQOS with respect to all tobacco products will be defined at MT_i based on Product use questionnaire at MT_i as:~~ ~~$\%IQOS = 100 * \frac{iPD_i}{\Sigma(iPD_i + CPD_i + ePD_i + oPD_i)}$~~ ~~Percent consumption of IQOS with respect to IQOS and CC (excluding all other tobacco products) will be calculated at MT_i based on IQOS Tobacco Sticks and CC reported in Product use questionnaire as:~~ ~~$\%IQOS2_i = 100 * \frac{iPD_i}{iPD_i + CPD_i}$~~ ~~In a similar way, $\%CPD_i$, $\%CPD2_i$, $\%OTP_i$ (respectively percent consumption of CC with respect to all tobacco products, CC with respect to IQOS and CC or Other Tobacco Products) will be calculated at MT_i based on the two formulas above using the corresponding product as the numerator.~~ ***Old Text:*** Percent consumption of IQOS with respect to all tobacco products will be defined at MT_i based on Product use questionnaire at MT_i as: $\%IQOS = 100 * \frac{iPD_i}{\Sigma(iPD_i + CPD_i + ePD_i + oPD_i)}$

Section	Changes
	Percent consumption of IQOS with respect to IQOS and CC (excluding all other tobacco products) will be calculated at MT_i based on IQOS Tobacco Sticks and CC reported in Product use questionnaire as: $\%IQOS2_i = 100 * \frac{iPD_i}{iPD_i + CPD_i}$ In a similar way, $\%CPD_i$, $\%CPD2_i$, $\%OTP_i$ (respectively percent consumption of CC with respect to all tobacco products, CC with respect to IQOS and CC or Other Tobacco Products) will be calculated at MT_i based on the two formulas above using the corresponding product as the numerator. ***Reason for Change:*** To clarify the definitions of percent consumption and to align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
12.2.2 Definition of Product Use Categories	***Amended Text:*** Product use pattern categories over a period ending at MT_i are defined in **Table 4** ~~Table 9~~ above. ***Old Text:*** Product use pattern categories over a period ending at MT_i are defined in Table 9 above. ***Reason for Change:*** To correct the error on table numbering
12.2.3 Sample Size	***Amended Text:*** ~~The sample size and the study duration is sufficient to detect with more than 80% power an incidence of cardiovascular disease at the year 4 analysis based on an occurrence of 882 cases in 220965 person years in smokers and at the year 5 analysis based on an occurrence of 251 cases in 86383 person years in never smokers as reported in Iso et al (5). The CC smokers will serve as a benchmark for the background incidence in smokers.~~

Section	Changes
	~~This incidence will be calculated at the final analysis with a precision of 0.239% based on the latter assumed incidence in smokers and using a Clopper-Pearson confidence interval.~~ This sample size is ~~also~~ sufficient to detect for the trajectories analysis, using the assumption of 20% participants switching to another group, an incidence of 1% of participants switching with a precision of less than 1.32% after one year using the first wave at the first analysis and up to 0.62% the final analysis. ***Old Text:*** The sample size and the study duration is sufficient to detect with more than 80% power an incidence of cardiovascular disease at the year 4 analysis based on an occurrence of 882 cases in 220965 person-years in smokers and at the year 5 analysis based on an occurrence of 251 cases in 86383 person-years in never-smokers as reported in Iso et al (5). The CC smokers will serve as a benchmark for the background incidence in smokers. This incidence will be calculated at the final analysis with a precision of 0.239% based on the latter assumed incidence in smokers and using a Clopper-Pearson confidence interval. This sample size is also sufficient to detect for the trajectories analysis, using the assumption of 20% participants switching to another group, an incidence of 1% of participants switching with a precision of less than 1.32% after one year using the first wave at the first analysis and up to 0.62% the final analysis. ***Reason for Change:*** To base the sample size only on measuring the transitions
12.4.3.2 Product Use Level	***Amended Text:*** Summary tables of use of tobacco and nicotine containing products over time for all enrolled participants will be presented **by Cohort at baseline, by CB (i) group and overall participants at MT (i) at post baseline, including:** • **Mean number of cigarettes smoked (per day) - CPD(i)** • **Mean number of THS Tobacco Sticks used (per day)- THSPD(i)**

Section	Changes
	• **Mean number of Heat-not-Burn products used (per day)- HnBPD(i)** • **Mean number of other cigarettes product used (per day)- OTPD(i)** • **Mean number of e-cigarettes used (per day)- ePD(i)** • **Percent of THS Tobacco Sticks used (%THS)** • **Percent of cigarettes used (%CC)** • **Percent of other cigarettes product used (%OTP)** • **Percent of e-cigarettes used (%e-cig)** • **Percent of Heat-not-Burn products used (%HnB)** **The table will be repeated by sex, age group and enrollment wave in the Study. Tables will also be presented by CB.** **The following figures will be provided at each measurement time.** **- Bar chart of CPD(i), THSPD(i), ePD(i) and OTPD(i) with 95% CI by CB(i-1) and CB(i) group at each measure time MT(i).** **Additional statistical analyses will be specified in the SAP.** ~~Summary tables of use of tobacco and nicotine containing products over time for all enrolled participants will be presented by current behavior group (Table 9: CB) and overall participants at MT, including:~~ ~~• Mean number of cigarettes smoked (per day) over time~~ ~~• Mean number of HeatSticks used (per day)~~ ~~• Mean number of times e-cigarettes used (per day)~~ ~~• Mean number of times other cigarettes product used (per day)~~ ~~The tables will be repeated by sex, age group and enrollment wave in Main Study. Tables may also be presented by IB.~~ ***Old Text:*** Summary tables of use of tobacco and nicotine containing products over time for all enrolled participants will be presented by current behavior group (Table 9: CB) and overall participants at MT, including: • Mean number of cigarettes smoked (per day) over time • Mean number of HeatSticks used (per day)

Section	Changes
	• Mean number of times e-cigarettes used (per day) • Mean number of times other cigarettes product used (per day) The tables will be repeated by sex, age group and enrollment wave in Main Study. Tables may also be presented by IB. ***Reason for Change:*** To align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
12.4.3.3 Product User Patterns	***Amended Text:*** **The table of current behavior, CB(i), at MT(i) will provide the information of product use patterns.** **Summary table of the product use patterns will be evaluated by CE(i) and presented by CB(i) group at MT(i). The product use patterns includes product switching, initiation, re-initiation, quitting attempt, cessation, relapse, consumption changes and product uptake. Additional product transition table will also be provided between CB(i-1) and CB(i). Participants who have tobacco and nicotine product use transitions will be tabulated by previous and current behavior at each study year. The median of time to first product use transitions (behavior switch) will be calculated via Kaplan-Meier estimators and presented by cohort, IB and CB.** **The following outputs will be repeated by sex, age group and enrollment:** **- Descriptive Statistics of Current Behavior** **- Descriptive Statistics of Current Event by Current Behavior** **- Descriptive Statistics of Uptake of HnB Products by Current Behavior** **- Descriptive Statistics of Transitions Across Behaviors** **Additional statistical analyses will be specified in the SAP.** ~~Summary tables of the product use patterns including product (%IQOS(i) and CE(i)) and product switching, uptake of products, rate of transitions and rate of cessation in the Study will be analyzed according to the CB(i) group at MT(i). Summary of current behavior will be presented separately by MT(i).~~

Section	Changes
	~~Product switch is defined as the participant who has different behavior between MT(i) and initial timepoint, which means CB(i) is not equal to CB(0). And product switching over time will be presented as the frequency of product switch across each CB(i) given the original CB(0) by each MT(i).~~ ~~For describing the incidence of products, the descriptive statistics will be provided based on the response of "products currently consumed (Q1)" of product use questionnaire by each MT(i).~~ ~~Participants who have tobacco and nicotine product use transitions will be tabulated and median of time to product use transitions will be presented as well. The overall product use transition table will summarize any CB switch during study regardless of initial behavior, CB (0). One participant could have multiple times to product use transition records if there are more than one CB changes during the whole study. Median time of the product use transition will be provided.~~ ~~The following outputs will be provided:~~ ~~— Uptake of products by CB(i) group and overall at each measurement time MT(i) until the analysis time~~ ~~— Percentage of IQOS product use by CB(i) group and overall at each measurement time MT(i) until the analysis time~~ ~~— Percentage of IQOS2 product use by CB(i) group and overall at each measurement time MT(i) until the analysis time~~ ~~— Frequency distribution of CB (i) group at each measurement time MT(i) until the analysis time and overall~~ ~~— Frequency distribution of CB(i) group and CE (i) group at each measurement time MT(i) until the analysis time~~ ~~— Time to product use transition at any time point during the study~~ ~~— Product switch across CB(i) by CB (0) group at each measurement time MT(i) until the analysis time~~ ~~— Product switch given each CB(i) and previous CB(i-1) at each measurement time MT(i) until the analysis time~~ ~~Frequency of product use transition and CE (i) group will also be~~

Section	Changes
	~~tabulated by previous behavior to current behavior.~~ ~~The tables will be repeated by IQOS brand for CB(i) as IQOS users (except table for uptake of products and product switch across CB(i) groups), sex, age group and enrollment wave.~~ ~~Note: For CB as the IQOS users, the %IQOS will also summarize by IQOS brand at each measurement time MT(i). One participant can be counted in more than on brand if he/she took more than one IQOS brand at certain time points.~~ The following figure~~s~~ will also be provided: - Bar chart of CB(i) group at each measurement time MT(i). ~~- Bar chart of CB(i) group at each measurement time MT(i) by IQOS brand for IQOS user.~~ ***Old Text:*** Summary tables of the product use patterns including product (%IQOS(i) and CE(i)) and product switching, uptake of products, rate of transitions and rate of cessation in the Study will be analyzed according to the CB(i) group at MT(i). Summary of current behavior will be presented separately by MT(i). Product switch is defined as the participant who has different behavior between MT(i) and initial timepoint, which means CB(i) is not equal to CB(0). And product switching over time will be presented as the frequency of product switch across each CB(i) given the original CB(0) by each MT(i). For describing the incidence of products, the descriptive statistics will be provided based on the response of "products currently consumed (Q1)" of product use questionnaire by each MT(i). Participants who have tobacco and nicotine product use transitions will be tabulated and median of time to product use transitions will be presented as well. The overall product use transition table will summarize any CB switch during study regardless of initial behavior, CB (0). One participant could have multiple times to product use transition records if there are more than one CB changes during the whole study. Median time of the product use transition will be provided.

Section	Changes
	The following outputs will be provided: - Uptake of products by CB(i) group and overall at each measurement time MT(i) until the analysis time - Percentage of IQOS product use by CB(i) group and overall at each measurement time MT(i) until the analysis time - Percentage of IQOS2 product use by CB(i) group and overall at each measurement time MT(i) until the analysis time - Frequency distribution of CB (i) group at each measurement time MT(i) until the analysis time and overall - Frequency distribution of CB(i) group and CE (i) group at each measurement time MT(i) until the analysis time - Time to product use transition at any time point during the study - Product switch across CB(i) by CB (0) group at each measurement time MT(i) until the analysis time - Product switch given each CB(i) and previous CB(i-1) at each measurement time MT(i) until the analysis time Frequency of product use transition and CE (i) group will also be tabulated by previous behavior to current behavior. The tables will be repeated by IQOS brand for CB(i) as IQOS users (except table for uptake of products and product switch across CB(i) groups), sex, age group and enrollment wave. Note: For CB as the IQOS users, the %IQOS will also summarize by IQOS brand at each measurement time MT(i). One participant can be counted in more than on brand if he/she took more than one IQOS brand at certain time points. The following figures will also be provided: - Bar chart of CB(i) group at each measurement time MT(i). - Bar chart of CB(i) group at each measurement time MT(i) by IQOS brand for IQOS user. ***Reason for Change:*** To align the analysis strategy as described in the

Section	Changes
	SAP version 2.0 (31 August 2017)
12.4.3.4 Quit Attempts	***Amended Text:*** **To characterize the quit attempts by cohort at study entry and by CB(i) group at each MT(i) post baseline**, ~~To describe the cessation rates of tobacco and nicotine containing products including CC by IB group at each MT(i) after month 12,~~ the following information will be presented in the: • ~~Rate of cessation of tobacco or nicotine containing products use, overall (Q4) as well as by consumption within a given timeframe based on the current event definition~~ • ~~Rate of cessation from CC use overall as well as by consumption within a given timeframe based on the cessation in current event~~ ***Old Text:*** To describe the cessation rates of tobacco and nicotine containing products including CC by IB group at each MT(i) after month 12, the following information will be presented in the: • Rate of cessation of tobacco or nicotine containing products use, overall (Q4) as well as by consumption within a given timeframe based on the current event definition • Rate of cessation from CC use overall as well as by consumption within a given timeframe based on the cessation in current event ***Reason for Change:*** To align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
12.4.3.5 Perceived Risks	***Amended Text:*** To assess the perception of risk associated with using CC, MRTPs and ENDs, the related information based on ~~IB group~~ **cohort at baseline and CB(i) group at post baseline** will be presented in tables ***Old Text:*** To assess the perception of risk associated with using CC, MRTPs

