PMI RESEARCH & DEVELOPMENT

Safety Update Report
Tobacco Heating System 2.2 Regular
Appendix A - Reference Safety Information

Report Number:	PMI_SURV_2015_SUR01
Period Covered:	01 May 2014 to 30 April 2015
Product Name:	Tobacco Heating System 2.2 Regular
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	Final v1.0
Date:	25 June 2015
Author:	Samia Reffas Jobin, PhD Senior Safety Scientist UBC: An Express Scripts Company
Reviewed and approved by:	Alexandr Meszaros, MD Senior Medical Scientist - Surveillance Philip Morris Products S.A. John Magnette, MD, DipPharmMed, FFPM Manager Product Surveillance Philip Morris Products S.A. Frank Lüdicke, MD Director PASS Philip Morris Products S.A.

Appendix A – Reference Safety Information

- Investigator's Brochure: list of changes during the review period
- Investigator's Brochure Edition 3.0, dated 14 April 2014
- Investigator's Brochure Edition 5.0, dated 27 April 2015

List of Changes During the Review Period

Product	Edition	Version	Approval date
THS 2.2 Regular	3	1.0	14 Apr 2014
THS 2.2 Regular	3	2.0	19 May 2014
THS 2.2 Regular	4	1.0	24 Nov 2014
THS 2.2 Regular	5	1.0	27 Apr 2015

From Edition 3 v. 1.0 to Edition 3 v. 2.0 (14 April 2014 - 19 May 2014)

From Edition 3 v. 1.0 to Edition 3 v. 2.0 (14 April 2014 - 19 May 2014)	
After a delay for the FDA submission, the IB was re-opened, for minor updates.	
Section & Paragraph	**Changes**
3.2. Description of the product - Product use	The number of puffs, "up to 12", was adjusted to "up to 14". This IB version went through the whole signature cycle, and was renamed Edition 3, version 2.0.
6.2. Guidance for the Investigator - Use of product	A new software allows the reduction of the pre-heating time from 30 to 20 sec.

From Edition 3 v. 2.0 to Edition 4 (19 May 2014 – 24 November 2014)

From Edition 3 v. 2.0 to Edition 4 (19 May 2014 – 24 November 2014)	
Section & Paragraph	**Changes**
Abbreviations	Table was updated.
Section 2.2 Table 2	Was updated with the mention of FR1 and Dorado II blends. Comparability between aerosol chemistry between two blends was added (included reference of comparability report)
Section 3.1 Table 3	Bill of Material was updated with data generated for Dorado II.
Section 3.1 Table 4	Tobacco plug composition was updated with data generated for Dorado II.
Section 3.1 Table 4	Reported aerosol fractions were updated with data generated for Dorado II.

From Edition 4 to Edition 5 (24 November 2014 – 27 April 2015)

From Edition 4 to Edition 5 (24 November 2014 – 27 April 2015)	
Section & Paragraph	**Changes**
Abbreviations	Table slightly updated.

Section 1.3	Update on THS 2.2 studies status
Section 2.1	Update on THS 2.2 studies status including presentation of PBA studies.
Section 2.2 Table 2	Added in footnote that Dorado II is also valid for IB Edition 5.
Section 3 Tables 3 and 4	Added a footnote that "*Values in this table are representative. They may slightly vary from batch to batch*" + an explanation in the text "*The average weights in the Tobacco Plug composition may slightly differ from batch to batch. Only batches within specifications are released for use*." This decision was taken to reflect slight changes in the numbers given in the tables, which vary slightly from batch to batch while remaining within specifications (a second batch "wave 2" had to be produced to cover needs of the whole ERS and PBA07 studies)..
Section 4.3.1	Reference to experiments with THS 1.0 was removed, as there are no more experimental data on this version (also in conclusion 6.9).
Section 5	Update on THS 2.2 studies status has been added, with clarification on those run with menthol or non-menthol P1 (+ NCT numbers).
Section 5.2.1	Reason for higher basal levels of o-toluidine was modified (enquiry has shown that it is unlikely to be due to fresh painting of one of the rooms on site, but rather to contamination by sampling material).
Section 5.4	Update on safety of THS 2.2
Section 5.5	iQOS launch was added
Section 6.5	Update on safety of THS 2.2
Section 6.9	Reference to experiments with THS 1.0 was removed.
Section 6.10	Update on safety of THS 2.2

PMI RESEARCH & DEVELOPMENT

Investigator's Brochure

THS 2.2

Sponsor:	Philip Morris Products S.A., Research & Development
Version number:	Version 1.0
Edition number:	Edition 3
Release date:	14 April 2014
Previous release date:	11 April 2013

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS AND ACRONYMS

1-OHP	1-hydroxypyrene
2-NA	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
3R4F	Kentucky 3R4F Reference Research Cigarette
4-ABP	4-aminobiphenyl
AE	Adverse event
AMES	Salmonella Reverse Mutation Assay
$AUC_{(0\text{-last})}$	Area under the concentration-time curve from T_0 to time of last quantifiable concentration
BoExp	Biomarker(s) of exposure
CC	Conventional cigarette
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
C_{max}	Maximum concentration
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CT	Cardiovascular toxicant
CYP1A2	Cytochrome P450 1A2
ECG	Electrocardiogram
EHCSS	Electrically Heated Tobacco System
FDA	U.S. Food and Drug Administration
FD&C Act	The Federal Food, Drug, and Cosmetic Act
GVP	Gas vapor phase
HCI	Health Canada Intensive
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHCs	Harmful and potentially harmful constituents
HR	Heart rate
HRV	Heart rate variability
ICH	International Conference on Harmonization
ISO	International Organization for Standardization

MHBMA	Monohydroxybutenyl mercapturic acid
MLA	Mouse Lymphoma TK Assay
MRTP	Modified risk tobacco product
NEQ	Nicotine equivalents
NFDPM	Nicotine free dry particulate matter
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
N/M	Not measures
NRT	Nicotine nasal spray
NRU	Neutral Red Uptake assay
OECD	Organisation for Economic Co-operation and Development
o-tol	o-toluidine
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMI	Philip Morris International
QSU	Questionnaire of Smoking Urge
RH	Room humidity
RPP	Rate-pressure product
SA	Smoking abstinence
SAE	Serious adverse event
S-PMA	S-phenylmercapturic acid
THS	Tobacco heating system
TPM	Total particulate matter
t_{max}	Time to the maximum concentration
WHO	World Health Organization

1 SUMMARY

One of Philip Morris International's (PMI) priorities is to develop tobacco products that are acceptable to smokers, that can substitute for conventional cigarettes (CC), and that exhibit less health-related risks compared to CC. Candidate modified risk tobacco products (MRTPs) such as the Tobacco Heating System (THS) replicate the ritual of smoking but without combustion. Many harmful and potentially harmful constituents (HPHCs) in cigarette smoke are formed due to the burning of tobacco [1]. Thus, lowering the temperature and heating the tobacco instead of burning it can substantially reduce or eliminate HPHCs. PMI's THS avoids combustion by heating tobacco to significantly lower temperatures than CC.

1.1 Description of the Product

THS 2.2 is comprised of three main components: (1) the THS Tobacco Stick, which is a single-use consumable item, (2) the Holder, which provides the power source for a single use and heating control electronics, and (3) the Charger, which enables the Holder to be recharged. To use THS 2.2, the consumer inserts the THS Tobacco Stick into the Holder to pre-heat it. Thereafter, the aerosol generated by the heating process is inhaled by placing the lips on the mouthpiece filter and drawing air through the THS Tobacco Stick. During use, the THS Tobacco Stick is warmed according to a carefully controlled temperature profile within the holder to heat the tobacco without combustion while at the same time providing an acceptable consumer experience in a consistent manner. When testing earlier development versions of THS in clinical studies, subjects were able to substantially reduce their exposure to selected HPHCs. However, consumer acceptance of those product versions was low, in part due to their design features. Based on this experience, THS has been improved and the temperature at which the Tobacco Stick is heated was further reduced to less than 350 °C in the current version, THS 2.2.

1.2 Non-Clinical Studies

The non-clinical assessment of THS supports the initiation of the new clinical studies described in this Investigator's Brochure. No new or increased toxicological hazard in the THS aerosol was detected compared with CC smoke. Chemical analysis of the aerosol confirmed that none of the measured HPHCs from THS 2.2 increased compared to CC. The biological activity of the aerosol was tested *in vitro* and *in vivo*. A number of *in vitro* assays were performed to assess the cytotoxicity and genotoxicity of the total particulate matter (TPM) and gas vapor phase (GVP) fractions of the aerosol. The subchronic toxicity of the aerosol *in vivo* was evaluated in a 90-day inhalation study in rats. *In vitro* and *in vivo* results corroborated the concept that the absence of combustion when heating tobacco substantially lowers toxic effects.

1.3 Product Experience in Humans

Several clinical studies were conducted on THS 1.0, an earlier development version of THS 2.2, in Europe, Asia, Africa and the United States. Information about the earlier development of THS is provided in Table 2. All studies showed reductions in exposure to the majority of measured HPHCs from both TPM and GVP fractions in subjects who used THS 1.0 as compared to subjects who continued to smoke CC, both in controlled and ambulatory conditions. No clinical studies were conducted with the next developmental version of THS, namely THS 2.0.

In 2012, THS 2.1, was tested in two exploratory clinical studies to measure the nicotine plasma pharmacokinetic (PK) profile and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1. The observed nicotine plasma PK profile for THS 2.1 was similar to CC, and there were significant reductions in the exposure to the majority of selected HPHCs. The clinical data available on the former THS versions is described in detail in Section 5.

Four clinical studies were initiated in 2013 to assess the PK of nicotine and reduced exposure to HPHCs with THS 2.2 for periods lasting up to 3 months. So far, clinical studies have revealed no safety concerns for either of the variants of THS tested, namely THS 1.0, 2.1 and 2.2.

2 INTRODUCTION

2.1 Tobacco Harm Reduction

PMI's approach to harm reduction for current smokers is to develop novel tobacco products, such as the candidate MRTP THS 2.2, to reduce the risk of tobacco-related diseases compared to CC by reducing or eliminating, to the extent possible, HPHCs in the aerosol. There is no 'safe' tobacco product and the best way to reduce the adverse health consequences of smoking is to quit tobacco use.

The Tobacco Advisory Group of the Royal College of Physicians opined in 2007 that "if nicotine could be provided in a form that is *acceptable and effective as a cigarette substitute*, millions of lives could be saved [2]. The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act [3] in the US, embraces this concept. Section 911 of the FD&C Act establishes two distinct pathways for approving the marketing, sale, and distribution of MRTP. Section 911(g)(1) permits approval of a "Reduced Risk" MRTP if the manufacturer demonstrates that the product, as actually used, significantly reduces the risk of tobacco-related diseases in individual tobacco users as compared to CC and will benefit the health of the population as a whole. Section 911(g)(2)

permits approval of a "Reduced Exposure" MRTP if the manufacturer demonstrates that the product reduces exposure to HPHCs and there is a reasonable likelihood that subsequent studies will demonstrate a measurable and substantial reduction in morbidity or mortality among individual tobacco users [4].

PMI intends to utilize smoking cessation/abstinence as the benchmark for assessing the risk reduction potential of its candidate MRTPs. PMI has conducted and plans to conduct more clinical studies with heated instead of burned tobacco products, such as THS 2.2, to measure changes in blood chemistry, risk factors and health effects in smokers who switch to a candidate MRTP, and to compare those changes to those observed in smokers who continue smoking and in smokers who cease using tobacco products.

Finally, the impact on population harm should take into account the potential benefit to the population that the MRTP could bring, and, as indicated by the FD&C Act, that individuals and the population as a whole would benefit from the introduction of an MRTP. The PMI assessment program is expected to generate evidence concerning the effect of a product's availability and marketing on tobacco product initiation, cessation, dual use, and relapse, in both individual smokers and in the population as a whole. A summary of the underlying principles of PMI's assessment is outlined in Table 1.

Table 1 Risk Assessment of MRTPs

Evidence	Assessments	Objectives
Hazard characterization	Physical and chemical comparison of the candidate MRTP aerosol to smoke from CC	To demonstrate that the proposed candidate MRTP aerosol reduces the levels of HPHCs in comparison to those in CC smoke
Toxicological evidence	*In vitro* and *in vivo* toxicological assays that can serve to demonstrate that the candidate MRTP is toxicologically less hazardous than CC in a way that may have clinical relevance	To demonstrate that the candidate MRTP's aerosol is less biologically active than CC smoke and can reveal a dose response relationship
Exposure assessment	Clinical evidence that adult smokers who switch from CC to the candidate MRTP significantly reduce their levels of biomarkers of exposure (BoExp), which provide direct, quantitative evidence of the presence of exposure to HPHCs or their metabolites in the body	To provide evidence in exposure studies that subjects who switch to the candidate MRTP have lower levels of all BoExp than those who smoke CC To evaluate how measured exposure reductions compare with levels of reductions observed in subjects who cease using tobacco products altogether

Evidence	Assessments	Objectives
Biological and functional effects	Clinical evidence from short- to long-term ambulatory clinical studies conducted under conditions of actual use of exposure reduction, and measurement of functional changes in subjects who switch from CC to a candidate MRTP. If observed changes in subjects are similar to the short- and long-term changes seen following smoking cessation, then it could be postulated that the proposed candidate MRTP reduces risk compared to CC	To assess indicators of "exposure response", including established risk factors for smoking related diseases To compare exposure reductions, risk factor, molecular and functional changes in smokers who switch to the candidate MRTP with the changes observed in smokers who cease using tobacco products
Risk characterization	Clinical, behavioral and post-market studies concerning the impact of the candidate MRTP on consumer perception, behavior, and health	To survey patterns of tobacco product consumption, perception, and understanding among adult smokers, never smokers, candidate MRTP users, and former smokers before and after a candidate MRTP is marketed

Randomized clinical studies are a central component of the THS development program and will advance the scientific evidence that the new candidate MRTP modifies the risk profile compared to CC use. This Investigator's Brochure, supports the THS 2.2 clinical development program that comprises initially three types of clinical studies:

1. Pharmacokinetic/Pharmacodynamic (PK/PD) studies.

2a. Reduced Exposure studies in confinement (up to 5 days of exposure to THS 2.2).

2b. Reduced Exposure studies in confinement with an ambulatory period (up to three months of exposure to THS 2.2).

3. Exposure Response studies in ambulatory conditions (for at least 6 months of exposure to THS 2.2)

PK/PD

The rate and extent of nicotine absorption during single stick use of THS are measured and compared to CC and to nicotine replacement therapy (NRT). This randomized cross-over, relative bioavailability pharmacokinetic study, after a single THS Tobacco Stick use, is part of the characterization of THS 2.2. It provides evidence on the relationship between plasma nicotine levels and the suppression of the urge to smoke in people who switch from CC (PD).

Reduced Exposure (Confined)

The study investigates reduction of BoExp to selected HPHCs after switching from CC to THS 2.2 in an optimal, clinical laboratory setting. Product use is monitored by the study staff. The subjects use THS 2.2 without restriction (ad libitum), but dual use of CC and THS 2.2 is not allowed. This comparative study includes THS 2.2, CC and smoking abstinence (SA) arms. Exposure to nicotine and subjective effects (craving, withdrawal symptoms, and product satisfaction) are being assessed systematically over a one week period of confinement. This short-term study will also provide safety data, such as vital signs and adverse events.

Reduced Exposure (Confined and Ambulatory)

The study has two distinct periods. The first part of the study is similar to the short-term Reduced Exposure studies, in that current smokers are confined for a week and BoExp are measured in subjects switching from CC to THS 2.2. In the second part of the study, subjects are followed over a period of one to three months in an ambulatory setting. The ambulatory, extended study period increases the understanding of product use and acceptance, as well as the achieved exposure reduction by THS 2.2, used either exclusively or in combination with CC.

Exposure and Smoking Cessation Response Studies (Ambulatory)

The exposure studies will assess clinical, physiological and biological changes observed during *ad libitum* THS 2.2 use in ambulatory conditions, compared to continued use of CC. A smoking cessation study will be conducted in parallel, and will be used as a benchmark. The comparison of changes in THS 2.2 users compared with smokers of CC and quitters will provide convincing evidence that THS 2.2 successfully modifies the risk profile.

2.2 The Tobacco Heating System

The development of Electrically Heated Cigarette Smoking System (EHCSS) started in the 1990s, and since then, PMI has continuously leveraged and improved the principle of heating versus burning tobacco in order to substantially reduce the exposure to HPHCs with THS. These developments have been ongoing through different versions and were focused on continuous improvement in order to achieve:

1. Increased reduction of HPHCs by reducing and controlling the heating temperature.
2. Improved taste to the point where smokers are prepared to accept the candidate MRTP as a replacement for CC.
3. Improved convenience in use and handling.

Table 2 Evolution of the Electrically Tobacco Heating System Development

Name of the Product	Development and Commercial Status	Key Characteristics	Improvements	Smoke Chemistry
EHCSS Series JLI	Middle of 1990s. The EHCSS Series JLI was test marketed in Richmond (USA) in 2002 as Accord® and in Osaka, Japan in 2002 as Oasis®	Energy control of the heating blades External Tobacco Stick heating Tobacco Stick design using coated cast leaf tobacco Usage limited to 8 puffs per cigarette Peak temperature of the tobacco material ~ 550°C	Substantially reduced CO delivery compared to CC Sidestream smoke significantly reduced compared to CC	↓HPHC yield relative to CC
EHCSS Series K6 (also referred to as THS 1.0)	EHCSS Series K6 (THS 1.0) was test marketed in Australia and Switzerland in 2006	Change from Series JLI: Addition of a highly activated carbon filter	Improved consumer acceptability compared with the earlier versions Reduced yields of GVP HPHCs compared to EHCSS Series JLI	↓HPHC yield relative to CC
THS 2.0	Development timing 2007-2010. No commercial or marketing activity	Temperature control of the heating blade Internal THS Tobacco Stick heating THS Tobacco Stick design using shredded cast leaf tobacco Usage limited to 6 minutes Heating blade temperature of 375°C Significant device size reduction and introduction of a two-piece system including a Charger and Holder	Overall reduction of HPHC delivery compared to THS 1.0 Consumer acceptability improved (taste and ergonomics)	↓HPHC yield relative to CC ↓HPHC yield relative to THS 1.0

Name of the Product	Development and Commercial Status	Key Characteristics	Improvements	Smoke Chemistry
THS 2.1	Development in 2011	Changes from THS 2.0: THS Tobacco Stick design using crimped cast leaf tobacco	Increased manufacturing consistency Improved consistency of sensory experience	↓HPHC yield relative to CC Comparable HPHC yield to THS 2.0
THS 2.2	Development from 2011	Changes from THS 2.1: Optimized heater blade temperature profile and (b) (4)) compared to THS 2.1	Improved puff by puff consistency and sensory satisfaction compared to THS 2.1	↓HPHC yield relative to CC Comparable HPHC yield to THS 2.0 and 2.1

The concept that lowering the temperature can effectively reduce the levels of HPHCs was confirmed early in tests using the first versions of the THS technology. It was also shown that such reduction in HPHCs leads to lower levels of BoExp in smokers who switched to THS and was instrumental to the decision to further develop the EHCSS.

A significant design change was made with the introduction of a two piece system of a Charger and Holder with THS 2.0, which is expected to have better user acceptance than the somewhat bulky, single piece THS 1.0 device. The temperature control and optimization was achieved through heating the THS Tobacco Stick internally instead of externally and optimal electronic control of the heating blade temperature, (b)(4) (Table 2).

3 DESCRIPTION OF THE PRODUCT

THS 2.2 has three distinct components, which perform different functions during use:

- A THS Tobacco Stick, which contains the tobacco plug.
- A Holder into which the THS Tobacco Stick is inserted.
- The Charger which is used to recharge the Holder after each use.

These three components are shown in Figure 1.

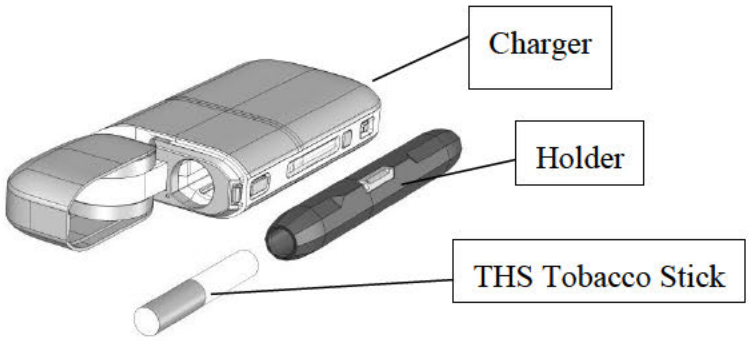

Figure 1 The Three Components of THS 2.2

3.1 The Product Components

3.1.1 The Holder

The Holder comprises 4 major components (Figure 2):

- The casing.
- The heater element, which is a glass-coated metallic resistive element through which electricity is passed to create the heating (heating blade).
- Control Electronics, which ensure the temperature control of the heating element and continuously measure the element temperature, allowing overheating to be detected and inhibited.
- A battery, which stores sufficient power for a single THS Tobacco Stick use.

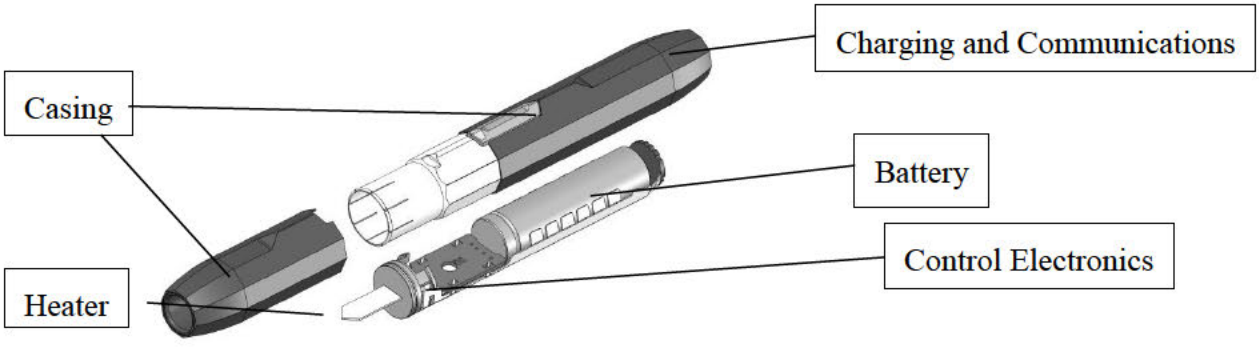

Figure 2 An exploded View of the Holder showing the component parts and assemblies

3.1.2 The Charger

The Charger (Figure 3) is designed to be portable (approximately the size of a pack of CC) and to recharge the Holder. The Electronics regulate both the charging of the Holder battery from the Charger battery and the charging of the Charger battery from an external power source.

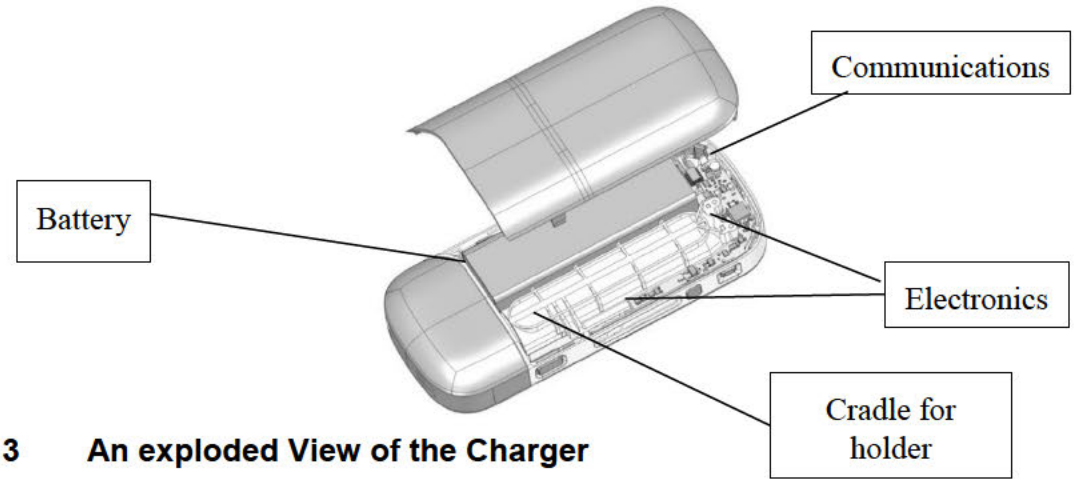

Figure 3 An exploded View of the Charger

3.1.3 The THS Tobacco Stick

The THS Tobacco Stick is similar in basic design to a CC, but is shorter, contains less tobacco material and has an additional filter section. The THS Tobacco Stick comprises a number of elements (Figure 4):

- A tobacco plug manufactured from crimped, cast-leaf tobacco. Glycerin is added to the cast-leaf to facilitate aerosolization.
- A hollow acetate tube which acts as a mechanical spacer between the tobacco plug and the first filter.
- A polymer-film filter, which reduces primarily phenol.
- A low-density cellulose acetate mouthpiece filter.
- The outer and tipping papers (standard papers used in CC).
- The mouth piece filter.

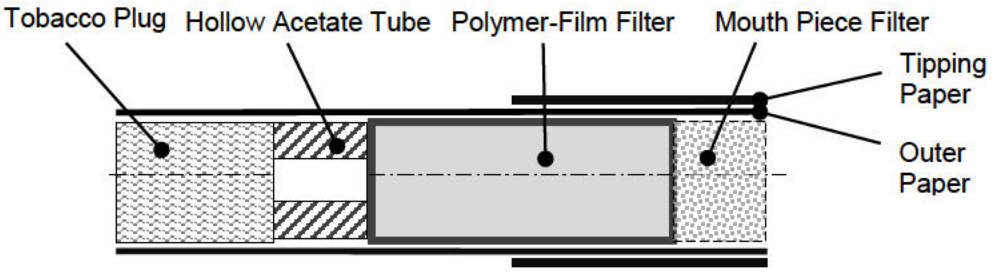

Figure 4 A Cross-sectional Diagram of the THS Tobacco Stick

3.1.3.1 Bill of Materials

The THS Tobacco Stick is made up of elements that includes those used in CCs and some new elements which have been developed specifically for the THS Tobacco Stick. All materials have been evaluated with regards to their toxicological potential and have been approved for use.

The overall composition of the THS Tobacco Stick is as shown in Table 3 below:

Table 3 Bill of Materials for the THS Tobacco Stick

Component	Approximate % of Total [1]	Average Weight (mg/THS Tobacco Stick) [1]	Comment
Tobacco Plug	39%	314	Specification is ± 25mg
Hollow Acetate Tube	10%	81	Calculated from bulk weighing
Polymer-film Filter	38%	300	Specification is ± 30mg
Mouth Piece Filter	7%	52	Calculated from bulk weighing
Outer Paper	3%	28	Calculated from known paper size and average density
Tipping Paper	2%	18	Calculated from known paper size and average density
Adhesives	1%	5	Estimate
Total	100	798	

[1] Values correct on 21 March 2014

3.1.3.2 The Tobacco Plug

The tobacco plug is made from the materials shown in Table 4. Nicotine content is 5.6 to 6.4 mg per Tobacco Stick.

Table 4 Tobacco Plug Composition

Component	Approximate % of Total	Average Weight (mg)
Tobacco	66.7%	211.7
Glycerin (pharmaceutical grade)	17.8%	56.4
Water	8.8%	27.9
Wrapper	2.3%	7.4
Guar (food grade, E412)	2.6%	8.5
Fibers	1.7%	5.6
Propylene Glycol	<< 1.0%	traces
Ethanol	<< 1.0%	traces
Flavors	<< 1.0%	traces
Total	100%	317.5

3.1.3.3 Aerosol Fractions Determined by International Organization for Standardization (ISO) and Health Canada Methods

Many countries require cigarette manufacturers to print the *per cigarette* yields of tar, nicotine, and carbon monoxide (CO) on the outside of the packaging. Per cigarette/Tobacco Stick tar, nicotine, and carbon monoxide yields are normally determined by standardized test methods. The most widely used test method is ISO 4387. PMI has developed a modified version of this method, which improves the determination of tar in products with high water content, which is typical for heated tobacco products [5]. Another method is the more intensive smoking method, Health Canada Intense (HCI) [6].

Table 5 lists ISO and HCI reported values:

Table 5 Reported Aerosol Fractions for the THS Tobacco Sticks

Constituent (mg/THS Tobacco Stick)	ISO [1]	Health Canada Intense regime [2]
Tar/NFDPM [3]	4	10.3
Nicotine	0.5	1.32
Carbon monoxide	1	0.6

[1] International Organization for Standardization ISO machine-smoking regimen. The analytical method has been modified to avoid inaccuracies as a result of condensation from high water-content aerosols.

[2] Health Canada Intense machine-smoking regimen (55 mL puff volume, 2-second puff duration, 30-second inter-puff interval) [6]

[3] NFDPM: nicotine free dry particulate matter

3.2 Product Use

To use THS 2.2, the THS Tobacco Stick is inserted into the Holder. The heating of the THS Tobacco Stick is initiated by pressing the button on the Holder and an LED indicates when the initial heating process is complete.

Once initial heating is complete, the product is used in much the same way as a CC:

- The user draws air through the THS Tobacco Stick.
- This initiates the use heating cycle, which follows a puff-by-puff heating profile designed to provide a consistent user experience throughout use.
- The Holder and THS Tobacco Stick can deliver up to 12 puffs over a period of approximately 6 minutes.
- Once this cycle is complete, the Holder must be recharged and a new THS Tobacco Stick must be used.

In use, the Holder/THS Tobacco Stick combination can be held and used in a manner very similar to a CC. Detailed user manuals are provided to study sites and subjects.

3.3 Product Stability

Stability tests have been performed under three sets of 12 month storage conditions. The conditions are a) 60% Room Humidity (RH), 22°C, b) 35% RH, 30°C, and c) 75% RH, 30°. The levels of nicotine, tar, carbon monoxide, glycerin, 29 other HPHCs and 3 flavor markers were measured as well as aerosol droplet size characteristics, the basic physical characteristics of the THS Tobacco Stick, and a qualitative sensorial assessment. (b) (4)

(b) (4) . Under condition b) the TPM fell below the expected level after 7 months. Water and glycerin showed a consistent reduction with time, but remained within specification as did all other measurements. (b) (4) . At 6 months the TPM level was below expectation, and after 9 months the glycerin was below specification. Other parameters showed some variation but remained within specification [7].

The conclusion is that under normal usage conditions the THS Tobacco Sticks show some variation, but deliveries of HPHCs and general performance remain consistent over a period of 12 months

4 NON-CLINICAL STUDIES

As described in section 1.1, the THS product consists of a THS Tobacco Stick and a THS Tobacco Stick Holder that is a separate component in which the THS Tobacco Stick is inserted in order to heat it and generate an inhalable aerosol. The initial step in the toxicological assessment process is the qualification of the materials and ingredients used in the manufacturing of the THS Tobacco Stick disclosed in the Bill of Material (Table 3). The qualification of the materials used in the Holder, the packaging materials and the indirect materials used in the manufacturing process are also included in the toxicological assessment process. The materials and ingredients mentioned above were toxicologically assessed and approved for their intended use.

The next step consists of the toxicological assessment of the aerosol generated from the heated THS Tobacco Stick on puffing. The endpoints for the *in vitro* part of the aerosol assessment include cytotoxicity and genotoxicity. For cytotoxicity, the neutral red uptake (NRU) assay is used, while for genotoxicity, gene mutation induced by the aerosol in bacterial and mammalian cells are evaluated with the Ames and the Mouse Lymphoma Assay (MLA), respectively. The *in vivo* toxicological assessment includes a 90-day aerosol inhalation study in rats.

The main studies conducted for non-clinical evaluation of THS 2.2 are summarized in Table 6.