Section	Changes
	and ENDs, the related information based on IB group will be presented in tables ***Reason for Change:*** To align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
12.4.3.6 Strength of Nicotine Dependence	***Amended Text:*** The strength of nicotine dependence of the Study will be analyzed by **cohort at baseline and by CB(i) group according to the behavior at MT(i) post baseline** ~~IB according to the behavior at MT(i)~~ as follows ***Old Text:*** The strength of nicotine dependence of the Main Study will be analyzed by IB group according to the behavior at MT(i) as follows ***Reason for Change:*** To align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
12.4.3.7 Self-Reported Signs and Symptoms and Hospitalizations	***Amended Text:*** **The self-reported signs and symptoms and the hospitalizations of the Study will be analyzed by** ~~IB~~ **CB(i) group** ~~in participants which did not transition to another behavior at MT(i).~~ **One participant can be counted only once with the worse scenario under overall category.** **The cough result will be analyzed by cohort at baseline and by CB(i) group and overall in participants at post baseline MT(i).** ~~A participant without transition to another behavior if he/she does not have product switch at current time point or before and his/her current behavior is equal to initial behavior.~~ **The tables will be repeated by sex, age group and enrollment wave for self-reported signs and symptoms, health related events (hospitalizations) and cough assessment questionnaire.** ~~The coughing tables will be also presented by CB(i-1) and CB(i).~~ ***Old Text:***

Section	Changes
	The self-reported signs and symptoms including cough and the hospitalizations of the Study will be analyzed by IB group in participants which did not transition to another behavior at MT(i). A participant without transition to another behavior if he/she does not have product switch at current time point or before and his/her current behavior is equal to initial behavior. The coughing tables will be also presented by CB(i-1) and CB(i). ***Reason for Change:*** To align the analysis strategy as described in the SAP version 2.0 (31 August 2017)
13.1.2 Sponsor	Information updated to include the new study scientist [redacted] replacing [redacted], new statistician [redacted] **MEng MSc** replacing [redacted] and new Medical Safety Officer [redacted] Replace [redacted] ***Reason for Change:*** Changes to the study team
13.6 Publication and Disclosure Policy	***Amended Text:*** This document is being provided solely for the purpose of evaluation and/or conducting this ~~clinical~~ study for the Sponsor ***Old Text:*** This document is being provided solely for the purpose of evaluation and/or conducting this clinical study for the Sponsor ***Reason for Change:*** This study is not a clinical study
15 Reference List	Reference List is replaced with the new one ***Reason for Change:*** Update the list with the references used in the body of the protocol

SYNOPSIS

Sponsor:

Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchatel
Switzerland

Name of Product:

IQOS

Study Title:

An observational cohort study in Japan to assess the patterns of product use and changes in health status associated with the use of HeatSticks with the IQOS tobacco heating system

Study Number:

P1-PMC-01-JP

Study Short Title:

Japanese Post-Market Cohort Study

Objectives and Endpoints:

The objectives and endpoints of this study will be analyzed in the study population of adults legally authorized to buy tobacco products. The Study will describe the patterns of use of tobacco and nicotine containing products and self-reported health outcomes and health related events in CC (Combustible Cigarette) smokers and IQOS users.

Originally, the Study included a Clinical Sub-Study which would further assess the population level differences in levels of Biomarkers of Exposure (BoExp) to Harmful and Potentially Harmful Constituents (HPHC) contained in cigarette smoke, Clinical Risk Endpoints (CREs) and self-reported health outcomes and health related events between CC smokers, IQOS users and never-smokers. However, as recruitment into this part of the study had extremely low acceptance and there was little interest in participation from those enrolled in what was called the Main Study, it was decided to terminate the Clinical Sub-Study earlier than planned. So far, out of the 570 participants to be enrolled in the Clinical Sub-Study during the first wave, only 5 had completed a Clinical Site Visit.

Study Objectives:

The objectives and endpoints of the Study are:

1. To characterize and describe patterns of use of tobacco and nicotine containing products
   Endpoints:

- Mean number of cigarettes smoked (per day and/or per week) over time
- Mean number of IQOS HeatSticks used (per day and/or per week) over time
- Mean number of times e-cigarettes are used (per day and/or per week) over time
- Product use patterns over time (individual and dual/poly use patterns)
- Rate of increase or decrease in product use over time

2. To identify intra-individual product use trajectories over time
   Endpoints:
   - Product switching
   - Uptake of new products
   - Rate of tobacco and nicotine product use transitions, within a given timeframe
3. To describe the cessation rates of tobacco and nicotine containing products including CC over time
   Endpoints:
   - Rate of cessation of tobacco or nicotine containing products use, overall as well as by consumption within a given timeframe
   - Rate of cessation from CC use overall as well as by consumption within a given timeframe
4. To identify and assess the motivations for quitting tobacco use and to characterize the quit attempts by product use over time
   Endpoints:
   - Rate and number of participants that want to quit
   - Reasons for wanting to quit
   - Rate and number of self-reported quit attempts
   - Characteristics of the quit attempts, including:
     - Length of quit attempt
     - Type of product used to help in quit attempts (if applicable)
     - Reasons for quit attempt
     - Outcome of quit attempt
5. To characterize the users of tobacco and nicotine containing products over time
   Endpoints:
   - Demographics and socioeconomic characteristics of tobacco and nicotine containing products users

- Smoking history of tobacco and nicotine containing products users
- Pre- IQOS tobacco and nicotine containing product usage and behaviors

6. To assess subjective effects including urge to smoke, product reinforcement and self-observed aesthetic improvements over time
   Endpoints:
   - Total score and factor scores from the Questionnaire on Smoking Urges-brief version (QSU-b) by product use
   - Subscales from the Modified Cigarette Evaluation Questionnaire (MCEQ) in IQOS users
   - Self-Reported Changes Questionnaire (SRCQ) in IQOS users.
7. To assess the perception of risk associated with tobacco and nicotine containing products by product use over time
   Endpoints:
   - Perceived Risk Instrument (PRI-P) to measure perception of risk associated with using CC, IQOS and e-cigarettes based on exposure group at the time of assessment using the following domains:
     - Perceived Health Risk
     - Perceived Addiction Risk
     - Perceived Harm to Others
8. To assess the strength of nicotine dependence by product use over time
   Endpoints:
   - Score from the Fagerström Test for Nicotine Dependence (FTND) questionnaire
9. To describe the rates of self-reported signs, symptoms and diagnoses by product use over time
   Endpoints:
   - Signs and symptoms
   - Cardiovascular disease diagnoses: myocardial infarction, stroke, new diagnoses of hypertension, unstable angina, or other cardiovascular diseases
   - Respiratory diseases diagnoses: new diagnoses of chronic obstructive pulmonary disease (COPD), or other respiratory diseases, including asthma exacerbations
   - Malignancy diagnoses: all malignancies, including smoking-related malignancies (i.e., lung, larynx, and bladder)
10. To summarize the number of health related events (hospitalizations)

Endpoints:

- Rate of prevalence of emergency room visits and/or hospitalization reported by product use over time
- Frequency of diagnoses associated with emergency room visits and/or hospitalizations reported over time

11. To assess coughing by product use
    Endpoints:
    - Cough impact assessed by Visual Analog Scale (VAS),
    - Frequency and intensity of cough using the cough assessment
    -

Evaluation Criteria:

The Study is observational in nature and therefore designed to identify product use patterns and assess the incidence of product use transitions and health outcomes in IQOS users and CC smokers.

Study Design:

This is a prospective, observational, open cohort study of adults, legally authorized to purchase tobacco products in Japan. The Study will describe the patterns of use of tobacco and nicotine containing products and self-reported health outcomes in CC smokers and IQOS users. Participants will be recruited into the cohort in annual waves over a period of about 4 years.

For IQOS users, the date of initiation of IQOS use is the trigger for all study assessments in the Study. However the process will be different for CC smokers for whom assessment timing will be based on the date of enrollment. IQOS users will be enrolled into the study at least 2 months after initiating use of IQOS (to ensure adoption of IQOS), but less than 12 months after initiating use of IQOS (to ensure that each annual wave targets new users), the study assessments will start at the next appropriate study time point after enrollment.

As this study is observational by design and is conducted in a post-market setting, adverse event (AE) reporting will follow the Sponsor's established post-market Safety Surveillance Procedures for spontaneously reported events. IQOS users will be reminded of the product quality complaints (including AEs) hotline that is available for all IQOS consumers in Japan.

IQOS users will be identified and invited for participation in the study until each annual wave of 500 participants is filled. Additionally, CC smokers will be recruited into the study, also in annual waves of 500, resulting in a total cohort size of 4000 participants (2000 per

exposure group) in the Study. Initially, there will be no quotas or restrictions on enrollment into the study; however, the study population will be monitored and quotas may be introduced to ensure representativeness within their target populations in the following annual waves.

All participants enrolled in the Study will answer the computer assisted self-interviews (CASIs) which will include demographic information, the core questionnaire (which is a questionnaire including questions about smoking history, detailed product use and intention to stop tobacco and nicotine containing product use), lifestyle assessments, socio-economic status, the Questionnaire on Smoking Urges-brief version (QSU-b), the Perceived Risk Instrument (PRI-P), the Fagerström Test for Nicotine Dependence (FTND) questionnaire, self-reported health outcomes (symptoms and diagnoses) and health related events (hospitalizations), and the cough assessment, IQOS users will also be administered the Modified Cigarette Evaluation Questionnaire (MCEQ) and the self-reported changes questionnaire (SRCQ). The CASI provider for wave 1 is [redacted] and from wave 2 onwards it will be [redacted].

Participant Identification and Enrollment:

IQOS users will be identified via: 1) Philip Morris – Japan (PM-JP)'s consumer database, and/or 2) through public advertisements, in which potential participants will be directed to log into the Study Database for screening and invited to participate in the Study. CC smokers will be identified in three ways: 1) through Philip Morris – Japan (PM-JP)'s consumer database, 2) market research and other available databases (e.g., [redacted]s market research database), and 3) through public advertisements, in which potential participants will be directed to log into the Study Database for screening and invited to participate in the study.

Potential participants for the Study will be sent an invitation for the study that will direct them to the Study Website where they will find more information about the Study. Interested participants, will click on a link that will re-direct them to the [redacted] portal for wave 1 participants and once wave 2 is launched, to the [redacted] portal to register for the Study. Participants will confirm registration by logging into the system where they will then complete the informed consent, before being administered the "screening domain" of the CASI which is the set of questions and questionnaires to evaluate the participants' eligibility for participation in the Study (i.e., inclusion and exclusion criteria, eligible participants). At the end of the "screening domain" eligible participants will be directed to the "enrollment domain" to confirm their participation in the Study. Once a participant confirms participation in the Study, they are considered enrolled. Enrolled participants will be presented with the "baseline domain", the set of questions and questionnaire to capture the detailed demographics, socio economic status and participant smoking status at their entry into the study. All IQOs participants will fill their baseline questionnaire at time of entry. After baseline CASI, the next CASI is dependent on the exposure time to IQOS. IQOS

participants will not complete a CASI if their baseline CASI is within the timeframe (± 4 weeks of the next required CASI). This aims to limit the time necessary for the study participant to complete the questionnaires. No data will be recorded in the Study Database for the potential participants that do not consent to participate in the study. After consenting for participation in the Study, participants can withdraw from it at any time, but all data already provided by them, will be retained in the Study Database and analyzed as per the analysis plan. The contact details including personal information and personal identifiers will be kept separate from the study data.

After Enrollment Through Month 18:

During the first 18 months of the Main Study the CASI 'follow-up domains' will be administered on a quarterly basis (every 3 months ± 4 weeks), for up to 6 times at Months 3, 6, 9, 12, 15 and 18 respectively.

After Month 18 Through Year 3:

During the second 18 months of the Main Study the CASI 'follow-up domains' will be administered on a bi-annual basis (every 6 months ± 4 weeks) in total 3 times, at Months 24, 30, and 36.

After Year 3 through Year 5:

During the last 2 years of the Main Study the CASI "follow-up domains" will be administered on an annual basis (every 12 months ± 4 weeks), up to 2 times, at Months 48, and 60 respectively.