Table 6 Non-Clinical Assessment of THS 2.2

Test System	Smoke generation regimen	THS Tobacco Sticks tested	Study report number
Smoke chemistry	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	RLS-ZRH-2012-252
NRU	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/CAST LEAF – CL/Flavor/Reynaldo	RLS-ZRH-2012-249

Test System	Smoke generation regimen	THS Tobacco Sticks tested	Study report number
Ames	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/CAST LEAF – CL/Flavor/Reynaldo	RLS-ZRH-2013-15
MLA	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	RLS-ZRH-2012-315
90-Day inhalation study	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	15006

4.1 Constituent Analysis of the THS aerosol

The following criteria have been used consistently through the THS development program for the selection of scientifically meaningful HPHC aerosol to be monitored:

1. Priority toxicants in tobacco smoke as listed by regulatory bodies, or proposed by cognizant authorities (Food and Drug Administration (FDA) [4], World Health Organization (WHO) [8], Health Canada [9])
2. HPHCs with established BoExp in human (smoke/aerosol constituents or metabolites)
3. HPHCs which are predominantly formed below 400°C
4. HPHCs which are predominantly formed above 400°C.

4.1.1 Reduction of HPHCs in THS 2.2 vs. 3R4F

Heating instead of burning tobacco excludes many constituents from forming as a result of tobacco combustion. By only heating the tobacco, the number and concentration of HPHCs in the aerosol are further reduced as compared to the 3R4F reference cigarette. University of Kentucky 3R4F reference cigarette (ISO tar 7.8 mg; nicotine 0.74 mg; CO 10.7 mg) serves as an international standard for research purposes and provides a basis for comparing data collected in various laboratories. The 3R4F reference cigarettes are the third production run and are considered to be representative of the US market cigarettes [10].

The constituents generated under HCI by THS 2.2 aerosol are qualitatively and quantitatively significantly reduced compared to the HPHCs measured for 3R4F reference cigarette on an equal nicotine basis (Figure 5).

4.1.2 Product and Design Evolution

With THS 1.0, THS Tobacco Sticks were heated up to 500 °C, subsequent developments enabled lowering the temperature for the THS 2.2 system to no more than 350 °C. When compared to its predecessors, THS 2.2 showed on a nicotine equivalent basis, similar or reduced levels of HPHCs in the generated aerosol.

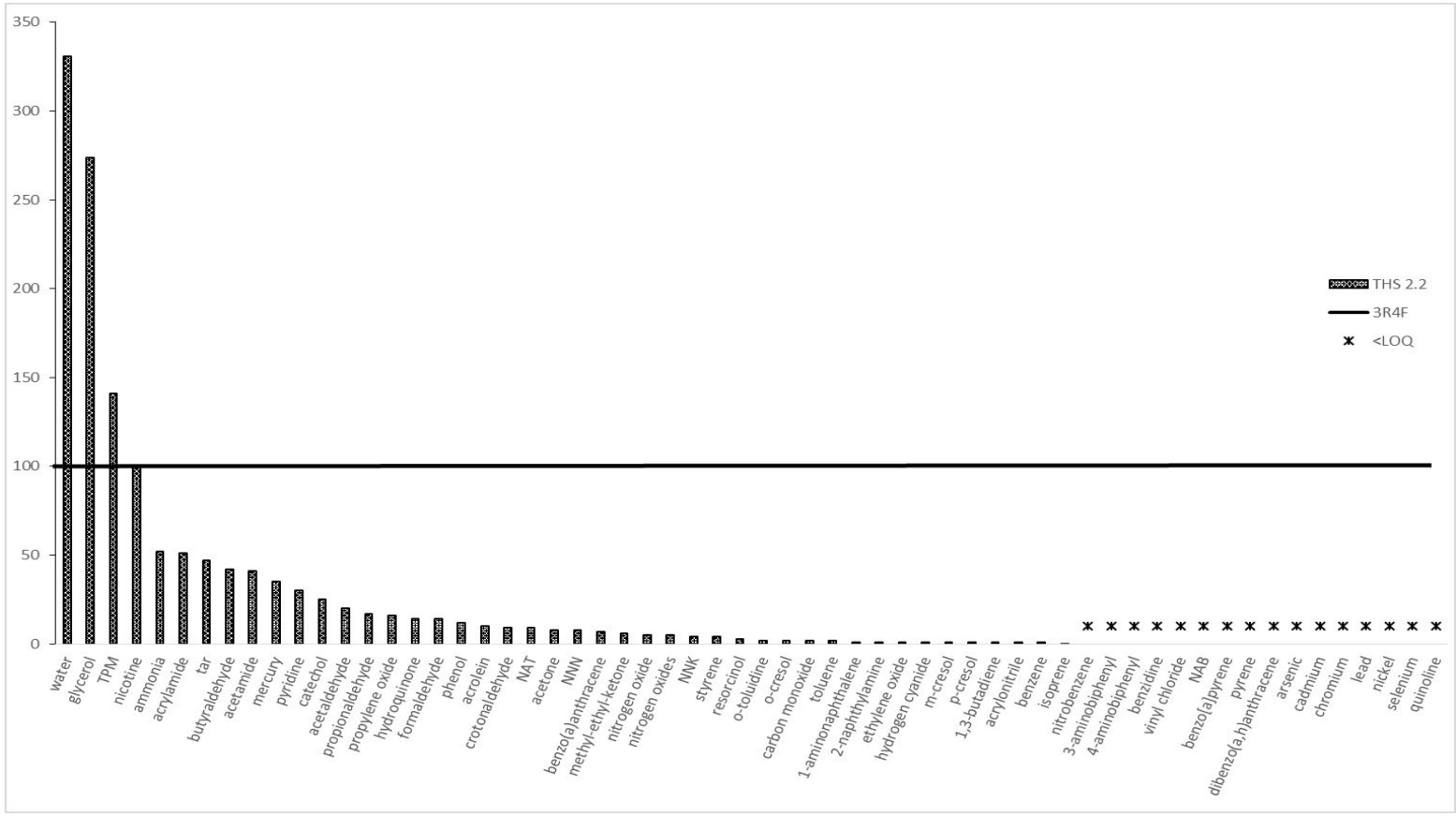

Figure 5 Comparison of Constituents of THS 2.2 to those from 3R4F, on a per mg Nicotine Basis (Constituents of 3R4F Set to 100%)

4.2 *In Vitro* Toxicology

4.2.1 Neutral Red Uptake Assay

The neutral red uptake *in vitro* cytotoxicity assay (NRU) has been widely used and accepted by the chemical and pharmaceutical industry, and by regulatory authorities, as a screening method to determine the cytotoxicity of compounds [11, 12]. It is known to be responsive to both the particle phase of CC smoke and to the GVP [13], and it can discriminate between different CC tobacco types [14, 15]. The assay is a well-established, reproducible, and standardized short-term test that responds to cytotoxic compounds in a dynamic range of five orders of magnitude [16].

On an equal nicotine basis, the cytotoxicity of the TPM and of the GVP for THS 2.2 were lower than those from 3R4F reference cigarette when smoked under Health Canada Intense (HCI) machine-smoking regimen conditions (Figure 6).

Figure 6 THS 2.2 Neutral Red Uptake Assay: Cytotoxicity of Cigarette Smoke and Aerosol Fractions and Percent Relative Difference (Health Canada Smoking Conditions)

4.2.2 Genotoxicity Studies

4.2.2.1 Bacterial Reverse Mutation Test

The Salmonella reverse mutation assay (Ames assay) is recommended both by the Organisation for Economic Co-operation and Development (OECD) and International Conference on Harmonization (ICH), as part of the standard testing battery for genotoxicity [17, 18]. The Ames test can detect and discriminate the mutagenic activity of different types of CC [13, 19] with different filter ventilation, filter efficiency, and paper porosity [20], and different tobacco types and CC smoke fractions [21]. The Ames assay is sensitive to TPM from CC smoke, but the sensitivity depends on the strain and the presence or absence of a metabolic activation system (S9). The strains that are the most sensitive toward TPM are TA98, TA100 and TA1537 with S9 (TA98>TA100>TA1537), TA98, TA100 and TA1537 without S9 and TA1535 with S9 show only marginal response. TA102 with and without S9 and TA1535 without S9 are not responsive to TPM [22].

The TPM (up to 2.5 mg/plate) and the GVP (up to 3.0 mg/plate) from THS 2.2 did not show any mutagenic activity in the different strains tested in presence or absence of S9 (data not shown). The TPM (from 50 µg/plate) and the GVP (from 200 µg/plate) from 3R4F were however reported as mutagenic in absence and presence of S9.

4.2.2.2 Mouse Lymphoma TK Assay

The mouse lymphoma TK assay (MLA) is recommended both by the OECD [23] and ICH [17], as part of the standard testing battery for genotoxicity. MLA measures the induction of forward mutations at the tk-locus in L5178Y/tk+/-3.7.2C mouse lymphoma cells. The response to TPM is in general very low, only up to a 3- to 5-fold increase over the background mutant frequency [24, 25], but the assay can nevertheless discriminate the mutagenic activity of different tobacco types [26].

On a nicotine equivalent basis, the relative mutagenicity of TPM and GVP from THS 2.2 was substantially lower than 3R4F with or without metabolic activation (S9) (Figure 7).

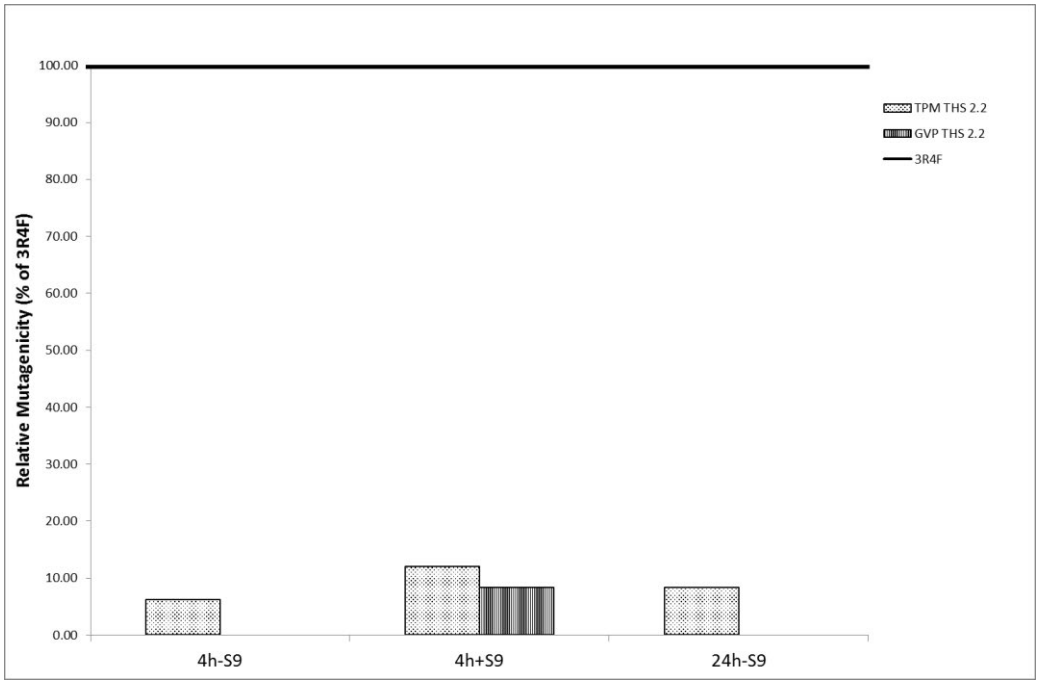

Figure 7 Relative Mutagenicity in MLA of TPM and GVP of THS 2.2 compared the 3R4F smoked under HCI, on an Equal Nicotine Basis, with and without S9 metabolic activation

4.3 *In Vivo* Toxicology

4.3.1 90-Day Rat Inhalation Study

Previous studies showed that a 90-day rat inhalation study is a suitable model for the detection of diluted mainstream smoke-related changes in systemic toxicity and histopathology of the respiratory tract [19, 27, 28]. The inhalation toxicity of THS 2.2 was investigated after sub-chronic exposure to the mainstream aerosol. The biological activities of the THS 2.2 aerosol were compared with those of 3R4F. The toxicological activity was determined in basic conformity with OECD guideline 413 with regard to the following parameters: body weight, food consumption, ophthalmologic changes, clinical observations, clinical chemical and hematological parameters, gross pathological observations, organ weights, and histopathological changes in the respiratory tract [29].

Measurement of aerosol HPHCs showed lower content of formaldehyde, acrolein, acetaldehyde and carbon monoxide in the THS 2.2 exposure chambers when compared to the 3R4F ones, thus validating the experimental paradigm.

The generated aerosol was reproducibly inhaled by the animals, as indicated by the measured BoExp COHb, and the urinary nicotine and selected BoExp [3-hydroxypropylmercapturic acid

-HPMA-, S-phenylmercapturic acid -SPMA-, 2-cyanoethylmercapturic acid -CEMA- and the sum of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone plus its glucuronide conjugates -Total NNAL-, for acrolein, benzene, acrylonitrile and NNK respectively]. Data showed a good correlation between measured BoExp and HPHC concentrations in the test atmospheres.

The overall evaluation of the data, summarized in Table 7, indicates that exposure to THS 2.2 aerosol induces less inflammation and fewer degenerative changes to the respiratory tract organs and does not result in additional hazards to those presented by smoking conventional cigarettes.

Table 7 Systemic Toxicity and Histopathology of Male and Female Rats Exposed to Mainstream Smoke from 3R4F and Mainstream Aerosol form THS 2.2 in a 90-Day Inhalation study

Findings [1]	3R4F	THS 2.2
Death	No death related to exposure up to 23 µg/L nicotine in test atmosphere	No death related to exposure up to 50 µg/L nicotine in test atmosphere.
Body weight	Reduced body weight gain.	Reduced body weight gain but less pronounced compared to 3R4F.
Organ weight	Dose-dependent increase of lung, larynx and trachea weight. Increase of liver weight at 23 µg/L nicotine. Increase of adrenal gland weight. Dose-dependent decrease of thymus and uterus weight.	Increase in lung, larynx and trachea weight less pronounced when compared to 3R4F. Increase of liver weight at 23 and 50 µg/L nicotine. Increase of adrenal gland weight. Decrease in thymus weight less pronounced than 3R4F. Dose-dependent decrease of uterus weight.
Respiratory physiology	Dose-dependent reduction in respiratory minute volume.	No change in respiratory minute volume.
Lung inflammation	Dose-dependent increase in immune cell counts present in bronchoalveolar lavage.	Minimal increase in immune cell counts present in bronchoalveolar lavage.
Clinical Chemistry	Dose-dependent increase in liver enzymes.	Dose-dependent increase in liver enzymes.
Histopathology	Nose: Reserve cell hyperplasia of the respiratory epithelium. Squamous epithelial metaplasia of the respiratory epithelium and olfactory epithelium. Ulceration and atrophy of olfactory epithelium. Larynx: Squamous epithelial metaplasia at base and distal base of epiglottis. Hyperplasia of squamous epithelium of vocal folds. Epithelial thickness at the floor of the larynx and at the lower medial region of vocal cords.	Significantly decreased histopathological changes compared to 3R4F.

Findings [1]	3R4F	THS 2.2
	Tracheal ring and bifurcation: Reserve cell hyperplasia. Goblet cell hyperplasia at tracheal epithelium. Lung: Presence of macrophages with and without yellow pigmentation in the alveolar lumen. Presence of neutrophilic granuloc§ytes in the alveolar lumen. Goblet cell hyperplasia at the main bronchus.	

[1] Study was performed in rats according to OECD TG 413 (2009); 90-day inhalation period, exposure for 6 h/d, 5 d/wk. Groups: sham, low, medium and high nicotine both for CC and THS 2.2. Three groups (sham, high CC and high THS 2.2) were kept for a 42 days post-inhalation period.

In conclusion, the exposure to the mainstream aerosol from THS 2.2 did not cause additional toxicity when compared to the smoke from the 3R4F reference cigarette. Moreover, the overall biological activity of the THS 2.2 aerosol with respect to the toxicity on respiratory tract organs was significantly decreased in comparison to 3R4F cigarette. Similar findings were observed in a former study where THS 1.0 was compared to 2R4F (reference cigarette used previously).

4.4 Conclusions

By heating instead of burning tobacco, the aerosol composition of the THS Tobacco Stick becomes less complex, and measured HPHCs are either substantially reduced or undetectable. It is, however, acknowledged that not all possible HPHCs in CC are known and can be analytically measured.

Even if the contribution of single constituents to induction of smoking related disease is not known and needs to be further investigated, it is nevertheless reasonable to assume that exposure to a less complex mixture and a substantial reduction in the measured HPHCs is likely to lead to a reduced toxicological hazard compared to CC smoke.

THS 1.0 and 2.1 were improved in design and features for consumer use, and the heating profile was further optimized and controlled and the heating temperature decreased. These changes resulted in even greater reductions in some of the HPHCs in THS 2.2 compared to former versions, leading to reduced *in vitro* cytotoxicity and genotoxicity in standard, internationally recognized biological assays.

Furthermore, the 90-day inhalation studies in rats revealed less toxicological effects in the respiratory tract from exposure to THS 2.2 and THS 1.0 than exposure to CC.

In summary, the results of chemical, in *vitro* and *in vivo* toxicological assessment of THS 2.2 and consistent results throughout the evolution of the THS support the conclusion that adult smokers in clinical studies will not be exposed to new or increased hazard compared to continuous CC use.

5 PRODUCT EXPERIENCE IN CURRENT SMOKERS

Several clinical studies with THS have been conducted by PMI and Philip Morris USA[1] from 2004 to 2008. Extensive data are available for THS 1.0, the EHCSS Series K6, and its predecessors, EHCSS Series E4 and EHCSS Series JLI. The clinical experience ranges from short-term studies in confinement to long-term studies in an ambulatory setting (Table 9).

In 2012 PMI conducted two exploratory clinical studies; one short-term PK/PD and one Reduced Exposure with THS 2.1 (see section 5.1.1 and 5.2.1).

The version 2.2 of THS is considered mature to the extent that sensorial qualities of the product and possible user acceptance are judged high by PMI. The decision was made to put THS 2.2 into a comprehensive assessment program including clinical studies and generation of qualifying evidence suitable for submission to regulatory agencies, the scientific community and risk assessment policy makers as new MRTP. PMI's phased approach includes first assessing THS 2.2 in relatively short-term studies and then gradually expanding the duration and resemblance to actual use in real world conditions in the global clinical development program.

PMI initiated four confirmatory clinical studies in 2013, including nicotine replacement therapy and/or smoking abstinence as points of reference and CC as a comparator to THS 2.2 [30-33], in Japan, Europe and USA. These studies are currently ongoing and aim at assessing the PK of nicotine and reduced exposure to HPHCs both in confined and ambulatory conditions.

All clinical studies are conducted in accordance with the Declaration of Helsinki which was effective at the time of each conducted study.

[1] PMI and Philip Morris USA Inc. are unaffiliated companies after Altria Group, Inc. completed the spin-off of Philip Morris International Inc. to shareholders of Altria Group, Inc. on March 28, 2008.

5.1 PK/PD

5.1.1 PK/PD with THS 2.1

An exploratory clinical study was conducted in the UK from May to September 2012 [34]. It was a randomized, crossover study comparing plasma nicotine profiles of THS 2.1 and CC. Twenty-eight adult smokers completed the study.

The shape of plasma nicotine concentration-time curves was similar for the two products, with a lower nicotine absorption following single use of THS 2.1 as compared to CC. Following single use, the extent of nicotine absorption ($AUC_{0\text{-last}}$) was 23% (90% CI: 15%, 30%) lower

on average for THS 2.1 than for CC. Similarly, the maximum nicotine concentrations (C_{max}) were 30% (90% CI: 18% to 40%) lower, on average, following single use of THS 2.1 compared to CC. Time to peak plasma concentration (t_{max}) was not different between both products (see Figure 8).

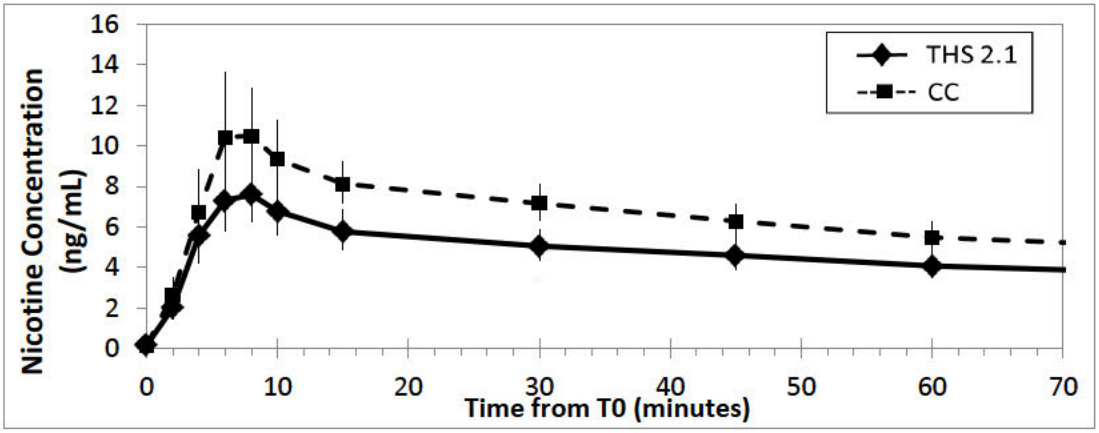

Figure 8 Nicotine Plasma Concentration Curves over Time (Presented as Mean and Confidence Interval)

Subjective and pharmacodynamic effects of product use were assessed using the brief questionnaire of smoking urges (QSU-brief). After 24 hours of smoking abstinence a single use of CC or THS resulted to in a 40% reduction of the urgent desire to smoke (see Figure 9).

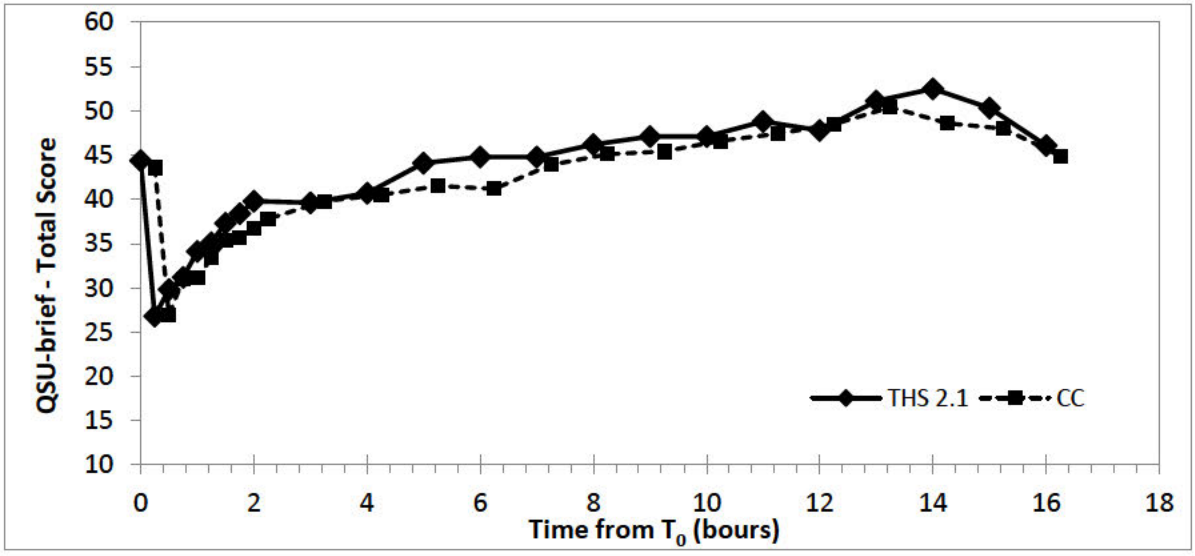

Figure 9 QSU-brief Total Score after Single Use of THS 2.1 and CC

5.2 Reduced Exposure

The FDA Center for Tobacco Products (CTP) has established an abbreviated list of 18 HPHCs [35] to be measured in smoke based on:

1. Availability of analytical methods.
2. Coverage of several chemical classes.
3. Representative sample of the FDA established full list of 93 HPHCs to be measured in smoke representing five key risks:
   a. Carcinogen
   b. Cardiovascular toxicant
   c. Respiratory toxicant
   d. Reproductive and development toxicant
   e. Addiction potential.

Table 8 summarizes results obtained from the one-week Reduced Exposure study conducted with THS 2.1 and similar studies done with THS 1.0 with exposure durations of between 5 and 35 days.

Table 8 Biomarkers of Exposure after Switching to THS - Percentage Change from Baseline CC Use

	HPHC (Organ Class Toxicity)		Acrolein (RT, CT)	Pyrene Surrogate for PAH	NNK (CA)	Benzene (CA, CT, RDT)	CO (RDT, CT)	1,3-Butadiene (CA, RT, RDT)	4-Aminobiphenyl (CA)	o-Toluidine (CA)	Crotonaldehyde (CA)	2-Amino-naphthalene (CA)	Acrylonitrile (CA, RT)	NNN (CA)
Product Version	**Study**	**Duration**	**3-HPMA[1]**	**1-OHP[2]**	**Total NNAL[3]**	**S-PMA[4]**	**COHb[5]**	**MHBMA[6]**	**4-ABP[7]**	**o-TOL[8]**	**3-HMPMA[9]**	**2-NA[10]**	**CEMA[11]**	**Total NNN[12]**
THS 2.1	ZRHX-EX-01	Day 5	-64%	-59%	-61%	-88%	-75%	-80%	-45%	-23%	N/M	-84%	-85%	-81%
THS 1.0	SPA04-01	Day 8	-36%	-63%	-55%	-79%	-70%	-54%	N/M	-62%	-53%	N/M	N/M	N/M
	SPA05-01	Day 8	-24%	-67%	-52%	-76%	-54%	-55%	-49%	-68%	-41%	-15%	N/M	N/M
	SPA05-03	Day 5/6	-28%	-68%	-55%	-83%	-57%	-19%	-41%	-53%	-59%	-12%	N/M	N/M
	CS06-02	Day 35	-2.63%	-36%	-49%	-48%	-55%	-29%	-43%	-30%	N/M	-43%	N/M	N/M

(1) 3-Hydroxypropyl-mercapturic acid; (2) Total 1-hydroxypyrene, (3) Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, (4) S-Phenyl-mercapturic acid, (5) Carboxyhemoglobin, (6) Monohydroxybutenyl-mercapturic acid, (7) 4-Aminobiphenyl, (8) o-Toluidine, (9) 3-Hydroxy-1-methylpropyl-mercapturic acid, (10) 2-Aminonaphthalene, (11) 2-Cyanoethylmercapturic acid, (12) Total N-nitrosonornicotine; Organ Class toxicity [4]

AD: addictive; CA: carcinogen; CT: cardiovascular toxicant; RDT: reproductive and developmental toxicant; RT: respiratory toxicant

BoExp for addiction potential (AD) "Nicotine" and its metabolites is measured in each study

N/M: Not measured in this study

There is a consistent reduction of BoExp in smokers who switch from CC to THS.

PMI has established validated analytical methods to measure BoExp to 14 of the 18 HPHCs in the abbreviated list of 18 HPHCs [4]. These BoExp represent 10 out of 13 chemical classes of compounds considered to be present in smoke as listed by the FDA and seven out of nine compounds mentioned by the WHO as HPHCs recommended to be lowered in cigarette smoke [8]. The BoExp assessed in PMI clinical studies cover all five major risks stipulated by FDA.

5.2.1 Reduced Exposure Study with THS 2.1

An exploratory clinical study was conducted in Poland from May to September 2012 [36]. It was a randomized, open-label, 2-arm, parallel group *ad libitum* smoking study comparing the use of THS Tobacco Sticks and CC. Subjects were confined in a controlled environment for nine days. Forty adult smokers completed the study.

At the end of the study, on day 5, the urinary concentration of BoExp adjusted for creatinine, with the exception of o-toluidine (-25.03%) decreased from baseline by at least 47.03% (4-ABP) and up to 85.05% (CEMA) (Figure 10). Differences between the two arms were statistically significant and were seen within 24-hours of starting use of THS 2.1. The lower than expected reduction of o-toluidine was investigated and renovation (painting) of the study site immediately before the study was identified as the potential cause.

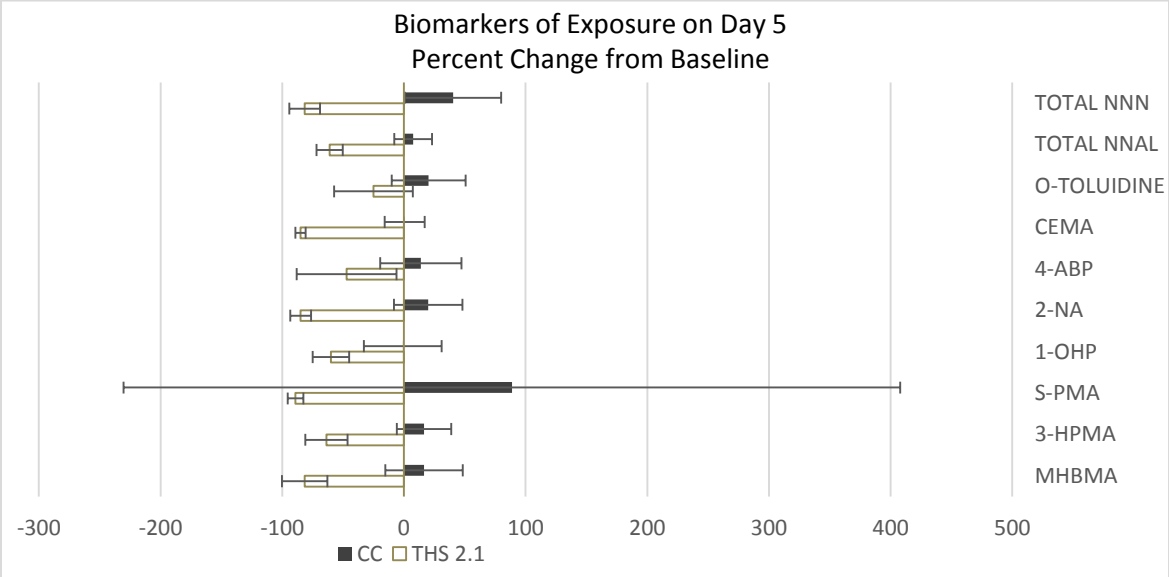

Figure 10 Changes in Biomarkers of Exposure in THS 2.1

At the end of the study on day 5, the percentage of COHb in blood decreased by 75% for the THS 2.1 arm and increased by 7.5% from baseline for the CC arm.

Cigarette Consumption:

Average cigarette consumption increased by 27.1% from Day 1 to Day 5 for THS 2.1 (from 21 to 27 THS Tobacco Sticks on average) and by 12.9% for CC (from 18 to 20 CC on average) from Day 1 to Day 5 (Figure 11).

Nicotine Equivalents (NEQ):

Excretion of nicotine and its metabolites in urine are well-established tobacco-specific BoExp to nicotine [37]. On a quantitative basis, the measured concentration of the molar sum of nicotine, cotinine, trans-3'-hydroxycotinine, and their respective glucuronide conjugates, expressed as NEQ in 24-h urine, provides an estimate of up to ~85% of total nicotine uptake and excretion in smokers [38].

Mean NEQ value at baseline and at Day 5 were within the same range for THS 2.1 (from 12.12 at baseline to 12.26 mg/g creatinine at Day 5) and slightly increased for CC (from 12.43 at baseline to 14.23 mg/g creatinine at Day 5) (Figure 11). The estimated median nicotine uptake at the end of the study was 1.01 mg nicotine per CC (range 0.75 – 2.01 mg) and 0.74 mg nicotine per THS Tobacco Stick (range 0.43 – 1.24 mg).