Study Population and Main Criteria for Inclusion:

Female or male adult participants meeting the following main criteria:

Inclusion Criteria:

- Adults legally authorized to buy tobacco products in Japan (20 years of age)
- The participant is Japanese
- Participant is able to understand the information provided in the Informed Consent form (ICF).
- Signed informed consent form
- Willing to participate in the study and has access to the internet
- For IQOS users:
  - Is currently using IQOS HeatSticks

- Has used at least 100 IQOS HeatSticks in their lifetime, and
- Has used IQOS HeatSticks for 2 months or more

Note: The use of IQOS HeatSticks defines the user as an IQOS user, regardless of other tobacco or nicotine product use.

- For CC smokers:
  - Is currently using CC
  - Is not currently using IQOS HeatSticks, and
  - Has used at least 100 CC in their lifetime

Exclusion Criteria:

- Tobacco industry employees
- Employed by the Sponsor, CRO or Clinical Site
- For IQOS users:
  - More than 12 months of IQOS use
- For Former Smokers:
  - Is not currently using CC
  - Is not currently using IQOS HeatSticks, and
  - Has used at least 100 CC and/or IQOS HeatSticks in their lifetime

-

Investigational Product; Dose; and Mode of Administration:

Not Applicable

Duration of Study:

The study will have a follow up of a maximum of 5 years, the recruitment will be open for the first 4 years of the study. The minimum planned follow-up for any given participant will be 1 year.

Statistical Methods:

All data will be presented in listings, ordered by product use group at study entry, unless otherwise specified.

Descriptive statistics will be provided by usage groups for endpoint parameters at each collection time point.

Descriptive statistics for continuous variables (number of participants [n], number and

percent of participants with data, mean, standard deviation [SD], median, first and third quartiles, minimum and maximum for continuous data, and the n and absolute and relative [%] frequency for categorical data) will be presented by arm at each time point. Summary statistics of the endpoints will include changes over time when applicable.

Sample Size:

A total of 4000 participants will be enrolled in the Main Study. Enrollment will happen in four annual waves.

Considering an annual drop-out rate of 5% and a maximum of 20% of participants changing from CC smoker or IQOS user to another group annually, the person-year pool in each group will be for each annual analysis as described in the below table:

Table 11 Summary of Person-Years - Pooled for Annual Analyses

Wave	Year 1 Report	Year 2 Report	Year 3 Report	Year 4 Report	Year 5 Report	Person-Years per Wave
1	375	281	210	157	117	1140
2		375	281	210	157	1023
3			375	281	210	866
4				375	281	656
Total (person-years)	**375**	**1031**	**1897**	**2920**	**3685**	

This sample size is sufficient to detect for the trajectories analysis, using the assumption of 20% participants switching to another group, an incidence of 1% of participants switching with a precision of less than 1.32% after one year using the first wave at the first analysis and up to 0.62% the final analysis.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	Adverse event
AT	Analysis Time
BoExp	Biomarker of exposure
CASI	Computer assisted self-interview
CB_i	Current Behavior
CC	Combustible cigarette
$CC\text{-}Cess_i$	CC Cessation at measurement time i
CC_i	Current CC smoker at measurement time i
$CCdec_i$	CC decrease at measurement time i
CE_i	Current Events
$CCinc_i$	CC increase at measurement time i
COPD	Chronic obstructive pulmonary disease
CPD_i	Average CC consumption
CRE	Clinical risk endpoint
$CCrel_i$	CC Relapse at measurement time i
CRF	Case report form
CRO	Contract research organization
$DU\_THS\_CC_i$	Dual THS – CC at measurement time i
$DU\_THS\_OTP_i$	Dual THS – OTP at measurement time i
EC	Ethics Committee
ePD_i	Average daily e-cigarette consumption at measurement time i
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
GEP	Good Epidemiological Practice

HnB	Heat-not-Burn products
$HnBuptake_i$	HnB uptake at measurement time i
HPHC	Harmful and potentially harmful constituent
I_{cci}	CC initiation at measurement time i
I_{OTPi}	OTP initiation at measurement time i
I_{THSi}	THS initiation at measurement time i
$I_{THSi\_brand\ name}$	THS initiation by brand at measurement time i
IB	Initial Behavior
IEA	International Epidemiological Association
ICF	Informed consent form
IOM	Institute of Medicine
IRB	Institutional Review Board
LB	Last Behavior
MCEQ	Modified Cigarette Evaluation Questionnaire
MRTPs	Modified risk tobacco products
MT_i	Measurement Time
Non_Smoker_i	Non User/Smoker
Occ_Smoker_i	Occasional User/Smoker at measurement time i
Occ_THS_i	Occasional THS User at measurement time i
$Occ\_THS\_CC_i$	Occasional THS – CC User at measurement time i
$Occ\_THS\_CC\_OTP_i$	Occasional THS – CC – OTP User at measurement time i
$Occ\_THS\_OTP_i$	Occasional THS – OTP User at measurement time i
OTP	Other tobacco product
$OTP\text{-}Cess_i$	OTP Cessation at measurement time i
$OTPD_i$	Average daily OTP consumption at measurement time i
$OTPrel_i$	OTP Relapse at measurement time i

PMI	Philip Morris International
PMP	Philip Morris Products S.A.
PM-JP	Philip Morris - Japan
PRI-P	Perception Risk Instrument
PT	Individual Person Time
QA_j	Quit Attempt at measurement time i
QSU-b	Questionnaire on smoking urges – short form
Re-I_{cci}	CC re-initiation at measurement time i
Re-I_{THSi}	THS re-initiation at measurement time i
QSU-b	Questionnaire on smoking urges – short form
SAP	Statistical analysis plan
SD	Standard deviation
SES	Socio-economic status
S_i	First Switch from Initial Behavior to another Behavior
SOP	Standard operating procedure
SRCQ	Self-Reported Changes Questionnaire
ST_i	Study Time
THS	Tobacco Heating System
$THSPD_i$	Average daily THS consumption at MT_i
$THS\text{-}Cess_i$	THS Cessation at measurement time i
$THSdec_i$	THS decrease at measurement time i
$THSinc_i$	THS increase at measurement time i
$THSrel_i$	THS relapse at measurement time i
THSuptake	THS uptake
WHO	World Health Organisation

Definitions of Terms

Cessation	Person who: • Is not currently using CC or IQOS HeatSticks • Has quit using CC and/or IQOS HeatSticks for at least 1 year • Has used at least 100 CC and/or IQOS HeatSticks in their lifetime
Current CC Smoker	Person who: • Is currently using CC • Is not currently using IQOS HeatSticks • Has used at least 100 CC in their lifetime
Current IQOS user	Person who: • Is currently using IQOS HeatSticks • Has used at least 100 IQOS HeatSticks in their lifetime.
Current Smoker	Person who: • Is currently using CC or IQOS HeatSticks • Has used at least 100 CC and/or IQOS HeatSticks their lifetime
Domain(s)	A domain is a set or group of questionnaires administered to a participant at a specific point in time. Screening Domain: the domain administered after informed consent to determine if a participant qualifies for participation in the study. Enrollment Domain: the domain administered after screening where participants confirm their participation in the study. Baseline Domain: the domain administered after the Enrollment Domain to capture the baseline information on each participant Follow-up Domain: the domain administered to collect the participant-reported study assessments at each study time point.
Former CC Smoker	Person who: • Is not currently using CC • Has used at least 100 CC in their lifetime.
Former IQOS user	Person who: • Is not currently using IQOS HeatSticks • Has used at least 100 HeatSticks in their lifetime.

Former-Smoker	Person who: • Is not currently using CC • Is not currently using IQOS HeatSticks • Has used at least 100 CC and/or IQOS HeatSticks in their lifetime.
Lost to follow-up (date)	The date of lost to follow-up corresponds to the date of the last contact attempt for the participant by [redacted] Helpdesk. •
Study completion:	The study enrollment will be completed once the 4th annual wave is closed, and the study will be concluded when 1 year of follow-up is complete on the last participant is enrolled.

1 ETHICS AND REGULATIONS

1.1 Institutional Review Board (IRB) Approval

Prior to the start of the study, the study protocol, together with its associated documents (informed consent forms [ICF] which include the participant information sheet and informed consent, participant recruitment procedures, written information to be provided to the participants, the Principal Investigator's (PI) curriculum vitae and/or other evidence of qualificationsand any other documents requested by the Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IRB. The IRB shall be appropriately constituted in accordance with the International Epidemiological Association (IEA) Guidance for Good Epidemiological Practice (GEP) (1) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (2).

A written confirmation of the IRB approval should be provided to the Sponsor. This should identify the study (PI's name, study number and title) and the documents that have been approved by the IRB, with dates and version numbers, as well as the date of approval. The composition of the IRB, including the name and occupation of the chairperson, should be supplied to the Sponsor.

The written approval from the IRB will be filed in the Investigator file, and another original copy will be filed in the study master file at the Sponsor or designated organization. The study must not start before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB.

Any substantial change or addition to this protocol will require a written protocol amendment that must be approved by the Sponsor and the PI. All amendments will be submitted to the IRB, and substantial amendments will only be implemented after approval by the IRB.

These requirements for approval should in no way prevent any action from being taken by the PI or sub-Investigator or by the Sponsor in order to eliminate immediate hazards to the participants. If such a change to the protocol is felt to be necessary by the PI, and is implemented for safety reasons, the Sponsor and the IRB should be informed immediately.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki 2013 (3) and are consistent with GEP (1), and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (2). The PI agrees to conduct the study in compliance with the protocol agreed upon with the Sponsor and approved by the IRB. The PI and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the declaration of Helsinki should be located in the PI's study file.

1.3 Participant Information and Consent

1.3.1 Informed Consent/ for the Study

Before the "screening domain" is administered, the participant will be informed about the nature and purpose of the study via the Study Website. Participants interested in participating in the Study initiate the informed consent process by clicking on the link from the Study Website that will re-direct them to the [redacted] portal for wave 1 participants and once wave 2 is launched, to the [redacted] portal to register for the study and give informed consent. The ICF will be administered electronically for participants of the Study and it will be recorded in the Study Database. Participants will be informed that they are free to discontinue their participation at any time.

No data will be recorded in the Study Database for the potential participants that do not consent to participate in the study. Participants will be informed that after consenting for participation in the study, they can withdraw from the study at any time, but that all data already provided by them, will be retained in the database and analyzed as per the analysis plan. The contact details including personal information and personal identifiers will be kept separate from the study data. They will also be informed about additional data analyses not mentioned in the protocol or the statistical analysis plan (SAP) that may be performed with the collected data at a later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.3.2 Amendment to the Informed Consent Form/Participant Information Sheet.

If a protocol amendment is required, an amendment may be required to one or more of the ICFs. If revision of the ICF is necessary, the PI will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IRB before participants are required to re-sign the ICF.

1.4 Good Epidemiological Practice

The procedures set out in this observational study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and the investigator abide by the principles of the guidelines on GEP (1). These guidelines apply specifically to epidemiological studies and therefore provide a robust and ethical framework for conducting observational studies. In addition, the PI or designee will carry out the study in accordance the Ethical Guidelines for Medical and Health Research Involving Human Subjects (2).

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Tobacco use is a major public health problem worldwide as it is a well-known risk factor for many life threatening diseases. Tobacco use leads most commonly to cardiovascular and pulmonary disease and is a major risk factor for myocardial infarction, stroke, chronic bronchitis, cancers of mouth, throat, voice box and pancreas (4). Half of all long-term smokers will die of a tobacco-related condition (5).

The best way to reduce the adverse health consequences of smoking is to quit smoking (6, 7). Because of the impact that smoking has on health and the fact that total smoking cessation is difficult to achieve (8, 9), the FDA drafted guidelines for application of modified risk tobacco products (MRTPs) that would either have reduced exposure to tobacco toxicants and/or reduced risk of developing tobacco-related diseases (10). For those smokers who are not willing to quit, Philip Morris Products (PMP) is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases under the FDA draft guidelines for MRTP (10).

PMP's approach to scientifically assessing the risk-reduction potential of its candidate MRTPs is described in the reference document (11). Smoking cessation is the only intervention proven to reduce the risk of smoking-related diseases in smokers. Accordingly, PMP utilizes smoking cessation/smoking abstinence as the benchmark for assessing the risk reduction potential of its candidate MRTPs. The Institute of Medicine (IOM) observed that cessation is the "gold standard" for assessing risk reduction, and that "the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be of achieving a net public health benefit" (12). PMP has already conducted studies and plans to conduct further clinical studies which observe measurable changes in blood chemistry, risk factors and health effects in smokers who switch to a candidate MRTP, comparing the changes with those observed in both smokers who continue smoking combustible cigarettes (CC) and smokers who stop using tobacco products.

In order to substantiate clinical study findings PMP according to FDA's draft guidelines, longer-term data from adults who continue to use the candidate MRTP will be needed. This is because not only decreased exposure to tobacco toxicants and reduced risk for smoking associated diseases need to be ascertained, but because patterns of use of the candidate MRTPs are vital to determine population harm.