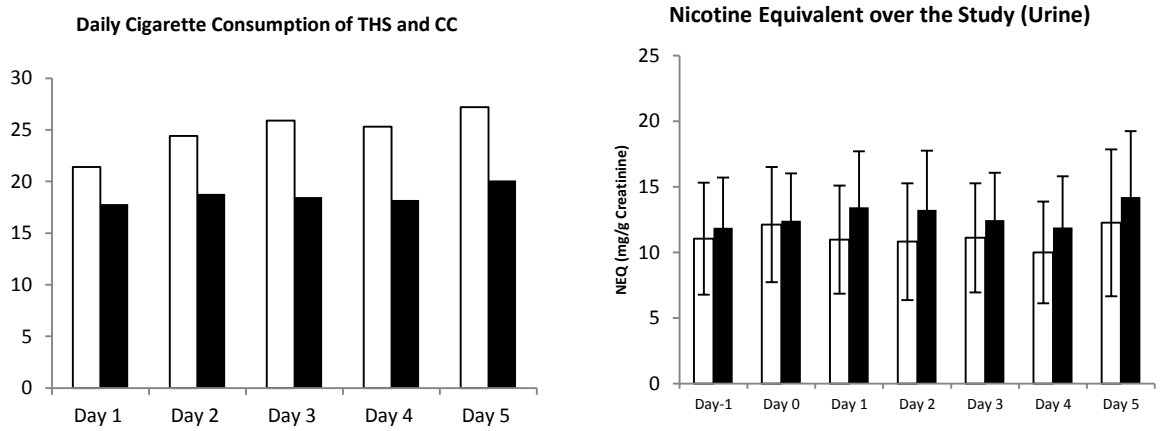

Figure 11 Cigarette Consumption and NEQ (mg/g Adjusted for Creatinine)
(□ THS 2.1; ■ CC)

The increased consumption of THS Tobacco Sticks reflects an adaptation process due to switching from CC to THS 2.1, which has a calculated lower median nicotine uptake per THS Tobacco Stick compared to CC. Also, different sensorial characteristics compared to the subjects' preferred CC brand contributed to the change in consumption pattern. Adaptation effects and consumption are currently being assessed in studies with longer duration (4 to 12 weeks) in an ambulatory, real world environment.

5.3 Other Relevant Clinical Findings

Clinical studies conducted jointly by PMI and Philip Morris USA[1] up to 2008 with an earlier version of THS, the Electrically Heated Cigarette Smoking System (EHCSS), in Europe, Asia, Africa, and in the US showed reductions in exposure to selected HPHCs present in both GVP and TPM of mainstream smoke in subjects who used the EHCSS, as compared to subjects continuing to smoke CC, in confined and ambulatory conditions.

Chemical analysis of smoke from the EHCSS-JLI cigarettes showed lower yields of formaldehyde and several reported HPHCs and a decrease in the CO yield [39]. Clinical evaluations also confirmed reduced exposure to selected HPHCs and reduced excretion of mutagenic material in urine [40, 41]. Further clinical evaluations concluded that switching from CC to the second-generation EHCSS-JLI cigarette improved prognostic markers for cardiac disease assessed by symptom-limited spiro-ergometry [42], heart rate and rate-pressure-product parameters [43] after three days of product switching.

Importantly, a 12-month randomized, parallel-group study in 97 adult male and female smokers of CC evaluated BoExp and cardiovascular risk factors after switching to EHCSS-JLI. There was a rapid and sustained reduction in all measured BoExp after switching to EHCSS. These reductions in exposure were associated with statistically significant and pathophysiological favorable changes in several cardiovascular risk factors, including white blood cell count, urine 11-dehydrothromboxane B2, and high-density lipoprotein cholesterol [41].

Table 9 presents the main conclusions from studies performed with former versions of THS 2.2.

Table 9 Conclusions from Selected Clinical Studies with EHCSS Series E4, EHCSS Series JLI and THS 1.0 (EHCSS Series K6)

Product	Study Title	Study Setting	Conclusions
EHCSS Series E4	**EHCE4/01/01** A single-center study to evaluate the short term exposure to smoke constituents of an electrically heated smoking system in adult smokers during controlled smoking [40, 44-47]	**EHCSS Series E4 exposed subjects:** 40 **Total subjects:** 110 **Exposure duration:** 8 days **Location:** USA This study evaluated BoExp (CO, COHb, nicotine, and urine mutagenicity) under controlled smoking conditions when adult smokers of one CC brand (CC1) were switched to an EHCSS or a low-tar CC (CC2) or no-Smoking (NS).	Compared to baseline, BoExp on Day 8 decreased by 53% to 93% ($p < 0.0001$) for EHCSS Series E4 groups and 18% to 39% ($p < 0.02$) for CC2. Environmental tobacco smoke arising from the smoking activities of the different study groups was measured in the air of a separate smoking room over 1-hour periods. Concentrations of respirable suspended particulates in both EHCSS Series E4 groups were about 90% lower than in the CC1 and CC2 groups, similar to the 95% reduction in the NS group. CO was undetectable in the EHCSS Series E4 and NS groups. Seventy-four subjects (67%) experienced at least one adverse event (AE) during the study. Headaches of mild to moderate intensity were the most common reported event across all study groups. None of the reported events was considered as a likely study-related event by the investigator. No clinically significant changes were observed for hematology, clinical chemistry, and urinalysis investigations for any of the study groups.
EHCSS Series JLI	**EHCJLI/01/02** A single-center study to evaluate the short term exposure to smoke constituents of an electrically heated cigarette smoking system in adult	**EHCSS Series JLI exposed subjects:** 40 **Total subjects:** 100 **Exposure duration:** 8 days **Location:** USA	After 8 days of smoking EHCSS Series JLI, BoExp decreased by 43% to 85% compared to baseline.

Product	Study Title	Study Setting	Conclusions
	smokers during controlled smoking [48-50]	This study evaluated eight BoExp (urine nicotine and five major metabolites, expressed as NEQ; plasma cotinine; total NNAL, total 1-OHP; COHb; 3-HPMA; S-PMA; and urine mutagenicity).	
EHCSS Series JLI	**EHCJLI/02/02** A 12-month, randomized, controlled study to evaluate the exposure to smoke constituents of an electrically heated cigarette smoking system in healthy adult smokers [41, 51-53]	**EHCSS Series JLI exposed subjects:** 64 **Total subjects:** 97 **Exposure duration:** 12 months **Location:** USA This study evaluated BoExp and cardiovascular risk markers. Smokers were either switched to EHCSS Series JLI or continued smoking CC for 12 months. BoExp and cardiovascular risk markers were measured at 0.5, 1, 2, 3, 4, 5, 6, 9, and 12 months.	There was a rapid and sustained reduction in all BoExp after switching to the EHCSS Series JLI, with statistically significant reductions from baseline in NEQ (–18%), plasma cotinine (–16%), total NNAL (–73%) total 1-OHP (–53%), urine mutagenicity (–52%), hemoglobin adducts of 4-ABP) (–43%), COHb $AUC_{7\text{-}23h}$ (–80%), and 3-HPMA (–35%). These reductions in exposure in the EHCSS Series JLI group were associated with statistically significant and pathophysiological favorable changes in several cardiovascular risk markers, including white blood cell count (WBC) (–0.78 × 103/µL), hemoglobin (–0.16 g/dL), hematocrit (–0.44%), urine 11-dehydrothromboxane B2 (–374 ng/24 h), and high-density lipoprotein (HDL) cholesterol (+5 mg/dL). Sixty-five of the 97 subjects (67%) reported at least 1 AE over the 12-month study period, with headache being the most commonly experienced AE. No product-related trends were noted in the AEs, physical examinations (including vital signs and larynx examination), clinical chemistry, urinalysis, or electrocardiogram findings.

Product	Study Title	Study Setting	Conclusions
THS 1.0 **(EHCSS Series K6)**	**FARMOVS 310/2002** A randomized controlled, crossover study assessing the exercise performance in adult smokers comparing electrically heated cigarettes, conventional cigarettes, and no-smoking (NS) [43]	**THS 1.0 exposed subjects:** 18 **Total subjects:** 18 **Exposure duration:** 9 days (3 days to THS 1.0) **Location:** South Africa	The effects of reduced smoke exposure on the prognostic parameters heart rate (HR) and rate–pressure-product (RPP) were investigated in smokers switching to THS 1.0 and NS. Exposure parameters declined from CC to THS 1.0 and to NS. Resting HR and RPP increased from NS to THS 1.0 and to CC. Chronotropic response/HR recovery were more pronounced in NS than in THS 1.0 and CC. RPP_{max} was similar in NS and THS 1.0 and lowest during CC. Exposure to THS 1.0 for 3 days improved the prognostic parameters HR and RPP in an apparently dose-dependent manner.
THS 1.0 **(EHCSS Series K6)**	**FARMOVS 127/2003** A pilot study to establish symptom-limited spiroergometry as a tool to distinguish between different exposure to cigarette smoke in adult smokers [42, 53, 54]	**THS 1.0 exposed subjects:** 18 **Total subjects:** 18 **Exposure duration:** 9 days (3 days to THS 1.0) **Location:** South Africa This study investigated whether the use of THS 1.0 or NS would improve exercise performance compared to continuing smoking CC. Randomization took place 3 days before performing symptom-limited spiro-ergometry.	Non-smoking (NS) and THS 1.0 vs. CC resulted in: -Less severe dyspnoea (NS, 44.4% [p < 0.01vs CC]; THS 1.0, 50% [p = 0.03 vs. CC]; CC, 88.9%) -Higher working capacity (NS, 2.92±0.4 W/kg [p = 0.06 vs. CC]; THS 1.0, 2.92 ± 0.4 W/kg [p = 0.04 vs. CC]; CC, 2.86±0.5 W/kg) -Higher peak oxygen uptake (NS, 2694±466 ml O_2/min [p = 0.08 vs. CC]; THS 1.0, 2830±606 mL O_2/min [p = 0.03 vs. CC]; CC, 2682±492 ml O_2/min) All data indicate that exposure to THS 1.0 and NS for 3 days may improve cardiovascular function as detected by symptom-limited spiro-ergometry.

Product	Study Title	Study Setting	Conclusions
THS 1.0 (EHCSS Series K6)	**SPA04-01** A randomized, controlled study comparing the short term exposure to smoke constituents of the EHCSS-K6 and EHCSS-K3 to Marlboro (6 mg ISO tar yield) and Philip Morris One (1 mg ISO tar yield) cigarettes in adults smokers during controlled smoking [55, 56]	**THS 1.0 exposed subjects:** 32 **Total subjects:** 160 **Exposure duration:** 8 days **Location:** UK **Location:** Korea	The levels of COHb and S-PMA in smokers using THS 1.0 were statistically significantly lower after 8 days of exposure than in smokers continuing smoking CC. The levels of BoExp: total NNAL, total 1-OHP, 3-HPMA, o-tol, and MHBMA were reduced in the THS 1.0 group as compared to CC group. In the study, 88 AEs reported (53 subjects) were of mild severity with 12.5% of reported AEs in the THS 1.0 group. All of the AEs except two (CC group: dyspepsia and vomiting) were not judged product-related. No serious adverse events (SAEs) were reported.
THS 1.0 (EHCSS Series K6)	**SPA05-01** A randomized, controlled, study comparing the short-term exposure to smoke constituents of EHCSS-K6 and EHCSS-K3 cigarettes to *Marlboro* (6 mg TIOJ tar yield) and *Lark One* (1 mg TIOJ Tar yield) cigarettes in adult smokers during controlled smoking [57]	**THS 1.0 exposed subjects:** 28 **Total subjects:** 128 **Exposure duration:** 8 days **Location:** Japan	BoExp COHb, S-PMA, total 1-OHP, MHBMA, o-tol, 4-ABP and total NNAL, 3-HPMA, were markedly reduced, excretion of mutagenic material in urine was moderately reduced and N-acetyl-S-(2-carbamoylethyl)-L-cysteine [AAMA], N-(R,S)-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine [GAMA], and 2-NA were minimally reduced in subjects using THS 1.0 as compared to subjects smoking CC at the end of exposure. In the study, all of the 12 AEs (9 subjects) were of mild intensity and none was serious or product-related. No SAEs were reported.
THS 1.0 (EHCSS Series K6)	**SPA05-03** A randomized, controlled study comparing the short term exposure to smoke constituents of the menthol version of EHCSS-	**THS 1.0 menthol exposed subjects**: 28 **Total subjects**: 100	The study was to determine BoExp to 12 selected HPHCs in cigarette smoke, excretion of mutagenic material in urine, and serum Clara cell 16-kDa protein, an indicator of lung epithelial injury. The mean decreases from baseline to Day 5/6 were statistically significant ($p < 0.05$) for exposure to 10

Product	Study Title	Study Setting	Conclusions
	K6 cigarettes to *Marlboro Menthol* (4 mg TIOJ Tar Yield) and *Lark Menthol* (1 mg TIOJ Tar Yield) cigarettes in adult smokers during controlled smoking [57]	**Exposure duration**: 6 days **Location**: Japan	of 12 HPHCs including the primary endpoint (CO) and urinary excretion of mutagenic material in the THS 1.0 menthol group (-12.3% to -83.4%). Serum Clara (Club) cell 16-kDa (CC-16) protein was not significantly different between groups. Three subjects (3%) reported an AE after randomization (5 AEs). None of the AEs were judged to be related to the study cigarettes or study procedures. All AEs resolved rapidly. Hematology examinations showed no notable changes during the study. Urinalysis revealed only sporadic cases of the presence of blood, ketones, leukocyte esterase, nitrite, and proteins in urine. There were no withdrawals due to an AE, and no occurrence of a SAE.
THS 1.0 **(EHCSS Series K6)**	**CS06-02** A 1 month, single-center, randomized, open-label, controlled clinical study to compare biomarkers of cardiovascular risk in smokers of EHCSS-K6 and smokers of CC. [56]	**THS 1.0 exposed subjects:** 237 **Total subjects:** 316 **Exposure duration:** 35 days **Location:** Poland	There were no statistically significant differences between THS 1.0 and CC arms for high sensitive C-reactive protein (hs-CRP) and WBC at the end of study (35 days), even though there was slight reduction from baseline in the THS 1.0 study arm. At the end of the study the THS 1.0 group had higher levels of HDL cholesterol, decreased levels of 11-dehydrothromboxane B2, red blood cells (RBC), hematocrit, and hemoglobin levels, as compare to CC group consistent with changes expected upon smoking cessation. This was not statistically significant. At the end of the study (35 days), the levels of the BoExp: COHb, o-tol, 2-NA, 4-ABP, total NNAL, total 1-OHP, NEQ were lower THS 1.0 than CC arms although an increase in cigarette consumption was observed. Overall, 299 AEs were reported for 316 subjects in this study with 52.7% in the THS 1.0 group. A total of 4% of AEs were considered to be related to the THS 1.0 product and no AEs were considered related to CC. Two SAEs were reported.

Product	Study Title	Study Setting	Conclusions
THS 1.0 **(EHCSS Series K6)**	**EHCK6/01/03** A clinical study to compare changes in spot urine and 24-hour urine collections of selected biomarkers of exposure in adult smokers switching from *Marlboro Ultra Lights* to the electrically heated cigarette smoking system (EHCSS-K) [58-61]	**THS 1.0 exposed subjects:** 60 **Total subjects:** 120 **Exposure duration:** 8 days **Location:** US	After switching from *Marlboro Lights* at baseline to THS 1.0 for 8 days, levels of 3-HPMA, COHb, total NNAL, MHBMA, total 1-OHP, S-PMA, and urine mutagenicity were reduced (>50%). Hematology parameters were not significantly different between the THS 1.0 group and the other groups when compared to the *Marlboro Lights* cigarette. A total of 76 AEs were reported by 45 subjects with 56% of the subjects being randomized to the THS 1.0 group. No SAEs were reported.
THS 1.0 **(EHCSS Series K6)**	**EHCK6/02/04** A 12-week, randomized, controlled, pilot study to evaluate exposure to smoke constituents of the electrically heated cigarette smoking system (EHCSS-K) in adult smokers [58]	**THS 1.0 exposed subjects:** 60 **Total subjects:** 90 **Exposure duration:** 12 weeks **Location:** US	After 12 weeks of exposure, BoExp NEQ, 3-HPMA, total NNAL, and S-PMA were reduced in subjects randomized to THS 1.0 compared to subjects randomized to CC. From Baseline to Week 12, there was a statistically significant decrease in mean hemoglobin, hematocrit, and RBC in the THS 1.0 group, compared to the CC group. There were no statistically significant differences between the groups in absolute change from baseline to week 12 for WBC or platelet counts. A total of 216 AEs were reported by 67 subjects with 62% of the AEs in the THS 1.0 group. All AEs were considered mild or moderate and not product-related. No SAEs were reported.

Product	Study Title	Study Setting	Conclusions
THS 1.0 **(EHCSS Series K6)**	**RESWBC_1008_06** A randomized, controlled, crossover study comparing heart rate variability in adult smokers of EHCSS-K, conventional cigarettes, and no-smoking [62, 63]	**THS 1.0 exposed subjects:** 30 **Total subjects:** 30 **Exposure duration:** 12 weeks **Location:** US Studies have indicated that increased variability in the heart's inter-beat interval is physiologically desirable. This study assessed the difference in heart rate variability (HRV) derived from the 24-hour ECG following different exposures of smoking CC, using THS 1.0, or NS for 3 days each.	Heart rate variability tended to increase with reduced HPHCs exposure.

5.4 Adverse Events

In total, around 655 subjects were exposed to THS 1.0 and its earlier development versions, namely EHCSS-K4 and EHCSS-JLI and 68 subjects were exposed to THS 2.1 in clinical studies. Four serious adverse events (SAEs) were reported in subjects using EHCSS Series JLI and three SAE in subjects using THS 1.0.

No SAE were reported for subjects exposed to THS 2.1.

No SAE were reported for subjects exposed to non-menthol THS 2.2 as of April 2014.

5.4.1 EHCSS Series JLI

Four SAE were reported in studies with EHCSS Series JLI (cervical neck pain, headache, and two episodes of appendicitis), all four in the Clinical Study EHCJLI/02/02.

The SAE occurred in the EHCSS Series JLI group and were all considered unrelated to the investigational or comparison product.

One subject was discontinued from the study due to hospitalization. Three SAEs resolved with sequelae. One SAE remained unchanged at the end of the study (cervical neck pain).

One subject experienced the SAE of neck pain (verbatim term "cervical neck pain"). At check-in the subject reported that she had been involved in a motor vehicle accident before the study and was diagnosed with an acute cervical sprain. During the study she was hospitalized for surgery to correct a disc problem.

One subject experienced the SAE of severe headache. At that time, the subject reported that she had been in the hospital overnight due to severe headache and underwent a spinal tap to rule out meningitis. The spinal tap was negative. The Investigator considered the SAE to be unrelated to the investigational or comparison product and the SAE resolved without sequelae.

5.4.2 THS 1.0

In total, three serious adverse events (SAEs) were reported in the THS 1.0 clinical studies. All three occurred in the Clinical Study CS06-02 with one SAE prior to randomization and no THS use:

1) One SAE was an acute myocardial infarction during screening period and was not randomized into the study.

2) The second SAE was a post-traumatic splenic injury not related to the investigational or comparison product.

3) The third SAE was an upper extremity deep vein thrombosis (DVT), which occurred one week after the study, in a male subject in the THS 1.0 study arm. The subject had a 20-year smoking history with a mean consumption of 25 CC per day. The event was resolved but required chronic treatment for thrombosis prevention. The investigator considered the event to be moderate in severity and related to the investigational product as smoking is a risk factor of DVT.

5.4.3 PK/PD Study with THS 2.1

No serious or severe AEs were reported. Table 10 provides a summary of events as recorded in the most recent short term PK/PD clinical study ZRHX-PK-02 performed in 2012.

Table 10 Summary of Most Frequent AEs in Clinical Study ZRHX-PK-02

	THS 2.1 (N=33)		CC (N=28)	
Preferred Term	**No. Events**	**No. Subjects**	**No. Events**	**No. Subjects**
Subjects with any AEs	26	14	16	10
Headache	5	5	2	2
Dizziness	4	4	2	2
Nausea	4	4	5	5
Presyncope	1	1	5	4

No withdrawals from the study due to an AE took place. Overall, there were 42 AEs reported in 19 of the 33 subjects in the safety population. More AEs were reported during the first study period (30 AEs in 16 subjects) than the second study period (nine AEs in five subjects). Fourteen subjects experienced AEs following THS 2.1 exposure and 10 subjects following CC exposure. The most frequently reported AEs were nausea, headache, dizziness, and presyncope. Other AEs included constipation, cold sweat and dermatitis contact, chest discomfort, fatigue, hyperhidrosis, vomiting and ear pain.

A total of six presyncope events were experienced by five subjects (one subject after THS 2.1 exposure and four subjects after CC use). It was suggested by the investigator that a light breakfast be allowed before product use in future studies to prevent such events.

The assessment of cough showed that the number of subjects who experienced a regular need to cough was low in both arms of the study (≤7 subjects during each single use day). No clinically relevant findings were reported in the hematology, clinical chemistry, urine analysis, vital signs, ECG, and spirometry exams.

5.4.4 Reduced Exposure Study with THS 2.1

No serious or severe AEs were reported. Table 11 provides a summary of events as recorded in the most recent Reduce Exposure clinical study ZRHX-EX-01 performed in 2012.

Table 11 Summary of Most Frequent AEs in Clinical Study ZRHX-EX-01

	THS 2.1 (N=20)		CC (N=20)	
Preferred Term	**No. Events**	**No. Subjects**	**No. Events**	**No. Subjects**
Subjects with any AEs	5	4	13	10
Blood triglycerides increased	0	0	2	2
Increased COHb	0	0	2	2
Oropharyngeal pain	1	1	1	1
Nasopharyngitis	1	1	1	1

No withdrawals from the study due to an AE took place. Overall, there were 18 AEs reported in 14 subjects after randomization. Four subjects experienced five AEs during the THS 2.1 exposure and ten subjects experienced 13 AEs during CC exposure. The most frequently reported AEs were increased blood triglycerides, oropharyngeal pain, constipation, hyperbilirubinaemia and nasopharyngitis. Other AE reported were hiccups and pharyngeal erythema.

The assessment of cough showed that the overall number of subjects who experienced a regular need to cough was l0 out of 20 subjects, almost equally distributed between CC and THS 2.1 arms.

No notable differences in the assessment of cough impact, cough intensity or assessment of sputum production were observed between study arms. No clinically relevant findings were

reported in the hematology, clinical chemistry, urine analysis, vital signs, ECG, and spirometry exams.

5.4.5 THS 2.2

As of March 2014, more than 400 subjects had been exposed to THS 2.2, for 1 to 8 days. No SAEs were reported for THS 2.2.

5.5 Market Experience

There is no THS 2.2 market experience.

THS 1.0 was marketed in Switzerland and Australia between 2006 and 2008 in two retail shops in Zurich and Melbourne respectively with very limited adult smoker consumer acceptance. The main reasons, as reported by consumers, were:

- Limited sensory satisfaction.
- No tangible benefit was obvious to and understood by consumers (e.g. no explanation was provided about the potential benefits of using THS 1.0 compared to CC).
- Limited distribution channel and therefore very limited product availability (one retail shop per market country only).

It was concluded that, when the product was presented to potential users for the first time, product acceptance and buying intention was high overall. However, when introduced in the market, repurchasing stayed at very low levels for the reasons described above.

The feedback provided by consumers was integrated in the further development and assessment program of THS.

5.6 Conclusions

The results of clinical studies conducted with THS 1.0 and its predecessors showed a consistent reduction of BoExp to HPHCs, substantiating, in combination with the results of the non-clinical assessment, a successful implementation and evolution of the principle of heating vs. burning tobacco to reduce exposure to HPHCs.

THS 2.1 tested in clinical studies showed further reduction of measured HPHCs to a level close to that described for smoking cessation [64]. In other studies, testing former versions of THS 2.2, namely CS06-02 and EHCJLI/02/02 [65, 66], the reduced exposure was also associated with favorable biological changes on selected biological parameters (e.g., 11-dehydrothromboxane B2, HDL),

A PK/PD exploratory study with the THS 2.1 (ZRHX_PK_02) indicated that the THS 2.1 is close to CC in terms of nicotine PK profile and overall exposure to nicotine resulting in a

reduction of the urge to smoke comparable to CC after single use. This is an important indicator towards potential product acceptance for smokers willing to switch from CC to THS 2.2. Pending data of four clinical studies initiated in 2013, which will generate further information on THS 2.2, both in terms of PK/PD response and in terms of changes in clinical risk endpoints. Clinical studies with THS revealed no safety concern for the versions tested in these studies. In summary, the clinical study results support the ongoing initiation of a comprehensive clinical assessment program with THS 2.2.

6 GUIDANCE FOR THE INVESTIGATOR

6.1 Target Populations

The target population for THS 2.2 is adult smokers.

6.2 Use of Product

To use THS 2.2, the consumer inserts the THS Tobacco Stick into the Holder to pre-heat it. Thereafter, the aerosol is inhaled by placing the lips on the THS Tobacco Stick mouthpiece and drawing air through the THS Tobacco Stick. Subjects need to be informed about the correct use of the product and the associated main unit. Once the Holder is switched on, the user can puff for approximately six minutes (although 30 seconds of this six minute period is for heating). The THS 2.2 Holder may warm up slightly when in use. A detailed user manual will be provided at the study sites and to subjects.

6.3 Product Variants

The THS 2.2 Holder, Charger and accessories are currently available in one format only. THS Tobacco Sticks are available in non-menthol and menthol options. This Investigator's Brochure describes the non-menthol variant of the THS Tobacco Sticks.

6.4 Warnings and Precautions

Although aerosol chemistry showed that heating instead of burning tobacco reduces the HPHCs compared to CC, given the current state of knowledge of THS 2.2 it has not been demonstrated that THS 2.2 reduces the risk of developing smoking-related diseases compared to CC.

Cigarette smoking causes cancer, pulmonary diseases, cardiovascular diseases, and many other related diseases. Smoking cessation has multiple benefits and is, by far, the best way to reduce any risks of developing such diseases.

Based on the results of the exploratory clinical studies on nicotine absorption and exposure with THS 2.1, it can be expected that THS 2.2 is similar to CC with regard to nicotine levels when used *ad libitum*. Due to sensorial and technological differences between THS 2.2 and CC, smokers may adapt their CC smoking behavior and consume more THS Tobacco Sticks than CC, without increase in overall nicotine exposure (section 5.2.1**)**. Confinement setting may also have an influence on smoking behavior, explaining an increase both in THS 2.2 and CC use.

A smoker using THS 2.2 may experience transient symptoms suggesting mild nicotine over-exposure such as stimulatory effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, decreased ability to concentrate), gastric acid secretion, and vomiting center. Individuals who experience adverse events (suggesting excessive stimulant effects) should be instructed to reduce their intensity of product use by increasing the interval between the use of a new THS Tobacco Stick, and/or by decreasing the number of puffs and/or the intensity of puffing.

6.5 Adverse Events

Table 12 provides a summary of the total THS product safety profile as recorded in clinical studies. More details are provided in section 5.4.

Table 12 THS Exposure and Adverse Events

THS Version	No. Studies	Exposure	Subjects (exposed to THS)	No. SAEs	No. AE
EHCSS JLI	3	Up to 1 year	307 (144)	4 SAEs	389
THS 1.0	9	Up to 1 month	980 (511)	3 SAEs	696
THS 2.1	2	Up to 6 days	73 (68)	0 SAEs	60

6.6 Smoke – Drug Interactions

It is established that smoking accelerates the metabolism of many drugs, particularly those primarily metabolized by CYP1A2. The CYP1A2 enzyme-inducing effects of cigarette smoke are thought to be related to exposure to polycyclic aromatic hydrocarbons and other combustion products [67]. Levels of these HPHCs are significantly lower in THS as compared to CC. The results of the ZRHX_EX_01 study (reduction of CYP1A2 activity of about 25% compared to Baseline) suggest that CYP1A2 activity will decrease with THS 2.2 use after five days. The magnitude of this effect appears to be similar to that observed following smoking cessation [68]. Therefore, smokers treated with theophylline, clozapine, olanzapine or any other drug primarily metabolized by CYP1A2 may need adjustment in the dosage regimen of these drugs.

6.7 Abuse and Dependence

Given current product knowledge, there is no reason to expect changes in abuse and dependence compared to that observed for CC.

6.8 Known Effects of Nicotine Overdose

Nicotine poisoning may occur from accidental ingestion, especially by small children, of one or more THS Tobacco Sticks, which are part of THS 2.2. Toxic effects of nicotine develop rapidly following acute overdose. Oral nicotine doses above 60 mg are probably lethal in adult humans. The gastric absorption of nicotine from tobacco taken by mouth is delayed because of slowed gastric emptying and the acidic environment in the stomach. As a result, vomiting caused by the central effect of the initially absorbed fraction may remove much of the tobacco remaining in the gastrointestinal tract. Signs and symptoms of acute nicotine intoxication include nausea, hyper-salivation, abdominal pain, vomiting, diarrhea, perspiration, headache, dizziness, hearing and visual disturbances, mental confusion, and marked weakness. Other subsequent conditions may also occur such as syncope, prostration, dyspnoea, seizures, hypotension, and a weak, rapid, and irregular pulse. Lethal doses rapidly produce seizures. Death may occur within a few minutes following severe nicotine overdose, usually as a result of respiratory failure secondary to paralysis of respiratory muscles [69].

Acute nicotine intoxication generally requires symptomatic and supportive care. There is no specific antidote for nicotine intoxication. If vomiting has not occurred following acute ingestion, the stomach should be emptied immediately by inducing emesis or by gastric lavage. Because acute nicotine intoxication can result in seizures, activated charcoal should be administered following gastric lavage and/or emesis to decrease absorption of nicotine. Alkaline solutions should be avoided. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation [70].

6.9 Summary of Non-Clinical Studies

The non-clinical assessment of THS consisted of evaluating the toxicological risk associated with the use of this alternative product for tobacco consumption by adult smokers.

Aerosol chemistry showed that heating instead of burning tobacco reduces the HPHCs compared to CC.

In vitro studies demonstrated a decreased biological activity of THS generated aerosol compared to CC smoke. The cytotoxicity monitored with the NRU assay was reduced by between 20 and 50% in THS 1.0 and subsequently reached more than 80% reduction in THS 2.0 and 2.2 compared to CC. The genotoxic activity in bacterial cells (Ames assay) and in mammalian cells (MLA) was decreased by 10% to 80% with THS 1.0 and the reduction could further be improved to 90% with THS 2.0 in comparison to CC. No genotoxic activity could be detected in bacterial cells (Ames) with THS 2.2. The genotoxic activity in mammalian cells (MLA) was decreased from 80% to 90% with THS 2.2 in comparison to CC.

In vivo 90-day inhalation study performed with THS 1.0 and THS 2.2 demonstrated their lower toxicity compared to the exposure to CC.

The non-clinical assessment performed with THS, including the THS 2.2 version, supports the conclusion that subjects in the 6-month exposure ambulatory study will not be exposed to increased or new hazards when compared to continued smoking of CC.

6.10 Summary of Clinical Studies

PMI and Philip Morris USA conducted a number of clinical studies in Europe, Asia, Africa and the United States with various versions of heated tobacco systems, namely EHCSS K4, EHCSS JLI and THS 1.0 from 2004 to 2008. In addition, PMI conducted two exploratory clinical studies with THS 2.1 in Europe in 2012.

In total, 655 subjects were exposed to THS 1.0 and its predecessor versions in clinical studies. As presented in Table 8, those studies showed incremental reductions in exposure to selected HPHCs in subjects who used THS technology as compared to subjects who continued to smoke CC, under both controlled and ambulatory conditions.

In 2012, two studies were performed by PMI with THS 2.1 in a total 68 subjects. The first study, a PK/PD Study (ZRHX_PK_02) suggested that the nicotine PK profile of THS 2.1 and related total exposure to nicotine is close to CC. The results of this study and the QSU brief evaluation, together, indicate that THS 2.1 was able to reduce craving to a level comparable to CC. It might be assumed that THS 2.2 would be an acceptable substitute of CC for adult smokers.

The second study, a 5-day exposure study in confinement (ZRHX_EX_01), showed a reduction of BoExp in the range of 47% to 90% compared to baseline CC smoking. With the exception of o-toluidine (see section 5.2.1), those results are in alignment with results from previous studies with THS. For some BoExp, levels of reduction were close to those observed when subjects cease smoking. The relatively lower reduction of o-toluidine of just 25% from baseline was most likely due to a renovation and painting of the study site immediately before the conducted study. The lower nicotine plasma concentration after single use of THS 2.1 compared to CC was not associated with an adaptation of smoking behavior. Subjects consumed more THS Tobacco Sticks during ad libitum use than CC, however with no difference in nicotine, cotinine or nicotine equivalents levels compared to CC, but did have reduced levels of biomarkers of exposure.