2.1.2 Description of the PMP's First Candidate MRTP and Scientific Findings

Thousands of chemicals - "smoke constituents" - are formed when tobacco is burned or combusted. More than 5000 smoke constituents have been identified (13, 14), and more than 100 of them have been categorized as harmful and potentially harmful constituents (HPHCs) (15). PMP's focus has been on the development of products that do not combust tobacco but heat tobacco while replicating the "smoking experience" as much as possible. The approach being used by heating tobacco at significantly lower temperatures than CC limits pyrolysis and combustion. PMP believes that such heat-versus-burn products present the best opportunity for reducing harm as they produce vastly lower levels of HPHCs and are more likely to be accepted by smokers as substitutes for cigarettes. Important to this effort has been providing nicotine in a way that closely parallels CC and closely replicate taste, sensorial experience and ritual of that of a CC.

The product developed by PMP, and to be assessed in this study, is the IQOS Tobacco Heating System (THS) (referred to as the IQOS). With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for CC, which can reach 900°C. The IQOS is composed of the 'Tobacco Stick Holder', dedicated special IQOS HeatSticks, a Charger, and different accessories. The energy of the IQOS Tobacco Stick Holder is sufficient to maintain approximately a 6-minute session. Unlike CC, the IQOS HeatSticks do not burn down during their consumption and their lengths remain constant after use.

The non-clinical assessment of IQOS supported the initiation of the clinical studies (16). No new or increased toxicological hazard in the product's aerosol was detected compared with CC smoke and aerosol chemistry studies have shown a reduction of up to 90% in HPHC's (16). Several clinical studies have been conducted on an earlier version of IQOS (THS 1.0), in Europe, Asia, Africa and the United States. All studies showed reductions in exposure to the majority of measured HPHCs from both aerosol fractions, total particulate matter (TPM) and gas vapor phase (GVP), in participants using the THS 1.0 as compared to participants continuing smoking CC, both, in controlled and ambulatory setting. THS 2.1, the immediate predecessor of the non-menthol current IQOS, was tested in two exploratory clinical studies to measure the nicotine pharmacokinetic profile (PK) (17) and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1 (18). The observed nicotine PK profile for THS 2.1 was similar to CC and there were significant reductions in the exposure to the majority of selected HPHCs. In 2013, eight clinical studies were initiated in US, Europe, and Japan in order to evaluate the nicotine PK profile, to demonstrate reduced exposure, and to determine functional and biological changes following the switching from CC to THS in smokers as compared to smokers continuing smoking CC and smoking abstinence (SA). The reporting of the results is currently ongoing.

Clinical studies conducted and ongoing so far on about 3000 participants revealed no safety concern for THS 2.2 and its earlier prototypes.

2.2 Study Rationale

In order to support PMP's pre-clinical and clinical programs in assessing the exposure and risk reduction of the IQOS, post-marketing and in particular observational data is needed to collect information on how the product is used in the 'real world' (19). This Study will therefore allow us to assess the patterns of product use and changes in health status associated with the use of the IQOS, compared to CC smokers.

Originally, the Study included a Clinical Sub-Study which would further assess the population level differences in levels of Biomarkers of Exposure to Harmful and Potentially Harmful Constituents (HPHC) contained in cigarette smoke, Clinical Risk Endpoints (CREs) and self-reported health outcomes and health related events between CC smokers, IQOS users and never-smokers. However, as recruitment into this part of the study was extremely low and there was little interest in participation from those enrolled in what was called the Main Study, it was decided to terminate the Clinical Sub-Study earlier than planned.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

There are no major benefits from participating in this study for the overall study population other than to collaborate to the understanding of how IQOS and other tobacco and nicotine containing products are used.

2.3.2 Anticipated Foreseeable Risks Due to Study Procedures

There are no anticipated risks associated with participation in the Study.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives and Endpoints

1. To characterize and describe patterns of use of tobacco and nicotine containing products
   Endpoints:
   - Mean number of cigarettes smoked (per day and/or per week) over time
   - Mean number of IQOS HeatSticks used (per day and/or per week) over time
   - Mean number of times e-cigarettes are used (per day and/or per week) over time
   - Product use patterns over time (individual and dual/poly use patterns)
   - Rate of increase or decrease in product use over time
2. To identify intra-individual product use trajectories over time
   Endpoints:
   - Product switching
   - Uptake of new products
   - Rate of tobacco and nicotine product use transitions, within a given timeframe
3. To describe the cessation rates of tobacco and nicotine containing products including CC over time
   Endpoints:
   - Rate of cessation of tobacco or nicotine containing products use, overall as well as by consumption within a given timeframe.
   - Rate of cessation from CC use overall as well as by consumption within a given timeframe
4. To identify and assess the motivations for quitting tobacco use and to characterize the quit attempts by product use over time
   Endpoints:
   - Rate and number of participants that want to quit
   - Reasons for wanting to quit
   - Rate and number of self-reported quit attempts
   - Characteristics of the quit attempts, including:
     - Length of quit attempt
     - Type of product used to help in quit attempt (if applicable)

- Reasons for quit attempt
- Outcome of quit attempt

5. To characterize the users of tobacco and nicotine containing products over time
   Endpoints:
   - Demographics and socioeconomic characteristics of tobacco and nicotine containing products users
   - Smoking history of tobacco and nicotine containing products users
   - Pre- IQOS tobacco and nicotine containing product usage and behaviors
6. To assess subjective effects including urge to smoke, product reinforcement and self-observed aesthetic improvements over time
   Endpoints:
   - Total Score and Factor scores from the Questionnaire on Smoking Urges-brief version (QSU-brief) by product use
   - Subscales from the Modified Cigarette Evaluation Questionnaire (MCEQ) in IQOS users
   - Self-Reported Changes Questionnaire (SRCQ) in IQOS users
7. To assess the perception of risk associated with tobacco and nicotine containing products by product use over time
   Endpoints:
   - Perceived Risk Instrument (PRI-P) to measure perception of risk associated with using CC, IQOS and e-cigarettes based on exposure group at the time of assessment using the following domains:
     - Perceived Health Risk
     - Perceived Addiction Risk
     - Perceived Harm to Others
8. To assess the strength of nicotine dependence by product use over time
   Endpoints:
   - Score from the Fagerström test for Nicotine Dependence (FTND) questionnaire.
9. To describe the rates of self-reported signs, symptoms and diagnoses by product use over time
   Endpoints:
   - Signs and symptoms

- Cardiovascular disease diagnoses: myocardial infarction, stroke, new diagnoses of hypertension, unstable angina, or other cardiovascular diseases
- Respiratory diseases diagnoses: new diagnoses of chronic obstructive pulmonary disease (COPD), or other respiratory diseases, including asthma exacerbations
- Malignancies diagnoses: all malignancies, including smoking-related malignancies (i.e., lung, larynx, and bladder)

10. To summarize the number of health related events (Hospitalizations) over time
    Endpoints:
    - Rate of prevalence of emergency room visits and/or hospitalization reported by product use over time
    - Frequency of diagnoses associated with emergency room visits and/or hospitalizations reported over time

11. To assess coughing by product
    Endpoints:
    - Cough impact assessed by Visual Analog Scale (VAS),
    - Frequency and intensity of cough using the cough assessment

4 INVESTIGATIONAL PLAN

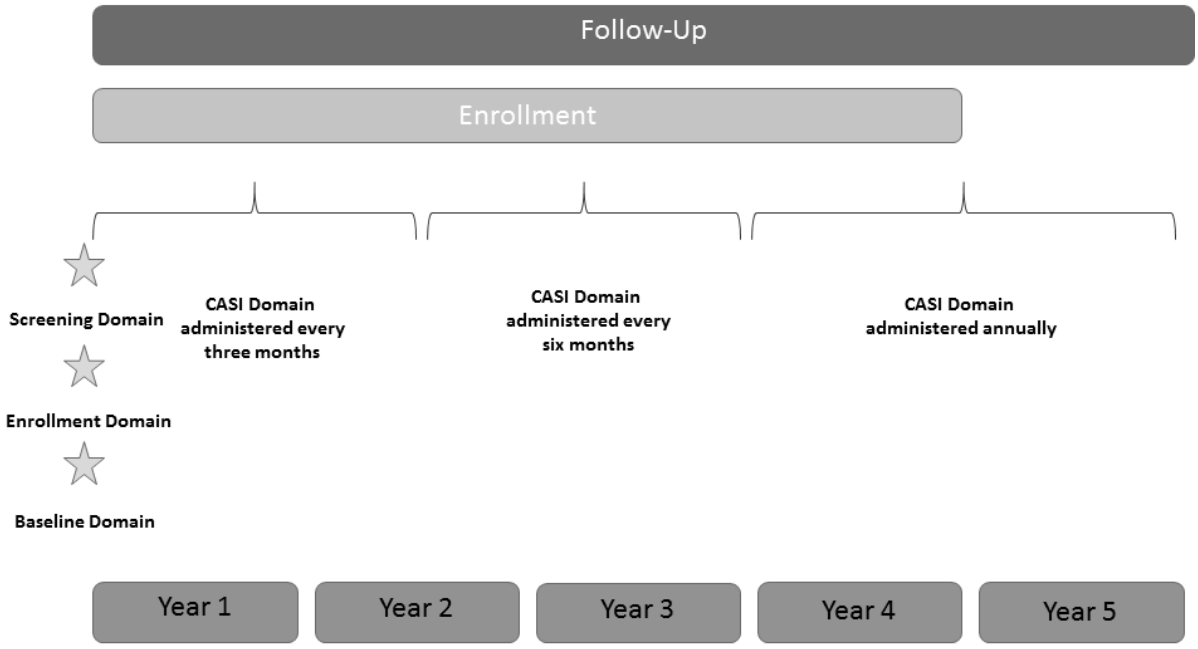
4.1 Overall Study Design and Plan

This is a prospective open observational cohort study of Japanese adults, legally authorized to purchase tobacco products in Japan. The Study will describe the patterns of use of tobacco and nicotine containing products and self-reported health outcomes and health related events in CC smokers and IQOS users.

Participants will be recruited into the cohort in 4 annual waves of 1000 participants per year (500 IQOS users and 500 CC smokers) until reaching the total study sample size of 4000 participants (2000 per exposure group). The aim of these annual waves is to ensure the recruitment of new IQOS users, as the demographic characteristics of new IQOS users might change over time.

For IQOS users, the date of initiation of IQOS use is the trigger for all study assessments the Study. However the process will be different for CC smokers for whom the questionnaire timing will be based on the date of enrollment. All participants enrolled in the Study will answer the computer assisted self-interviews (CASIs) which will include the following questionnaires: demographic information, core questionnaire (which is a questionnaire including questions about smoking history, detailed product use and intention to stop tobacco and nicotine containing product use), lifestyle assessments, SES, QSU-b, PRI-P, FTND, self-reported health outcomes (symptoms and diagnoses) and health related events (hospitalizations) questionnaire, and cough assessment questionnaire while IQOS users will also be administered the MCEQ and SRCQ. The CASI provider for wave 1 is [redacted] and from wave 2 onwards it will be [redacted].

Figure 1 Study Design



4.1.1 Identification of Potential Participants

IQOS users will be identified via: 1) PM-JP's consumer database, and/or 2) through advertisements, in which potential participants will be directed to the Study Website where they can obtain more information on the study and register their interest in participating in the study.

The PM-JP's consumer database collects information on consumers that buy and/or register their IQOS tobacco heating system device. During the registration process consumers can record their contact information and agree to the Terms and Conditions of PM-JP's consumer database. Consumers that both provide contact information and have agreed to the Terms and Conditions will be contacted via email and invited to participate in the Study. The email will contain a link to the Study Website where they will get information about the study and if interested in participation they will be able to connect to [redacted]s portal for wave 1 participants and once wave 2 is launched, to the [redacted] portal.

CC smokers will be identified in three ways: 1) PM-JP's consumer database, 2) through market research or other available databases, and 3) through advertisements as previously described for IQOS users. CC smokers identified through the other databases will be contacted via email/SMS and invited to register for the study.

4.1.2 Enrollment

The "enrollment domain" is only made available to participants that qualify to enroll in the study, it asks participants to confirm their participation in the study. Once a potential participant confirms their participation they are considered enrolled in the study. These participants will then be administered the "baseline domain" which includes the following questionnaires: lifestyle assessments, SES, QSU-b, PRI-P, FTND, core baseline questionnaire self-reported health outcomes (signs, symptoms and diagnoses) and health related events (hospitalizations), cough assessment and the MCEQ. All IQOs participants will fill their baseline questionnaire at time of entry. After baseline CASI, the next CASI is dependent on the exposure time to IQOS. IQOS participants will not complete a CASI if their baseline CASI is within the timeframe (± 4 weeks of the next required CASI).