In conclusion, the clinical studies revealed no safety concern to preclude adult smokers from using THS. Study results from THS 1.0 and the more recent version THS 2.1, and the fact that THS 2.2 is expected to have a better product performance, make THS 2.2 the candidate tobacco heated technology system with which to perform a comprehensive clinical study program and to demonstrate a modified risk profile compared to CC. Data from four clinical studies initiated in 2013 are expected to provide further evidences of reduced exposure to HPHCs and potentially of reduced health risk and a 6-month exposure study is expected to show mid-term changes that are not likely to be seen in a shorter period.

7 REFERENCES

1. Borgerding M, Klus H. Analysis of complex mixtures – Cigarette smoke. Exp Toxicol Pathol. 2005; 57:43-73.
2. Royal College of Physicians (RCP). Harm reduction in nicotine addiction: helping people who can't quit. A report by the Tobacco Advisory Group of the Royal College of Physicians. 2007 ISBN 978-1-86016-319-7.
3. Family Smoking Prevention and Tobacco Control Act. Pub L. No 111-31, 123 Stat. 1776 (June 22, 2009).
4. U.S. Department of Health and Human Services. Docket No. FDA-2012-N-0143: Harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Fed Regist. 2012; 77(64):20034-7.
5. Ghosh A, Jeannet C. An improved Cambridge Filter pad extraction methodology to obtain more accurate water and tar values: in situ Cambridge filter pad extraction methodology. Forthcoming. 2014.
6. Health Canada, Tobacco Control Programme. Determination of "Tar", Nicotine and Carbon Monoxide in Mainstream Tobacco Smoke. T-115. 1999.
7. Philip Morris Products S.A., Campelos P, Hadju Schenk R. *Unpublished on file data:* Report - Zurich finished product qualification (9A199D). WBS J-1002RDA0016. 2014.
8. WHO Study Group, Ashley DL, Burns D, Djordjevic M, Dybing E, Gray N, et al. The scientific basis of tobacco product regulation: second report of a WHO study group. World Health Organ Tech Rep Ser. 2008; (951):1-277, 1 p following
9. Health Canada. Consolidation - Tobacco reporting regulations. DORS/2000-273. 2013.
10. Chepiga TA, Morton MJ, Murphy PA, Avalos JT, Bombick BR, Doolittle DJ, et al. A comparison of the mainstream smoke chemistry and mutagenicity of a representative sample of the US cigarette market with two Kentucky reference cigarettes (K1R4F and K1R5F). Food Chem Toxicol. 2000; 38(10):949-62.
11. National Institute of Health (NIH), National Toxicology Program (NTP), Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). Report of the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity - NIH Publication No: 01-4499. 2001.
12. Babich H, Borenfreund E. Cytotoxic and morphological effects of phenylpropanolamine, caffeine, nicotine, and some of their metabolites studied In vitro. Toxicol In Vitro. 1992; 6(6):493-502.
13. Tewes FJ, Meisgen TJ, Veltel DJ, Roemer E, Patskan G. Toxicological evaluation of an electrically heated cigarette. Part 3: Genotoxicity and cytotoxicity of mainstream smoke. J Appl Toxicol. 2003; 23(5):341-8.

14. Bombick DW, Putnam K, Doolittle DJ. Comparative cytotoxicity studies of smoke condensates from different types of cigarettes and tobaccos. Toxicol In Vitro. 1998; 12:241-9.

15. Stabbert R, Voncken P, Rustemeier K, Haussmann HJ, Roemer E, Schaffernicht H, et al. Toxicological Evaluation of an Electrically Heated Cigarette. Part 2: Chemical Composition of Mainstream Smoke. J Appl Toxicol. 2003; 23:329-39.

16. Borenfreund E, Babich H, Martin-Alguacil N. Comparisons of two in vitro cytotoxicity assays - the neutral red (NR) and tetrazolium MTT tests. 1988.

17. ICH S2 (R1). Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. Available from: http://wwwichorg/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S2_R1/Step4/S2R1_Step4pdf. 2011.

18. OECD (Organization for Economic Co-operation and Development). Guidelines for the testing of chemicals: bacterial reverse mutation test [test 471]. Avialble from: http://wwwoecdorg/chemicalsafety/risk-assessment/1948418pdf. 1997.

19. Roemer E, Teredesal A, Terpstra P, Vanscheeuwijck PM, Haussmann HJ, Philip Morris USA. The discriminative power of rat inhalation studies investigating the irritative property of inhalants. Poster presented at the Validity of Animal Models of Human Respiratory Disease Conference, Santa Fe, NM, USA. 1998; Available from http://legacy.library.ucsf.edu/tid/agp67e00/.

20. Tewes FJ, Meisgen TJ, Gomm WA, Roemer E, Carchman RA. Cigarette parameters that influence the mutagenicity of mainstream smoke condensate. Poster presented at the 38th Society of Toxicology Meeting, New Orleans, LA, USA. 1999.

21. DeMarini DM. Genotoxicity of tobacco smoke and tobacco smoke condensate. Mutat Res. 1983; 114:59-89.

22. Roemer E, Tewes FJ, Meisgen TJ, Veltel DJ, Carmines EL. Evaluation of the potential effects of ingredients added to cigarettes. Part 3: In vitro genotoxicity and cytotoxicity. Food Chem Toxicol. 2002; 40:105-11.

23. OECD (Organization for Economic Co-operation and Development). Guidelines for the testing of chemicals: in vitro mammalian cell gene mutation test [test 476]. Available from: http://wwwoecd-ilibraryorg/docserver/download/9747601epdf?expires=1396856312&id=id&accname=guest&checksum=AF32E093BEC632C14B1E9CAED2C65968. 1997.

24. Clive D, Johnson KO, Spector JF, Batson AG, Brown MM. Validation and characterization of the L5178Y/TK+/- mouse lymphoma mutagen assay system. Mutat Res. 1979; 59:60-108.

25. Mitchell AD, Evans EL, Jotz MM, Riccio ES, Mortelmans KE, Simmon VF. Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: in vitro mutagenesis and DNA damage. Environment International. 1981; 5:393-401.

26. Schramke H, Tewes FJ, Roemer E. Using the mouse lymphoma TK assay to compare the mutagenicity of mainstream smoke condensate from research cigarettes. Poster presented at the 41st Society of Toxicology Meeting, Nashville, TN, USA. 2002; Available from: http://legacy.library.ucsf.edu/tid/tcu80g00/pdf.

27. Terpstra PM, Teredesai A, Vanscheeuwijck PM, Verbeeck J, Schepers G, Radtke F, et al. Toxicological evaluation of an electrically heated cigarette. Part 4: Subchronic inhalation toxicology. J Appl Toxicol. 2003; 23(5):349-62.

28. Vanscheeuwijck PM, Teredesai A, Terpstra PM, Verbeeck J, Kuhl P, Gerstenberg B, et al. Evaluation of the potential effects of ingredients added to cigarettes. Part 4: subchronic inhalation toxicity. Food Chem Toxicol. 2002; 40(1):113-31.

29. OECD (Organization for Economic Co-operation and Development). Test Guideline No. 413: OECD Guideline for testing of chemicals. Subchronic Inhalation Toxicity: 90-day Study. Revised version available from http://iccvamniehsnihgov/SuppDocs/FedDocs/OECD/OECD-TG413pdf. 2009.

30. Philip Morris Products S.A. A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of THS 2.2 following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine gum [ZRHR-PK-02-JP]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01959607 NLM Identifier: NCT01959607.

31. Philip Morris Products S.A. A randomized, controlled, open-label, 3-arm parallel group, single center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the THS 2.2 or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement (ZRHR-REXC-03-EU). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01959932 NLM Identifier: NCT01959932.

32. Philip Morris Products S.A. Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 (THS 2.2)[ZRHR-PK-01-EU]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01967732 NLM Identifier: NCT01967732.

33. Philip Morris Products S.A. A controlled, 3-arm parallel group study to demonstrate reductions in exposure to smoke constituents in smoking subjects switching to THS 2.2 or to smoking abstinence, compared to smoking conventional cigarettes for 5 days in confinement [ZRHR-REXC-04-JP]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01970982 NLM Identifier: NCT01970982.

34. Philip Morris Products S.A. A single-center, open-label, randomized, controlled, crossover study to explore the nicotine pharmacokinetic profile and safety of Tobacco Heating System (THS) 2.1 compared to conventional cigarettes following single and ad libitum use in smoking, but otherwise healthy subjects [ZRHX-PK-02]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 May 03]. Available from: http://clinicaltrials.gov/show/NCT01780688 NLM Identifier: NCT01780688.

35. FDA (Food and Drug Administration). Guidance for industry and FDA staff - "Harmful and Potentially Harmful Constituents" in tobacco products as ssed in Section 904(e) of the Federal Food, Drug, and Cosmetic Act. 2011.

36. Philip Morris Products S.A. A single-center, open-label, randomized, controlled, 2-arm parallel group study to evaluate the exposure to selected smoke constituents in smoking, but otherwise healthy subjects switching from conventional cigarettes to the Tobacco Heating System (THS) 2.1 [ZRHX-EX-01]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 -[cited 2013 May 03]. Available from: http://clinicaltrials.gov/show/NCT01780714 NLM Identifier: NCT01780714.

37. Tricker AR. Biomarkers derived from nicotine and its metabolites: a review. Contributions to Tobacco Research. 2006; Vol 22:147-75.

38. Benowitz NL, Jacob P, 3rd, Fong I, Gupta S. Nicotine metabolic profile in man: comparison of cigarette smoking and transdermal nicotine. J Pharmacol Exp Ther. 1994; 268(1):296-303.

39. Roemer E, Stabbert R, Veltel D, Muller BP, Meisgen TJ, Schramke H, et al. Reduced toxicological activity of cigarette smoke by the addition of ammonium magnesium phosphate to the paper of an electrically heated cigarette: smoke chemistry and in vitro cytotoxicity and genotoxicity. Toxicol In Vitro. 2008; 22(3):671-81.

40. Roethig HJ, Kinser RD, Nelson BL, Oey J, Wang N. Short term clinical exposure evaluation of conventional and electrically heated cigarettes. Poster presented at the American College of Clinical Pharmacology Meeting, San Francisco, CA, USA. 2002.

41. Roethig HJ, Feng S, Liang Q, Liu J, Rees WA, Zedler BK. A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2008; 48(5):580-91.

42. Unverdorben M, der Bijl A, Potgieter L, Liang Q, Meyer BH, Roethig HJ. Effects of levels of cigarette smoke exposure on symptom-limited spiroergometry. Prev Cardiol. 2007.

43. Unverdorben M, van der Bijl A, Potgieter L, Venter C, Munjal S, Liang Q, et al. Effects of different levels of cigarette smoke exposure on prognostic heart rate and rate-pressure-product parameters. J Cardiovasc Pharmacol Ther. 2008; 13(175).

44. Roethig HJ, Kinser RD, Lau RW, Walk RA, Wang N. Short-term exposure evaluation of adult smokers switching from conventional to first-generation electrically heated cigarettes during controlled smoking. J Clin Pharmacol. 2005; 45:133-45.

45. Roethig HJ, Oey J, Nelson BL, Walk RA. Investigations of carboxyhemoglobin of adult smokers of conventional cigarettes and an electrically heated cigarette Poster presented at the 29th Annual Meeting of the Japanese Society of Toxicology, Nagoya, Japan. 2002.

46. Roethig HJ, Gogova M, Mould D, Sarkar M. A population pharmacokinetic model for nicotine. Poster presented at the 32nd Annual Meeting of the American College of Clinical Pharmacology, Tampa, FL, USA. 2003.

47. Lau RW, Hirnikel DJ, Roethig H-J, Philip Morris USA. Environmental tobacco smoke from conventional and electrically heated cigarettes. Poster presented at the Annual Meeting of ISEA/ISEE, BC, Vancouver, Canada. 2002; Available from: http://legacy.library.ucsf.edu/tid/khi96g00/pdf.

48. Roethig HJ, Zedler BK, Kinser RD, Feng S, Nelson BL, Liang Q. Short-term clinical exposure evaluation of a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2007; 47:518.

49. Oey J, Kinser R, Feng CR, Nelson BL, Liang Q, Roethig H, et al. Clinical exposure evaluation of a new electrically heated cigarette smoking system. Poster presented at the 32nd American College of Clinical Pharmacology Meeting, Tampa, FL, USA. 2003.

50. Oey J, Lau, R.W., Roethig, H.J. . Determination of environmental tobacco smoke from a second-generation electrically heated cigarette smoking system. Beitr Tabakforsch Intl. 2008; 23:1-7.

51. Rees WA, Zedler BK, Roethig HJ, Kinser RD, Liang Q, Nelson BL, et al. A 12-month clinical evaluation of an electrically heated cigarette smoking system: biomarkers of exposure. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

52. Zedler BK, Roethig HJ, Rees WA, Liang Q, Kinser RD, Nelson BL, et al. A 12-month clinical evaluation of an electrically heated cigarette smoking system: biomarkers of potential harm. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

53. Unverdorben M, van der Bijl A, Potgieter L, Liang Q, Sica D, Roethig H. Blood pressure monitoring in adult smokers comparing a conventional cigarette to an electrically heated cigarette smoking system. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

54. Unverdorben M, van der Bijl A, Potgieter L, Liang Q, Roethig H. Spiroergometry in adult smokers comparing a conventional cigarette to an electrically heated cigarette smoking system. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA, and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

55. Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol. 2012; 64(2 Suppl):S45-53.

56. Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, Lindner D, Kulesza A, Magnette J. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: a one-month, randomized, ambulatory, controlled clinical study in Poland. J Regul Toxicol Pharmacol. 2012; 64; (2 Suppl):S74-84.

57. Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK, et al. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012; 64:S64-S73.

58. Frost-Pineda K, Zedler BK, Oliveri D, Feng S, Liang Q, Roethig HJ. Short-term clinical exposure evaluation of a third-generation Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers. Regul Toxicol Pharmacol. 2008; 52:104-10.

59. Oliveri D, Liang Q, Feng S, Kinser R, Roethig H, Zedler B, et al. A clinical study comparing the short term exposure to smoke constituents of a third generation EHCSS to conventional cigarettes in adult smokers. Poster presented at the American College of Clinical Pharmacology Meeting, Cambridge, MA, USA. 2006.

60. Kapur S, Sarkar M, Muhammed R, Serafin R, Liang Q, Feng S, et al. Early morning urine void is an ideal alternative to 24 hour urine collection for determination of biomarkers of exposure in adult smokers. Poster presented at the American Society for Clinical Pharmacology and Therapeutics Meeting, Anaheim, CA, USA. 2007; Available from: http://legacy.library.ucsf.edu/tid/ifj30i00.

61. Scherer G, Urban M, Hagedorn HW, Serafin R, Feng S, Kapur S, et al. Determination of methyl-, 2-hydroxyethyl- and 3-cyanoethylmercapturic acids as biomarkers of exposure to alkylating agents in cigarette smoke. J Chromatogr B Analyt Technol Biomed Life Sci. 2010; (878):2520-8.

62. Munjal S, Koval T, Muhammad R, Jin Y, Demmel V, Roethig HJ, et al. Heart rate variability increases with reductions in cigarette smoke exposure after 3 days. J Cardiovasc Pharmacol Ther. 2009; 14(192).

63. Koval T, Munjal S, Muhammad R, Jin Y, Roethig H-J, Mendes P, et al. White blood cell count in adult smokers declines with reduction in cigarette smoke exposure and after 3 days of no smoking. Poster presented at the American College of Clinical Pharmacology (ACCP), Philadelphia, PA, USA. 2008.

64. Carmella SG, Chen M, Han S, Briggs A, Jensen J, Hatsukami DK, et al. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. Chem Res Toxicol. 2009; 22(4):734-41.