4.1.3 Follow-up

During the Main Study the follow-up CASIs will be administered:

Quarterly (every 3 months ± 4 weeks) for the first 18 months (up to 6 times), at Months 3, 6, 9, 12, 15 and 18,

- Bi annually (every 6 months ± 4 weeks) for the second 18 months (up to 3 times), at Months 24, 30, and 36,
- Annually (every 12 months ± 4 weeks), for the last 2 years (up to 2 times), at Months 48, and 60.

The follow-up domain will include the following questionnaires: core follow-up questionnaire , lifestyle assessments, SES, QSU-b, PRI-P, the FTND, self-reported health outcomes (signs, symptoms and diagnoses) and health related events (hospitalizations) questionnaire, cough assessment questionnaire and for IQOS users the MCEQ and the SRCQ as defined in the Schedule of Events.

Participants will complete the follow-up domains online, without the need to attend the Clinical Site or a data collection center.

4.2 Rationale for Study Design and Control Group(s)

This study is part of PMP's assessment program for IQOS, providing information on how this product is used in "real life". This includes consideration of areas such as the expected rates of use of the tobacco product by current tobacco users, the use of the tobacco product in conjunction with other tobacco products".

This study will:

- Provide a perspective of product use in a "real world setting", where smoking CC in addition to IQOS is likely to occur (dual use).
- Describe the incidence of smoking related diseases and symptoms in the different exposure groups.

4.3 Appropriateness of Measurements

Endpoints related to subjective effects are selected based on their relevance as clinical phenomena connected to smoking or smoking cessation

The questionnaires included in this study, for which there is an associated scoring algorithm, have been validated by other parties and have been reported in the literature (QSU-b, MCEQ, FTND) or have been validated internally (PRI-P). The different instruments and standalone items included in this study will undergo cognitive debriefing and linguistic validation prior to administration in the study.

4.4 Study Duration

This study is an open cohort which will have a follow-up duration of up to 5 years. With a minimum follow-up per participant of 1 year.

The cohort will remain open for enrollment for the first 4 years, with annual waves of 500 IQOS users and 500 CC smokers for the Study.

4.5 Study Objectives and Endpoints

The objectives and endpoints of the Study are:

1. To characterize and describe patterns of use of tobacco and nicotine containing products
   Endpoints:
   - Mean number of cigarettes smoked (per day and/or per week) over time
   - Mean number of IQOS HeatSticks used (per day and/or per week) over time
   - Mean number of times e-cigarettes are used (per day and/or per week) over time
   - Product use patterns over time (individual and dual/poly use patterns)
   - Rate of increase or decrease in product use over time
2. To identify intra-individual product use trajectories over time
   Endpoints:
   - Product switching

- Uptake of new products
- Rate of tobacco and nicotine product use transitions, within a given timeframe

3. To describe the cessation rates of tobacco and nicotine containing products including CC over time
   Endpoints:
   - Rate of cessation of tobacco or nicotine containing products use, overall as well as by consumption within a given timeframe.
   - Rate of cessation from CC use overall as well as by consumption within a given timeframe
4. To identify and assess the motivations for quitting tobacco use and to characterize the quit attempts by product use over time
   Endpoints:
   - Rate and number of participants that want to quit
   - Reasons for wanting to quit
   - Rate and number of self-reported quit attempts
   - Characteristics of the quit attempts, including:
     - Length of quit attempt
     - Type of product used to help in quit attempt (if applicable)
     - Reasons for quit attempt
     - Outcome of quit attempt
5. To characterize the users of tobacco and nicotine containing products over time
   Endpoints:
   - Demographics and socioeconomic characteristics of tobacco and nicotine containing products users
   - Smoking history of tobacco and nicotine containing products users
   - Pre- IQOS tobacco and nicotine containing product usage and behaviors
6. To assess subjective effects including urge to smoke, product reinforcement and self-observed aesthetic improvements over time
   Endpoints:
   - Total Score and Factor scores from the Questionnaire on Smoking Urges-brief version (QSU-brief) by product use
   - Subscales from the Modified Cigarette Evaluation Questionnaire (MCEQ) in IQOS users

- Self-Reported Changes Questionnaire (SRCQ) in IQOS users

7. To assess the perception of risk associated with tobacco and nicotine containing products by product use over time
   Endpoints:
   - Perceived Risk Instrument (PRI-P) to measure perception of risk associated with using CC, IQOS and e-cigarettes based on exposure group at the time of assessment using the following domains:
     - Perceived Health Risk
     - Perceived Addiction Risk
     - Perceived Harm to Others
8. To assess the strength of nicotine dependence by product use over time
   Endpoints:
   - Score from the Fagerström test for Nicotine Dependence (FTND) questionnaire.
9. To describe the rates of self-reported signs, symptoms and diagnoses by product use over time
   Endpoints:
   - Signs and symptoms
   - Cardiovascular disease diagnoses: myocardial infarction, stroke, new diagnoses of hypertension, unstable angina, or other cardiovascular diseases
   - Respiratory diseases diagnoses: new diagnoses of chronic obstructive pulmonary disease (COPD), or other respiratory diseases, including asthma exacerbations
   - Malignancies diagnoses: all malignancies, including smoking-related malignancies (i.e., lung, larynx, and bladder)
10. To summarize the number of health related events (Hospitalizations) over time
    Endpoints:
    - Rate of prevalence of emergency room visits and/or hospitalization reported by product use over time
    - Frequency of diagnoses associated with emergency room visits and/or hospitalizations reported over time
11. To assess coughing by product
    Endpoints:
    - Cough impact assessed by Visual Analog Scale (VAS),
    - Frequency and intensity of cough using the cough assessment

5 STUDY POPULATION

5.1 Selection of Study Population

4000 participants will be enrolled in the Study, including 2000 IQOS users and 2000 CC smokers.

The study will be an observational open cohort of Japanese adults legally authorized to buy tobacco products in Japan.

5.1.1 Inclusion Criteria

At the screening, in order for each participant to be enrolled must meet the following criteria:

Table 12 Inclusion Criteria

Inclusion Criteria
18. Adults legally authorized to buy tobacco products in Japan (20 years of age)
19. Japanese
20. Participant is able to understand the information provided in the informed consent form (ICF).
21. Signed informed consent form
22. Willing to participate in the study and has access to the internet
23. For IQOS users: o Is currently using IQOS HeatSticks o Has used at least 100 IQOS HeatSticks in their lifetime; and o Has used IQOS HeatSticks for at least 2 months NOTE: The use of IQOS HeatSticks defines the user as an IQOS user, regardless of other tobacco or nicotine product use
24. For CC smokers: o Is currently using CC o Is not currently using IQOS HeatSticks, and o Has used at least 100 CC in their lifetime

5.1.2 Exclusion Criteria

Participants who meet any of the following exclusion criteria at screening must not be enrolled into the study.

Table 13 Exclusion Criteria

Exclusion Criteria
1. Tobacco industry employees 2. Employed by the Sponsor, CRO or Clinical Site 3. For IQOS users: o More than 12 months of IQOS use 4. For former smokers: o Is not currently using CC o Is not currently using IQOS HeatSticks, and o Has used at least 100 CC and/or IQOS HeatSticks in their lifetime o

5.2 Recruitment Strategies and Retention

As described in section 4.1.1, participants will be recruited into this study using:

- The PM-JP's consumer database (for both IQOS users and CC smokers)
- Market research or other available databases (specifically CC smokers)
- Study Website advertisements and optimization, and advertisements in public locations, which direct potential participants to the Study Website where they can obtain more information on the study and register their interest in participating in the study.

The retention strategies will focus on contacting participants on a regular basis to keep them engaged in the study as well as payment for continued participation. Every time a CASI is completed the participant will be reimbursed for their time and effort. Participants will be provided a reward code for obtaining Rakuten tokens of appreciation to redeem for purchases at the Rakuten website.

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Enrollment and attrition rates will be monitored during the study. In particular, the enrollment strategy may be adapted and sample size may be increased, depending on the actual attrition rate observed during the study conduct.

5.3 Discontinuation of Participants from the Study

Participants will be informed that they are free to withdraw from the Study at any time. Participants can log into the Study Website at any time to discontinue from the Study. They will be asked to record the reason for discontinuation, although they are not obliged to

disclose it. Data collected for enrolled participants prior to the participant's withdrawal will still be used in the analysis.

Participants may be discontinued from the Study for any of the following reasons:

- Withdrawal of informed consent
- The Sponsor terminates the study. If the Sponsor decides to prematurely terminate the study, the participants and IRB will be promptly informed. Lost to follow-up

Participants that discontinue from the study cannot re-enter the study.

5.4 Loss to Follow-Up

[redacted] Helpdesk will perform a reasonable number of attempts to contact the participant including email correspondence and phone calls should be done and documented. The date of the last completed follow-up domain will be recorded and can be used as required for the analyses.

5.5 Violation of Selection Criteria

Eligibility for the Study is assessed using the self-report participant information recorded in the screening domain. Participants not meeting the enrollment criteria will not be enrolled into the Study.

6 RESTRICTIONS AND SUPPORT DURING THE STUDY

Not Applicable

7 STUDY PROCEDURES

An overview of all study procedures is shown in the schedule of events (Appendix 1). In this section, only the expected/planned time points for the various measurements are described. As not all participants will undergo a procedure at the same time, adequate time windows are given for each study procedure and each time point (Appendix 1).

7.1 Study Assessments

7.1.1 Questionnaires

The participant questionnaires used in this study will be entered by the participant directly in the CASI survey. All questionnaires, as well as instructions will be provided in Japanese (the local language).

See Appendix 1 for the time points of assessment.

7.1.1.1 Demographics

Demographic data corresponding to inclusion/exclusion criteria (i.e., sex, age, ethnicity) will be recorded in the screening domain, at this stage potential participants will also be asked how they heard about the study (i.e., invite from PM-JP's consumer database, advertisements, market research or other available databases). Additional demographic questions will be administered in the baseline domain.

See Appendix 1 for the time points of assessment.

7.1.1.2 Core Questionnaires (Baseline and Follow-Up)

The Core Questionnaire is composed of a set of multiple questions (47 questions in the Core Baseline Questionnaire and 151 in the Core Follow-up Questionnaire) (Appendix 2). These questions will be administered specifically based on the subject's product use. These questions include the following domains:

- Detailed tobacco and nicotine containing product use.
- Smoking History
- Intention to stop using tobacco and nicotine containing products

See Appendix 1 for the time points of assessment.

7.1.1.3 Socio-Economic Status (SES)

As part of the characterization of the study population it is important to measure variables that have been shown to be related to nicotine dependence and tobacco product reinforcing value. Based on prior tobacco research these factors include age, gender, tobacco use history, educational as well as socio-economic status.

SES information is recorded in similar manner in the clinical program, in behavioral research and in this study it will be assessed in the post-market setting.

At screening the participants will be informed in details about the exams and evaluations planned during the study, and similarly notified about the SES assessments which will be done at enrollment after they provided informed consent and were enrolled in the study.

Participants will be asked a series of questions related to their education, occupational status, size and annual income of their household (Appendix 33). If the participant does not want to answer the questionnaire, he/she will not be withdrawn from the study.

See Appendix 1 for the time points of assessment.

7.1.1.4 Cough Assessment Questionnaire

Participants will be asked to assess the respiratory symptom 'cough' on a VAS, on three Likert scales, and with an open question. Assessment of cough will be conducted irrespective of the time. Participants will be asked if they have experienced a regular need to cough, e.g., whether they have coughed several times in the previous 24 hours prior to assessment. If the answer is 'yes', participants will be asked to complete a VAS, 3 Likert scales and to answer the open question (Appendix 44).

On the VAS, participants will assess how bothersome their cough was during the previous 24 hours (Appendix 44). The VAS ranges from 'not bothering me at all' to 'extremely bothersome.' Furthermore, participants will assess the intensity and frequency of cough and the amount of sputum production during the previous 24 hours on Likert scales.

The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with 1 =very mild – 2 = mild – 3 = moderate – 4 = severe – 5 = very severe.

The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5, with

1 = rarely – 2 = sometimes – 3 = fairly often – 4 = often – 5 = almost always.

The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3, with 0 = no sputum – 1 = a moderate amount of sputum – 2 = a larger amount of sputum – 3 = a very large amount of sputum.

See Appendix 1 for the time points of assessment.

7.1.1.5 Modified Cigarette Evaluation Questionnaire

Product evaluation will be assessed using the Modified Cigarette Evaluation Questionnaire (MCEQ) (20) (Appendix 5). The MCEQ assesses the degree to which participants experience the reinforcing effects of smoking, by measuring:

- Smoking satisfaction (satisfying, tastes good, enjoys smoking)
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger)
- Aversion (dizziness, nauseous)
- Enjoyment of respiratory tract sensations (single-item assessment)
- Craving reduction (single-item assessment)

The MCEQ will be completed by IQOS users through the CASI.

See Appendix 1 for the time points of assessment.

7.1.1.6 Questionnaire of Smoking Urges (QSU-b)

To assess the urge-to-smoke, all participants will be asked to fill-in a 10-item brief version of the QSU (21) (Appendix 6). The QSU-b items are rated on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores in this questionnaire indicate a higher urge to smoke.

The QSU-b will be completed by the participant through the CASI.

See Appendix 1 for the time points of assessment.

7.1.1.7 Lifestyle Assessment

The lifestyle questionnaire consists of 8 questions on different dietary and physical activity habits (Appendix 7).

- Question 1 frequency of fast food consumption
- Question 2 frequency of alcoholic beverage intake
- Questions 3 and 4 frequency and amount of physical activity
- Question 5 inquires about length of sleep
- Question 6 asks if the household includes a CC smoker
- Questions 7 and 8 self-reported height and weight

Details about when this questionnaire will be administered can be found on the schedule of events (Appendix 1)

7.1.1.8 Perceived Risk Instrument (PRI-P)

The PRI-P is a self-report instrument that has been developed by PMP to assess the perceived risks associated with the use of tobacco and nicotine containing products such as CC, Electronic nicotine devices (ENDs), Modified Risk Tobacco Products (MRTPs). More specifically, the PRI-P aims at assessing the perceived risks to the individual respondent. The PRI-P is comprised of three domains (Appendix 8):

- Perceived Health risk
- Perceived Addiction risk
- Perceived Harm to others

Details about when this questionnaire will be administered can be found on the schedule of events (Appendix 1)

7.1.1.9 Fagerström Test of Nicotine Dependence

The Fagerström Test for Nicotine Dependence is a standard instrument for assessing the intensity of physical addiction to nicotine. The test was designed to provide an ordinal measure of nicotine dependence related to cigarette smoking. It contains six items (Appendix 9). This questionnaire consists of 6 questions which will be answered by the subject himself/herself. The scores obtained on the test permit the classification of nicotine dependence into 3 levels: mild (0-3 points), moderate (4-6 points) and severe (7-10 points) (22).

- How soon after waking does the participant have their first cigarette
- Difficulty in refraining from smoking
- Their ability to give up specific a smoking experience
- Number of cigarettes smoked
- Intensity of smoking during the day
- Smoking during illness

Details about when this questionnaire will be administered can be found on the schedule of events (Appendix 1).

7.1.1.10 Self-reported Changes Questionnaire (SRCQ)

The SRCQ will be administered at enrollment and then throughout the first year of follow-up until month 12 within the CASI. The SRCQ will focus on self-observed aesthetic changes seen after adopting IQOS HeatSticks. It is composed of 6 questions about:

- Skin appearance

- Ease of exercise
- Sense of smell
- Sense of taste
- Own and/or Spouse's perception of participant's breath
- Teeth appearance

This questionnaire can be found in (Appendix 10)

7.1.1.11 Self-Reported Health Outcomes and Events Questionnaire

A self-reported health outcomes questionnaire will be administered at enrollment, annually as well as Months 9 and 30 within the CASI. The self-reported outcomes and events questionnaire will focus on signs, symptoms and diagnoses of smoking-related diseases as well as on health related events such as hospitalizations. The self-reported health questionnaire can be found in Appendix 11.

8 SAFETY REPORTING

8.1 Definitions

- For adverse events for tobacco products: an AE is any health-related event associated with the use of tobacco product in humans, which is adverse or unfavorable, whether or not it is considered related to the tobacco product.
- Serious adverse event – A serious adverse event is an adverse event that results in any of the following: death; a life-threatening condition or event; persistent or substantial disability or incapacitation; hospitalization or prolonged hospitalization; or a congenital anomaly or birth defect.

8.2 Assessment of Adverse events

As this study is observational by design and is conducted in a post-market setting, adverse event (AE) reporting will follow the sponsor's already established post-market Safety Surveillance Procedures for spontaneously reported events. IQOS users will be reminded of the product quality complaints (including AEs) hotline that has been established for all users of IQOS in Japan.

The PMP hotline information is printed on the packaging and included in the product information. Study personnel will be informed about the PMP hotline. Calls to the Study hotline by IQOS participants reporting spontaneously adverse events will be transferred to the PMP hotline.

9 STUDY ACTIVITIES

A detailed schedule of assessments can be found in Appendix 1.

9.1 Screening

Screening will be done entirely online as defined in section 4.1.2.

9.2 Recruitment Period

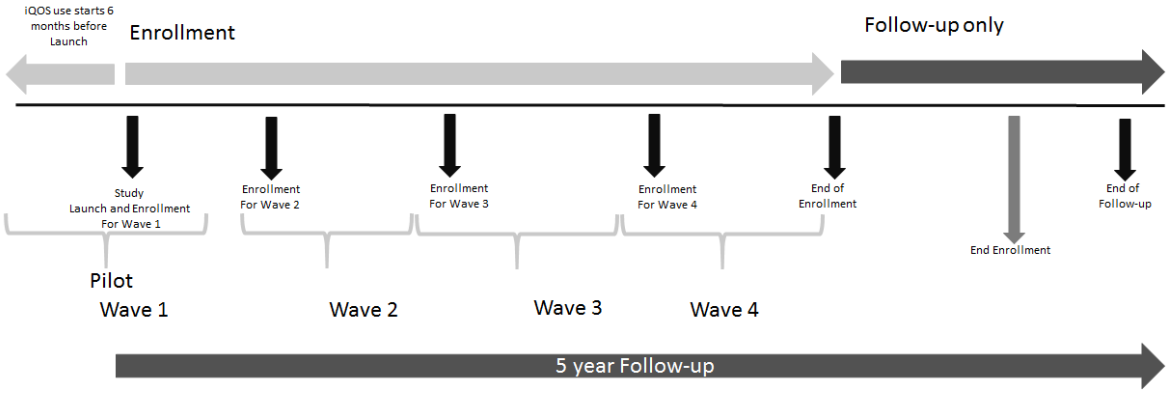
This cohort will be open for recruitment for about 4 years. Recruitment will be performed in 4 annual waves. Each annual wave will span a one year period, however, the definition of an annual wave will vary for IQOS users and CC smokers.

For IQOS users, an annual wave is defined by when the IQOS users start using IQOS. The first wave (i.e., the pilot wave) will cover IQOS users who initiate IQOS within 6 months prior to the launch of the study. Enrollment for IQOS users will remain open for any given wave until the wave is full (500 IQOS users) or 12 months after the last possible initiation date for the annual wave. Additionally, for wave 2 a new CASI system will be launched and the wave definition for IQOS users will start 4 months prior to the system launch. **.** The question flow of the new CASI system is dynamic. In order to ensure collecting consistent data, the questions asked depend of answers provided during the current and during the last CASI. Therefore wave 1 data that are required to display dynamically in order to administer the questions of wave 2 CASI will be transferred and classified. During this transition period there will be no enrollment into the Study. Subsequent waves will follow sequentially. A graphic representation of the waves can be found in Figure 2.

For CC smokers, an annual wave is defined by the date of enrollment into the study. The first wave will start with study launch and run for a period of 12 months. This means only 1 wave can be open for enrollment at a given time for CC smokers. In the event that enrollment is met in less than 12 months for a CC wave, the next annual wave will open for enrollment in alignment with the IQOS wave. A graphic representation of the waves can be found in Figure 3.

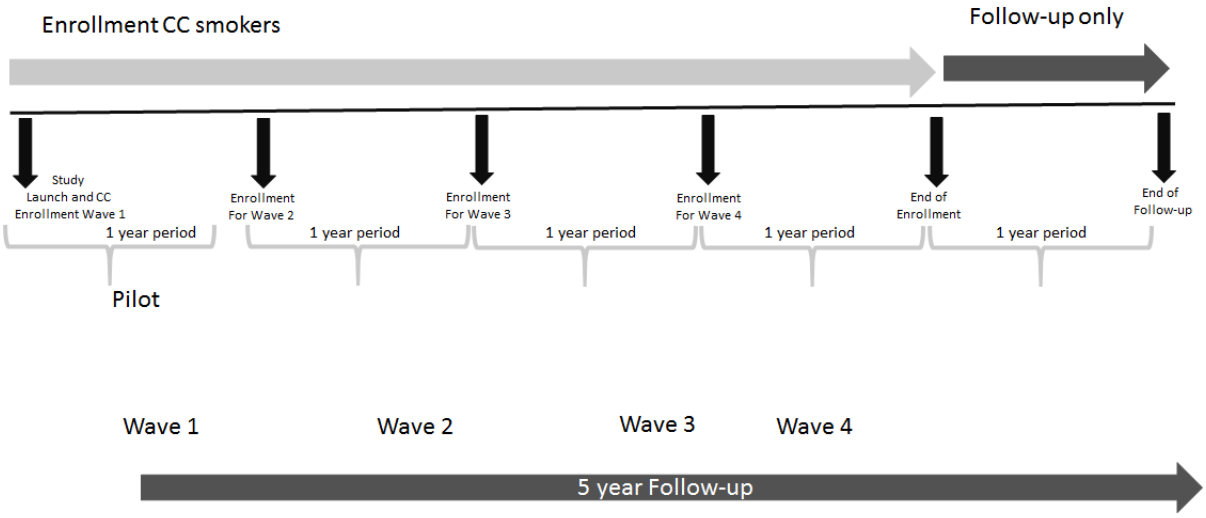
In general, although the study is open to all participants that register, because of the timing of the product launch and the start of the study the pilot wave will, by definition, target IQOS users in Nagoya, and therefore the recruitment plan will reflect this to ensure equal considerations are given to the CC participants registering into the study.

Figure 2 Definition of Annual Waves for IQOS users



- According to this scheme an iQOS wave is defined by the time in a calendar year that the iQOS users have started using iQOS.
- Enrollment will end when the yearly quotas have been reached or it is not possible to enroll iQOS users based in the Wave definition (more than 1 year of use). In this sense, there can be more than 1 Wave open for enrollment
- If the enrollment finishes earlier (enrollment is optimal and all subjects have been enrolled as per the quotas) the start of the next wave is still at the beginning of the next 'calendar year of iQOS use'
- Waves are not associated to geographical area of subjects included, only by time of iQOS use start.
- Subjects will complete a minimum of 1 year follow-up and a maximum of 5-years follow-up.

Figure 3 Definition of Annual waves for CC smokers



- According to this scheme a wave for CC is defined by the time in a calendar year that the CC smoker is enrolled.
- End enrollment is for CC smokers end after 12 months from the beginning of wave enrollment.
- If CC enrollment is completed earlier, the next wave enrollment can start at the earliest aligned with enrollment for the iQOS wave.
- Waves are not associated to geographical area of subjects included.
- Subjects will complete a minimum of 1 year follow-up and a maximum of 5-years follow-up.

10 QUALITY CONTROL AND QUALITY ASSURANCE

Not Applicable.

10.1 Training of Staff

Not Applicable.

10.2 Audits and Inspections

Good Epidemiological Practice guidelines do not specify independent inspections of clinical program activities, however, in order to guarantee adequate site performance, such inspections may be performed at any time before, during and/or after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or an IRB/IEC may perform audits or inspections. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed and accurately reported according to the protocol, GEP guidelines (1), the Ethical Guidelines for Medical and Health Research Involving Human Subjects (2) and any applicable regulatory requirements. The PI or designee will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their site.

11 DATA MANAGEMENT ACTIVITIES

All data management activities will be described in details in the data management plan (DMP) and documents specified therein. The electronic systems used and CASI, to collect participant data will be FDA 21 CFR Part 11 compliant.

11.1 Data Capture

11.1.1 Data Capturing Tool and Study Records

All questionnaires including screening and enrollment domains will be provided in electronic form (through the data capturing tool) to the participant in Japanese. The participants' questionnaires and the VAS will be entered by the participants directly in their computer or electronic device. The data capturing tool allows participants to use different devices to submit their entries on the device they are using at the time of receiving the reminder to complete a (set of) questionnaire(s).The participants will enter surveys via the link embedded in the survey reminder message they will receive once enrolled and the subsequent questionnaire is due.

11.1.2 Protocol Deviations

Protocol deviations at the individual participant level should be minimal in an observational study such as this one, but erroneous inclusions and other deviations from protocol could potentially take place. In addition, deviations in the execution of the study (such as not following the sampling procedure outlined in the protocol) could affect the outcomes or interpretability of the study, even though they are not associated with a particular subject. For this matter, the statistical analysis plan (SAP) will detail the documentation of eligibility protocol deviations from the data received from [redacted]. Any other protocol deviations identified during the study will be recorded into the Protocol Deviation tracker.

The overall procedure for managing protocol deviations is described in the SOPs and/or agreed upon procedure of the CRO team.

11.2 Data Handling

All study data, collected with [redacted] CASI system will be managed by the data management team and the statistical team at the CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the CRO data management team. The data management team at the CRO will prepare a DMP, to be reviewed and approved by the Sponsor, prior to the go life of systems used to capture study

data. This document will describe, in details, the data management-related procedures and processes.

All data collected during the study are declared property of the Sponsor, irrespective of the location of the database and the data management CRO.

Additional details are covered in the DMP.

11.2.1.1 Data Validation

The data will be validated as defined in the DMP and Data Validation Specifications. Discrepancies will be reported as defined in DMP and Data Validation Plan.

11.2.1.2 Data Reconciliation

The wave 1 participants will be migrated to the new wave 2 [redacted] CASI system. Only data used for participant identification and the data used for dynamic question flow will be migrated from wave 1 CASI to wave 2 new CASI. Therefore the reconciliation of the data extracted out of the 2 CASI system will be done outside the CASI systems by the CRO data management team. The data reconciliation process will be defined in the DMP.

11.2.1.3 Database Lock

When all outstanding Data Management issues have been resolved and all validation, quality review, and cleaning activities are complete, the database or selected data is/are declared soft locked. Access to change data in the soft-locked database or to change selected data at this time is limited.

After the data is reviewed by the Sponsor, resolution of all raised queries and QC of the changed data, database, or selected data upon Sponsor approval as applicable, is declared locked.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the Data Management and Statistical Team at the CRO. Any of those changes must be documented in the database log file.

After study completion, the Study database will be transferred to the Sponsor in the format specified in the DMP in Clinical Data Interchange Standards Consortium's Study Data Tabulation Model Data Structure Specifications.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

The results from this study will be analyzed by annual wave and overall (including all available waves) and will be reported annually.

Full details of the statistical analysis will be given in a statistical analysis plan (SAP). Any changes to the planned statistical methods will be documented in the study report. The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Definitions

Independent of recruitment waves, calendar time will be translated into **study time** (**ST_i**) ranging from the start of the study (0) to 60 months.

Measurement times (**MT**) are in ST_i (study entry, 3 months, 6 months …) as defined in Appendix 1.

Individual person time (**PT**) is the total duration that an individual has spent in the study at any MT_i. Of note, for IQOS users product use periods prior to entering the study are added to their person-time.

Current behavior at MT_i (i being ST in months), will be denoted CB_i and will be defined as described [redacted]. Additional CB_i or sub-category CB_i may be added during data analysis which will be specified in the SAP.

Table 14 Current Behaviors Definitions (percentages defined in 12.2)

CB(i)	Notation at MT(i)	Definition
Daily THS	Daily THS_i	• THS ≥ 1/day, • each OTP <1/day, • CC < 1/day
Daily CC Smoker	Daily CC_i	• THS = 0/day, • CC ≥ 1/day, • each OTP < 1/day
Daily OTP user	Daily OTP_i	• THS = 0/day, • 0 ≤ CC < 1/day, • At least one OTP ≥ 1/day
Dual THS – CC	DU_THS_CC_i	• THS ≥ 1/day,

CB(i)	Notation at MT(i)	Definition
		• CC ≥ 1/day, • each OTP <1/day
Dual THS – OTP	DU_THS_OTP$_i$	• THS ≥ 1/day, • At least one OTP≥ 1/day, • CC < 1/day
THS – CC-OTP	PU_THS_CC_OTP$_i$	• THS ≥ 1/day, • at least one OTP ≥ 1/day, • CC≥ 1/day
Occ THS	Occ_ THS$_i$	• THS < 1/day, • all OTP <1/day, • CC < 1/day
Occ THS-CC-OTP	Occ_THS_CC-OTP$_i$	• THS < 1/day, • CC ≥ 1/day • at least one OTP ≥ 1/day
Occ THS-CC	Occ_THS_ CC$_i$	• THS < 1/day, • CC ≥ 1/day • all OTP < 1/day
Occ THS-OTP	Occ_THS_ OTP$_i$	• THS < 1/day, • at least one OTP ≥ 1/day • CC < 1/day
Non User/Smoker	Non_Smoker$_i$	• THS = 0/day, • CC = 0/day, • each OTP = 0/day,
Occ User/Smoker	Occ_Smoker$_i$	• THS = 0/day, • 0 ≤ CC < 1/day, • each OTP must be: 0 ≤ OTP <1/day • not (CC=0 and OTPs=0)

Note: OTP includes other Heat-not-Burn products (HnB) except THS
Note: ePD is considered as one of the other tobacco product (OTP) when we determine the CB.

Last behavior (LB) is the behavior at assessment time. When MT_i=AT, LB=CB_i

The behavior at study entry will be named **initial behavior (IB)**. IB will be either C_0 or I_0 for the participants enrolled as CC smoker or IQOS user respectively.

Events assessed at MT_i (i being ST in months), will be denoted **Current Events (CE_i)** and will be defined as described [redacted] . Additional CE_i may be added during data analysis which will be specified in the SAP.

Table 15. Events Definition

CE_i	Notation at MT(i)	Definition
Switching		
First Switch from Initial Behavior to another Behavior	S_i	CBi≠CBi-1 | for any j<i CBj=IB
Initiation		
CC Initiation	I_{CCi}	$CPD_i \geq 1$| for any j<i CPDj<1 Has not used 100 CC in their lifetime
THS Initiation	I_{THSi}	$THSPD_i \geq 1$| for any j<i THSPDj<1 Has not used 100 THS (heatsticks) products in their lifetime
THS Initiation by brand	$I_{THSi\_brand\ name}$	$THSPD_i \geq 1$(stratified by brand) Has not used 100 THS (HeatSticks) products in their lifetime
OTP Initiation	I_{OTPi}	$OTPD_i \geq 1$ Has used OTP less than daily used or not used (wave 1) Has not ever used OTP or not used regularly (wave 2 and following waves) Has not used 100 Ploom capsules in their lifetime (Wave2 and following waves) Has not used 100 Glo Neostiks® in their life (Wave2 and following waves)
CC Re-Initiation	Re-I_{CCi}	$CPD_i \neq 0 \mid CPD_k = 0$, for any k in [j; i-1] where i and j differ by more than 12 months.
THS Re-Initiation	Re-I_{THSi}	$THSPD_i \neq 0 \mid THSPD_k = 0$, for any k in [j; i-1] where i and j differ by more than 12 months.
Quitting attempt/cessation/relapse		
Quit Attempt	QA_i	A quit attempt is defined according to the participant's answer to the intention to stop and quit attempt questionnaire at MT(i)
CC Cessation	CC-$Cess_i$	$CPD_k = 0 \mid CPD_j \neq 0$, for any k in (j; i] where i and j differ by more than 12 months.

CE_i	Notation at MT(i)	Definition
		Has used at least 100 CCs in their lifetime
THS Cessation	$THS\text{-}Cess_i$	$THSPD_k=0 \mid THSPD_j \neq 0$, for any k in (j; i] where i and j differ by more than 12 months.
		Has used at least 100 THS (heatsticks) in their lifetime
OTP Cessation	$OTP\text{-}Cess_j$	$OTPD_k=0 \mid OTPD_j \neq 0$, for any k in (j; i] where i and j differ by more than 12 months.
		Has used OTP daily (wave 1)
		Has used at least 100 heatsticks in their lifetime (wave 1)
		Has used regularly OTP (wave 2 and following waves)
		Has used at least 100 other HnB products (except THS) in their lifetime (wave 2 and following waves)
CC Relapse	$CCrel_i$	$CPD_i \neq 0 \mid CPD_k=0$, for any k in [j; i-1] where i and j differ by strictly less than 12 months.
THS Relapse	$THSrel_i$	$THSPD_i \neq 0 \mid THSPD_k=0$, for any k in [j; i-1] where i and j differ by strictly less than 12 months.
OTP Relapse	$OTPrel_i$	$OTPD_i \neq 0 \mid OTPD_k=0$, for any k in [j; i-1] where i and j differ by strictly less than 12 months.
Consumption changes		
CC Increase	$CCinc_i$	$(CPD_i\text{-}CPD_{i-1})/\ CPD_{i-1} \geq 10\%$
CC Decrease	$CCdec_i$	$(CPD_{i-1}\text{-}CPD_i)/\ CPD_{i-1} \geq 10\%$
THS Increase	$THSinc_i$	$(THSPD_i\text{-}THSPD_{i-1})/\ THSPD_{i-1} \geq 10\%$
THS Decrease	$THSdec_i$	$(THSPD_{i-1}\text{-}THSPD_i)/\ THSPD_{i-1} \geq 10\%$
Product uptake		
THS uptake	$THSuptake_i$	The new THS product one participant uses at specific timepoint and was not used in the previous timepoint based on product use questionnaire
		$THSPD_i \neq 0,\ THSPD_{i-1}=0$
HnB uptake	$HnBuptake_i$	The new HnB products one participant uses at specific timepoint and was not used in the previous timepoint based on product use questionnaire
		$HnBPD_i \neq 0,\ HnBPD_{i-1}=0$

Note: CPD_i, $THSPD_i$, $HnBPD_i$ and $OTPD_i$ are defined in section 12.2.1

Note: The CC Initiation is defined for THS user cohort participants; the THS Initiation is defined for CC smoker cohort participants.

12.1.2 Descriptive Statistics

Descriptive statistics for continuous variables will include number of participants [n], number and percent of participants with data, mean, standard deviation [SD], median, first and third quartile, minimum and maximum. For categorical variables absolute and relative [%] frequency for categorical data) will be presented.

12.1.3 Handling of Missing Values and of Values outside the Detection Limits

For questionnaire data, total scores and domain or subscale scores may be derived using imputation by averaging across neighboring non-missing variables.

Product use at MT(i) if missing, can be interpolated by averaging across neighboring product use at MT(i-1) and MT(i+1). There will be no imputation for missing CE(i). Only the reported CE(i) will be used in the analysis.

Further details will be provided in the SAP.

12.1.4 Significance Level for Inferential Statistics

No inferential statistics are planned.

12.2 Derived and Computed Variables

12.2.1 Product use

Percent consumption of THS, CC, OTP, e-cig and HnB, respectively, with respect to THSPD, CPD, ePD and OTPD will be calculated at MT_i based on THS Tobacco Sticks, CC, e-cigarettes and OTP reported in Product use questionnaire as:

$$\%THS_i = 100 * \frac{\mathrm{THSPD_i}}{THSPD_i + CPD_i + OTPD_i}$$

$$\%CC_i = 100 * \frac{\mathrm{CPD_i}}{THSPD_i + CPD_i + OTPD_i}$$

$$\%OTP_i = 100 * \frac{\mathrm{OTPD_i}}{THSPD_i + CPD_i + OTPD_i}$$

$$\%e-cig_i = 100 * \frac{\mathrm{ePD_i}}{THSPD_i + CPD_i + OTPD_i}$$

$$\%HnB_i = 100 * \frac{\text{HnBD}_i}{THSPD_i + CPD_i + OTPD_i}$$

where CPD_i is the average daily Cigarettes consumption at MT_i, $THSPD_i$ is the average daily THS consumption (Marlboro Heatsticks with iQOS device), $OTPD_i$ is the average daily other tobacco products consumption, $HnBPD_i$ is the average daily HnB products consumption and ePD_i is the average daily e-cigarette products consumption, which is part of the other tobacco products consumption will also be calculated.

Additional percent consumption of tobacco products may be added and will specified in the SAP.

12.2.2 Definition of Product Use Categories

Product use pattern categories over a period ending at MT_i are defined in Table 4 above.

12.2.3 Sample Size

A total of 4000 participants will be enrolled in the Study. Enrolment will happen in four annual waves.

Assuming an annual drop-out rate of 5% and a maximum of 20% of participants changing from CC smoker or IQOS user to another behavior per year, the person-time pool in each group will be for each annually analysis as described in Table 16:

Table 16 Expected person-time pool for each annual analysis

Wave	Year 1 Report	Year 2 Report	Year 3 Report	Year 4 Report	Year 5 Report
1	375	281	210	157	117
2		375	281	210	157
3			375	281	210
4				375	281
Total (Person-Years)	**375**	**1031**	**1897**	**2920**	**3685**

This sample size and the study duration is sufficient for an assumed 1% of participants for a particular period (CB_i; CB_{i-1}) to estimate this behavior with a precision of less than 1.32% at the first annual analysis and up to less than 0.62% at the final annual analysis.

12.3 Analysis Populations

All participants that enroll in the Study and complete at least one baseline questionnaire (at a minimum the product use questionnaire) as part of the enrollment process will be included and reported as the Study Population.

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12.4 Study Analysis

12.4.1 Study Endpoints

See section "Study Objectives and endpoints" for a description of the Study endpoints.

12.4.2 Baseline Comparability

Not applicable.

12.4.3 User Group and Product Use Behavior

See section 12.1.2 "Descriptive Statistics" for a description of the methodology for descriptive statistics in the study.

12.4.3.1 Demographics and Baseline Characteristics

All data will be presented in listings, ordered by baseline usage group and subject, unless otherwise specified. Demographic data include age, sex, occupation, etc.

Descriptive statistics for continuous variables (number of subjects [n], number and percent of subjects with missing data, mean, standard deviation, median, first and third quartiles, minimum and maximum for continuous data, and the n and absolute and relative (%) frequency for categorical data) will presented by usage group and overall at each time point, where applicable.

12.4.3.2 Product Use Level

To assess objective 1, the following analysis will be conducted.

Summary tables of use of tobacco and nicotine containing products over time for all enrolled participants will be presented by Cohort at baseline, by CB (i) group and overall participants at MT (i) at post baseline, including:

- Mean number of cigarettes smoked (per day) - CPD(i)
- Mean number of THS Tobacco Sticks used (per day)- THSPD(i)
- Mean number of Heat-not-Burn products used (per day)- HnBPD(i)
- Mean number of other cigarettes product used (per day)- OTPD(i)
- Mean number of e-cigarettes used (per day)- ePD(i)
- Percent of THS Tobacco Sticks used (%THS)
- Percent of cigarettes used (%CC)
- Percent of other cigarettes product used (%OTP)
- Percent of e-cigarettes used (%e-cig)
- Percent of Heat-not-Burn products used (%HnB)

The table will be repeated by sex, age group and enrollment wave in the Study. Tables will also be presented by CB.

The following figures will be provided at each measurement time.

- Bar chart of CPD(i), THSPD(i), ePD(i) and OTPD(i) with 95% CI by CB(i-1) and CB(i) group at each measure time MT(i).

Additional statistical analyses will be specified in the SAP.

Corresponding information is provided in participant data listings.

12.4.3.3 Product Use Patterns

The table of current behavior, CB(i), at MT(i) will provide the information of product use patterns.

Summary table of the product use patterns will be evaluated by CE(i) and presented by CB(i) group at MT(i). The product use patterns includes product switching, initiation, re-initiation, quitting attempt, cessation, relapse, consumption changes and product uptake. Additional product transition table will also be provided between CB(i-1) and CB(i). Participants who have tobacco and nicotine product use transitions will be tabulated by previous and current behavior at each study year. The median of time to first product use transitions (behavior switch) will be calculated via Kaplan-Meier estimators and presented by cohort, IB and CB.

The following outputs will be repeated by sex, age group and enrollment:

- Descriptive Statistics of Current Behavior
- Descriptive Statistics of Current Event by Current Behavior
- Descriptive Statistics of Uptake of HnB Products by Current Behavior
- Descriptive Statistics of Transitions Across Behaviors

Additional statistical analyses will be specified in the SAP.

The following figure will also be provided:

- Bar chart of CB(i) group at each measurement time MT(i).

Corresponding information is provided in participant data listings.

12.4.3.4 Quit Attempts

To characterize the quit attempts by cohort at study entry and by CB(i) group at each MT(i) post baseline,, the following information will be presented in the:

- Rate and number of self-reported quit attempts
- Characteristics of the quit attempts, including:
  - Length of quit attempt
  - Type of product used to help in quit attempts (if applicable)
  - Reasons for quit attempt
  - Outcome of quit attempt (Success or Restart using tobacco products)

More detail will be given in the Statistical Analysis Plan.

12.4.3.5 Perceived Risks

To assess the perception of risk associated with using CC, MRTPs and ENDs, the related information based on cohort at baseline and CB(i) group at post baseline will be presented in tables at each MT(i) using the following domains:

- Perceived health risk scale
- Perceived addiction risk scale
- Perceived harm to others single items

The tables will be provided separately for CCs, MRTPs and ENDs.

The details of score calculation rule are specified in SAP.

Summary statistics will be also provided by current behavior regardless of time point in table for perception of risk associated with using CC, MRTPs and ENDs.

12.4.3.6 Strength of Nicotine Dependence

The strength of nicotine dependence of the Main Study will be analyzed by cohort at baseline and by CB(i) group according to the behavior at MT(i) post baseline as follows:

- Total score from the Fagerström Test for Nicotine Dependence (FTND) questionnaire

The tables will be repeated by CB(i), CB(i-1) and CB(i), sex, age group and enrollment wave.
Summary statistics will be also provided by current behavior regardless of timepoint for total score from FTND.

Corresponding information is provided in participant data listings.

12.4.3.7 Self-Reported Signs and Symptoms and Hospitalizations

The self-reported signs and symptoms including cough and the hospitalizations of the Study will be analyzed by CB(i) group. One participant can be counted only once with the worse scenario under overall category.

The cough result will be analyzed by cohort at baseline and by CB(i) group and overall in participants at post baseline MT(i).

To describe the rates of self-reported signs, symptoms and diagnoses from health outcome questionnaire, the following information will be presented:

- Signs and symptoms: It is counted when any kind of symptoms or diseases reported associated with cardiovascular or respiratory disease, or cancer. It can be from the conditions/diseases or symptoms.
- Cardiovascular disease diagnoses: myocardial infarction, stroke, new diagnoses of hypertension, unstable angina, or other cardiovascular diseases
- Respiratory diseases diagnoses: new diagnoses of chronic obstructive pulmonary disease (COPD), or other respiratory diseases, including asthma exacerbations
- Malignancy diagnoses: all malignancies, including smoking-related malignancies (i.e., lung, larynx, and bladder)

To summarize the number of health related events (hospitalizations) from health outcome questionnaire, the following information will be presented:

- Rate of prevalence of emergency room visits and/or hospitalization reported by product use over time
- Frequency of diagnoses associated with emergency room visits and/or hospitalizations reported over time

To assess coughing by product use from cough assessment questionnaire, the following two tables will be provided:

- Frequency and intensity of cough using the cough assessment
- Cough impact assessed by Visual Analog Scale (VAS)

If there is more than one response of specific participant during study from cough assessment, the worst response (worst answer or highest score) will be used in the overall summary.

The tables will be repeated by sex, age group and enrollment wave for self-reported signs and symptoms, health related events (hospitalizations) and cough assessment questionnaire.

Corresponding information is provided in participant data listings.

12.4.4 Inferential Analyses

All analyses in this study are descriptive. Therefore, no inferential analysis is planned.

12.5 Interim Analysis

There will be annual descriptive interim reports on the study objectives but no decision will be made based on the results. In addition to the specified analyses, additional administrative evaluation of study progress may be conducted.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Study Investigator and Study Administrative Structure

13.1.1 Principal Investigator – Main Study

Name: Dr [redacted]	Institution: [redacted] Address: [redacted], Nagoya, [redacted] Japan Phone: +81[redacted] Email: [redacted]

13.1.2 Sponsor

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[redacted] Clinical Data Manager	Phone: +41 (58) [redacted] Mobile: +41 (79) [redacted] E-Mail: [redacted]

13.1.3 Other Responsibilities

[redacted]

[redacted] is the Contract Research Organization designated by PMI to manage and monitor the study: all duties and responsibilities transferred to [redacted] by PMI will be defined in the agreement signed between the two parties.

[redacted]

13.2 Participant Confidentiality

All information obtained during the conduct of the study with respect to the participants' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the participant. An agreement to disclose any such information will be obtained in compliance with all local and national data protection and privacy legislation. Participants will sign the agreements electronically

The anonymity of participants participating in this study will be maintained. Participants will be identifiable by the Sponsor (or Sponsor's authorized representative) on pertaining documents by their participant number/code, sex and date of birth, but not by name, initial, or any other details relating to identifiable person (e.g., address, health insurance ID card, medical chart number, etc.). The assignment of a participant number/code for participant identification will be based on the appropriate data protection rules.

[redacted] Helpdesk and [redacted] or [redacted] will have access to email, geographical data and phone number. This is in order to be able to contact the participants to remind them to complete their CASIs, or to discuss with them any other information/query.

In the exceptional case where an IQOS user a) is recruited into the study through PM-JP's consumer database, and b) communicates in one of the follow-up CASIs of his/her intention to quit smoking or using IQOS. His/Her email address will be shared with PM-JP so that this participant no longer receives any commercial communication from the Sponsor moving forward. No other identifiers will be shared with the Sponsor so that no study data will be linked to that email address.

13.3 Access to Source Documentation

NA.

13.4 Record Retention

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced must be retained by the PI or the head of the investigational site for a minimum of:

- At least 15 years after completion or discontinuation of the study, or
- At least 2 years depending on, for example, the circumstances, or
- After formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

Examples of essential records/documents include, but are not limited to:

- Record of all communications between the PI and the IRB, composition of the IRB
- Record of all communications/contact between the PI, Sponsor, and its authorized representatives
- Study specific questionnaires (and associated data/scoring)
- All other source documents or any electronically captured study source data
- Information regarding participants' discontinuation and any follow-up

It is the responsibility of the Sponsor to inform the PI/head of investigational site as to when these documents no longer need to be retained.

The PI/head of investigational site must take measures to prevent accidental or premature destruction of these documents.

If the head of the investigational site wishes to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

The Sponsor or Sponsor's authorized representative will maintain documentation relating to the study for 15 years after the CSR has been finalized.

13.5 Study Report

The Sponsor must ensure that a study report for this study is prepared regardless of whether the study is completed or prematurely terminated. In certain circumstances, an abbreviated study report may be acceptable. Submission of the study report to the IRB will be complied with as requested by local requirements.

The results of the additional variables for analysis will be presented in reports separate from the study report.

13.6 Publication and Disclosure Policy

This document contains data, information and trades secretes that are confidential and proprietary to the Sponsor. This document is being provided solely for the purpose of evaluation and/or conducting this study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IRB, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice will be given to the Sponsor prior to any such disclosure.

The Sponsor plans to disclose details of the study protocol on a web-based, publicly available, clinical trial register database (e.g., ClinicalTrials.gov).

13.7 Insurance

For the conduct of this type of study, an insurance plan is not necessary.

14 APPENDICES

Appendix 1 Schedule of Events

Assessments		Screening Domain	Baseline Domain	Observational Period (in months of exposure to IQOS)										
	Study Month[a]			Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 48	Month 60
	Time Point	t_0	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}
ICF		•												
Inclusion and exclusion criteria		•												
Participant characteristics and contact details		•												
Enrollment		•												
Demographics			•											
SES questionnaire			•				•			•		•	•	•
Core Questionnaire		•		•	•	•	•	•	•	•	•	•	•	•
Lifestyle assessment			•	•	•	•	•			•		•	•	•
MCEQ[b]			•	•	•	•	•			•				
QSU-b			•	•	•	•	•							
Fagerström Test for Nicotine Dependence			•	•	•	•	•	•	•	•	•	•	•	•
Perceived Risk Instrument (PRI-P)			•				•			•		•	•	•

Assessments		Screening Domain	Baseline Domain	Observational Period (in months of exposure to IQOS)										
	Study Month[a]			Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 48	Month 60
	Time Point	t_0	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}
SRCQ[b]				•	•	•	•							
Self-reported signs and symptoms & health outcomes questionnaires			•			•	•			•	•	•	•	•
Cough assessment questionnaire			•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations ICF = Informed consent form; MCEQ = Modified Cigarette Evaluation Questionnaire; SES = Socio-economic status; QSU-b = Questionnaire for Smoking Urges-brief;

[a] Study months – for IQOS users the study months are calculated from the self-reported date that they stated using IQOS, for CC smokers the study months are equivalent to months of follow-up.

[b] For IQOS users only

Appendix 2 Core Questionnaires

The “Smoking History Questionnaire” will be provided in a separate document.

Appendix 3 Socio-Economic Status Questionnaire

The “Socio-Economic Status Questionnaire” will be provided in a separate document.

Appendix 4 Cough Assessment Questionnaire

The “Cough Assessment Questionnaire” will be provided in a separate document.

Appendix 5 MCEQ Questionnaire

The “MCEQ Questionnaire” will be provided in a separate document.

Appendix 6 QSU-b Questionnaire

The “QSU-b Questionnaire” will be provided in a separate document.

Appendix 7 Lifestyle Questionnaire

The “Lifestyle Questionnaire” will be provided in a separate document.

Appendix 8 Perceived Risk Instrument (PRI-P)

The "Perceived Risk Instrument (PRI-P) Questionnaire" will be provided in a separate document.

Appendix 9 Self-reported Changes Questionnaire

The “Self-reported Changes questionnaire” will be provided in a separate document.

Appendix 10 Fagerström Test for Nicotine Dependence

The “Fagerström Test for Nicotine Dependence Questionnaire” will be provided in a separate document.

Appendix 11 Signs and Symptoms & Self-Reported Outcomes Questionnaire

The “Signs and Symptoms & Self-Reported Outcomes Questionnaire” will be provided in a separate document.

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