65. Philip Morris Products S.A. *Unpublished on file data:* [CS06-02] A 1-month, single-centre, randomised, open-label, controlled clinical study to compare biomarkers of cardiovascular risk in smokers of electrically heated cigarettes (EHCSS-K6) and smokers of conventional cigarettes. 2008.

66. Philip Morris USA. *Unpublished on file data:* [EHCJLI/02/02] A 12-month, randomized, controlled study to evaluate the exposure to smoke constituents of an electrically heated cigarette smoking system in healthy adult smokers. 2003.

67. Benowitz NL. Clinical Pharmacology of Nicotine: Implications for Understanding, Preventing, and Treating Tobacco Addiction. Clinical pharmacology & Therapeutics. 2008; 83(4).

68. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clin Pharmacol Ther. 2004; 76(2):178-84.

69. Hibbs RE, Zambon AC. Goodman & Gilman's - The pharmacological basis of therapeutics. Brunton LL, Chabner Bae, Knollman Bae, editors. 12th ed.: McGraw-Hill; 2011. Agents acting at the neuromuscular junction and autonomic ganglia. p. 255-76.

70. The Merck Manual for Health Care Professionals (online). Tobacco use. In: Health Care Professionals; Special Subjects. 2014- [cited 2014 Mar 14]; Available from http://www.merckmanuals.com/professional/special_subjects/tobacco_use/tobacco.html?qt=nicotine.

8 SIGNATURE PAGE

Sponsor:	Philip Morris Products S.A., Research & Development Quai Jeanrenaud 5, Neuchâtel, Switzerland, 2000 Neuchatel, Switzerland
Product name:	THS 2.2
Edition:	Edition 3
Version number:	Version 1.0
Release date:	14 April 2014
Previous Release Date:	11 April 2013

I, the undersigned, confirm that this Investigator's Brochure is accurate.

Signed: _____ Date: 14 Apr 2014

John Magnette, MD, FFPM, DipPharmMed
Manager Medical Office

PMI RESEARCH & DEVELOPMENT

Investigator's Brochure

THS 2.2

Sponsor:	Philip Morris Products S.A., Research & Development
Version:	Final
Edition Number:	Edition 5
Release Date:	27 April 2015
Previous Release Date:	24 November 2014

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS AND ACRONYMS

1-OHP	1-hydroxypyrene
2-NA	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
3R4F	Kentucky 3R4F Reference Research Cigarette
4-ABP	4-aminobiphenyl
AE	Adverse event
BoExp	Biomarker(s) of exposure
CC	Conventional or combustible cigarette
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
Cmax	Maximum concentration
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CYP1A2	Cytochrome P450 1A2
ECG	Electrocardiogram
EHCSS	Electrically Heated Tobacco System
FDA	U.S. Food and Drug Administration
FD&C Act	The Federal Food, Drug, and Cosmetic Act
GVP	Gas vapor phase
HCI	Health Canada Intense
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HPHCs	Harmful and potentially harmful constituents
HR	Heart rate
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
MHBMA	Monohydroxybutenyl mercapturic acid
MLA	Mouse lymphoma TK assay

MRTP	Modified risk tobacco product
NEQ	Nicotine equivalents
NFDPM	Nicotine free dry particulate matter
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
N/M	Not measured
NRT	Nicotine replacement therapy
NRU	Neutral red uptake assay
OECD	Organisation for Economic Co-operation and Development
o-tol	*o*-toluidine
PBA	Perception and behavior assessment
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMI	Philip Morris International
QSU	Questionnaire of Smoking Urges
RH	Relative humidity
RPP	Rate-pressure product
SAE	Serious adverse event
S-PMA	S-phenylmercapturic acid
THS	Tobacco Heating System
TPM	Total particulate matter
t_{max}	Time to the maximum concentration
WHO	World Health Organization

1 SUMMARY

One of Philip Morris International's (PMI) priorities is to develop tobacco products that are acceptable to smokers, that can substitute for conventional or combustible cigarettes (CC), and that exhibit less health-related risks compared to CC. Candidate modified risk tobacco products (MRTPs) are tobacco products sold and distributed for use to reduce harm or the risk of diseases associated with commercially marketed tobacco products [1]. Candidate MRTPs such as the Tobacco Heating System (THS) replicate the ritual of smoking but without combustion. Many harmful and potentially harmful constituents (HPHCs) in cigarette smoke are primarily formed due to the burning of tobacco [2]. Thus, lowering the temperature and heating the tobacco instead of burning it can substantially reduce or eliminate HPHCs. PMI's THS avoids combustion by heating tobacco to significantly lower temperatures than CC.

1.1 Description of the Product

Several menthol and non-menthol variants of the product are available. This IB focuses on the non-menthol variant of THS 2.2.

THS 2.2 is comprised of three main components: (1) the THS Tobacco Stick, which is a single-use consumable item, (2) the Holder, which provides the power source for a single use and heating control electronics, and (3) the Charger, which enables the Holder to be recharged.

To use THS 2.2, the consumer inserts the THS Tobacco Stick into the Holder to pre-heat it. Thereafter, the aerosol generated by the heating process is inhaled by placing the lips on the mouthpiece filter and drawing air through the THS Tobacco Stick. During use, the THS Tobacco Stick is warmed according to a carefully controlled temperature profile within the holder to heat the tobacco without combustion while at the same time providing an acceptable consumer experience in a consistent manner. When testing earlier development versions of THS in clinical studies, subjects were able to substantially reduce their exposure to selected HPHCs. However, consumer acceptance of those product versions was low, in part due to their design features. Based on this experience, THS has been improved and the temperature at which the Tobacco Stick is heated was further reduced to less than 350 °C in the current version, THS 2.2.

1.2 Non-Clinical Studies

The non-clinical assessment of THS 2.2, using Tobacco Sticks, supports the initiation of the new clinical studies described in this Investigator's Brochure. No new or increased toxicological hazard in the THS aerosol was detected compared with CC smoke. Chemical analysis of the aerosol confirmed that none of the measured HPHCs from THS 2.2 increased compared to CC. The biological activity of the aerosol was tested *in vitro* and *in vivo*. A number

of *in vitro* assays were performed to assess the cytotoxicity and genotoxicity of the total particulate matter (TPM) and gas vapor phase (GVP) fractions of the aerosol. The subchronic toxicity of the aerosol *in vivo* was evaluated in a 90-day inhalation study in rats. *In vitro* and *in vivo* results corroborated the concept that the absence of combustion when heating tobacco substantially lowers toxic effects.

1.3 Product Experience in Humans

Several clinical studies were conducted on THS 1.0, an earlier development version of THS 2.2, in Europe, Asia, Africa and the United States. Information about the earlier development of THS is provided in Table 2. All studies showed reductions in exposure to the majority of measured HPHCs from both TPM and GVP fractions in subjects who used THS 1.0 as compared to subjects who continued to smoke CC, both in controlled and ambulatory conditions. No clinical studies were conducted with the next developmental version of THS, namely THS 2.0.

In 2012, THS 2.1, was tested in two exploratory clinical studies to measure the nicotine plasma pharmacokinetic (PK) profile and to assess the reduction of exposure to HPHCs when switching from CC to THS 2.1. The observed nicotine plasma PK profile for THS 2.1 was similar to CC, and there were significant reductions in the exposure to the majority of selected HPHCs. The clinical data available on the former THS versions is described in detail in section 5.

Overall the majority of the recorded AEs were mild in severity. Seven severe AEs were recorded in CS06-02 with the THS 1.0. In studies with THS 2.1, no severe AEs were observed. The most frequently reported AEs were headache, dizziness and nausea.

Four clinical studies were initiated in 2013 to assess the PK of nicotine and reduced exposure to HPHCs with THS 2.2 for periods lasting up to 3 months. These studies are currently in different phases of finalization: results and safety profile will be incorporated in the next edition of the IB.

So far, clinical studies have revealed no safety concerns for any of the versions of THS tested, namely THS 1.0, 2.1 and 2.2.

PMI is now initiating 1) a 6-month exposure response study (with the non-menthol version of THS 2.2), followed by a 6-month extension period, 2) a smoking cessation study, that will be used to compare the effects of switching to THS 2.2 in the exposure response study vs. quitting smoking and 3) a perception and behavior assessment (PBA) study that will investigate how U.S. adult daily smokers of CC actually use the THS 2.2 product in a close to real-world conditions environment.

2 INTRODUCTION

2.1 Tobacco Harm Reduction

PMI's approach to harm reduction for current smokers is to develop novel tobacco products, such as the candidate MRTP THS 2.2, to reduce the risk of tobacco-related diseases compared to CC by reducing or eliminating, to the extent possible, HPHCs in the aerosol. There is no 'safe' tobacco product and the best way to reduce the adverse health consequences of smoking is to quit tobacco use.

The Tobacco Advisory Group of the Royal College of Physicians opined in 2007 that "if nicotine could be provided in a form that is *acceptable and effective as a cigarette substitute*, millions of lives could be saved [3]. The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act [1] in the US, embraces this concept. Section 911 of the FD&C Act establishes two distinct pathways for approving the marketing, sale, and distribution of MRTP. Section 911(g)(1) permits approval of a "Reduced Risk" MRTP if the manufacturer demonstrates that the product, as actually used, significantly reduces the risk of tobacco-related diseases in individual tobacco users as compared to CC and will benefit the health of the population as a whole. Section 911(g)(2) permits approval of a "Reduced Exposure" MRTP if the manufacturer demonstrates that the product reduces exposure to HPHCs and there is a reasonable likelihood that subsequent studies will demonstrate a measurable and substantial reduction in morbidity or mortality among individual tobacco users [4].

PMI intends to utilize smoking cessation/abstinence as the benchmark for assessing the risk reduction potential of its candidate MRTPs. PMI has conducted and plans to conduct more clinical studies with heated instead of burned tobacco products, such as THS 2.2, to measure changes in blood chemistry, risk factors and health effects in smokers who switch to a candidate MRTP, and to compare those changes to those observed in smokers who continue smoking and in smokers who cease using tobacco products.

Finally, the impact on population harm should take into account the potential benefit to the population that the MRTP could bring, and, as indicated by the FD&C Act, that individuals and the population as a whole would benefit from the introduction of an MRTP. The PMI assessment program is expected to generate evidence concerning the effect of a product's availability and marketing on tobacco product initiation, cessation, dual use, and relapse, in both individual smokers and in the population as a whole. A summary of the underlying principles of PMI's assessment is outlined in Table 1.

Table 1 Risk Assessment of MRTPs

Evidence	Assessments	Objectives
Hazard characterization	Physical and chemical comparison of the candidate MRTP aerosol to smoke from CC	To demonstrate that the proposed candidate MRTP aerosol reduces the levels of HPHCs in comparison to those in CC smoke
Toxicological evidence	*In vitro* and *in vivo* toxicological assays that can serve to demonstrate that the candidate MRTP is toxicologically less hazardous than CC in a way that may have clinical relevance	To demonstrate that the candidate MRTP's aerosol is less biologically active than CC smoke and can reveal a dose response relationship
Exposure assessment	Clinical evidence that adult smokers who switch from CC to the candidate MRTP significantly reduce their levels of biomarkers of exposure (BoExp), which provide direct, quantitative evidence of the presence of exposure to HPHCs or their metabolites in the body	To provide evidence in exposure studies that subjects who switch to the candidate MRTP have lower levels of all BoExp than those who smoke CC To evaluate how measured exposure reductions compare with levels of reductions observed in subjects who cease using tobacco products altogether
Biological and functional effects	Clinical evidence from short- to long-term ambulatory clinical studies conducted under conditions of actual use of exposure reduction, and measurement of functional changes in subjects who switch from CC to a candidate MRTP. If observed changes in subjects are similar to the short- and long-term changes seen following smoking cessation, then it could be postulated that the proposed candidate MRTP reduces risk compared to CC	To assess indicators of "exposure response", including established risk factors for smoking related diseases To compare exposure reductions, risk factor, molecular and functional changes in smokers who switch to the candidate MRTP with the changes observed in smokers who cease using tobacco products
Risk characterization	Clinical, behavioral and post-market studies concerning the impact of the candidate MRTP on consumer perception, behavior, and health	To survey patterns of tobacco product consumption, perception, and understanding among adult smokers, never smokers, candidate MRTP users, and former smokers before and after a candidate MRTP is marketed

Randomized clinical studies are a central component of the THS development program and will advance the scientific evidence that the new candidate MRTP modifies the risk profile compared to CC use. This Investigator's Brochure, supports the THS 2.2 clinical development program that comprised initially three types of clinical studies:

1. Pharmacokinetic/Pharmacodynamic (PK/PD) studies.

2a. Reduced Exposure studies in confinement (up to 5 days of exposure to THS 2.2).

2b. Reduced Exposure studies in confinement with an ambulatory period (up to three months of exposure to THS 2.2).

3. Exposure Response study in ambulatory conditions (6 months of exposure to THS 2.2), which will be followed by a 6-month extension study.

PK/PD

The rate and extent of nicotine absorption during single stick use of THS are measured and compared to CC and to nicotine replacement therapy (NRT). These randomized cross-over, relative bioavailability pharmacokinetic studies, after a single THS Tobacco Stick use, are part of the characterization of THS 2.2. They provide evidence on the relationship between plasma nicotine levels and the suppression of the urge to smoke in people who switch from CC (PD). Four PK/PD studies were conducted, two in Japan (ZRHR-PK-02-JP; NCT01959607 [5] and ZRHM-PK-05-JP; NCT01967706 [6]), one in Poland (ZRHR-PK-01-EU; NCT01967732 [7] and one in the US (ZRHM-PK-06-US; NCT01967719 [8]). The results of the studies conducted with the menthol variant of the product (i.e. ZRHM-PK-05-JP and ZRHM-PK-06-US) will be reported in the THS 2.2 Menthol IB. Results with the non-menthol variant (i.e. ZRHR-PK-02-JP and ZRHR-PK-01-EU) will be reported when clinical study reports will be completed.

Reduced Exposure (Confined)

These studies investigate reduction of BoExp to selected HPHCs after switching from CC to THS 2.2 in an optimal, clinical laboratory setting. Product use is monitored by the study staff. The subjects use THS 2.2 without restriction (*ad libitum*), but dual use of CC and THS 2.2 is not allowed. These comparative studies include THS 2.2, CC and smoking abstinence arms. Exposure to nicotine and subjective effects (craving, withdrawal symptoms, and product satisfaction) are being assessed systematically over a one week period of confinement. These short-term studies will also provide safety data, such as vital signs and adverse events. Two Reduced Exposure Confined studies were conducted, in Japan (ZRHR-REXC-04-JP; NCT01970982 [9]) and in Poland (ZRHR-REXC-03-EU; NCT01959932 [10]). Results will be reported in this IB when clinical study reports will be completed.

Reduced Exposure (Confined and Ambulatory)

These studies have two distinct periods. The first part of the studies is similar to the short-term reduced exposure studies, in that current smokers are confined for a week and BoExp are measured in subjects switching from CC to THS 2.2. In the second part of the studies, subjects are followed over a period of one to three months in an ambulatory setting. The ambulatory, extended study period increases the understanding of product use and acceptance, as well as the achieved exposure reduction by THS 2.2, used either exclusively or in combination with CC. Two Reduced Exposure Confined and Ambulatory studies were conducted, in Japan (ZRHM-REXA-07-JP; NCT01970995 [11]) and in the US (ZRHM-REXA-08-US; NCT01989156 [12]). As these studies were conducted with THS 2.2 Menthol, the results will be reported in the THS 2.2 Menthol IB.

Exposure and Smoking Cessation Response Studies (Ambulatory)

The exposure response study will assess clinical, physiological and biological changes observed during *ad libitum* THS 2.2 use in ambulatory conditions, compared to continued use of CC (ZRHR-ERS-09-US; NCT0239638 [13]). This study will last 6 months, and will be extended by an additional 6-month period (ZRHR-ERS-09-EXT-US) A smoking cessation study is being conducted in parallel, and will be used as a benchmark. The comparison of changes in THS 2.2 users compared with smokers of CC and quitters should provide convincing evidence that THS 2.2 successfully modifies the risk profile.

The conduct phase of the PK/PD and reduced exposure studies is completed and data are currently being compiled and analyzed. Exposure (+ extension) and smoking response studies will be conducted in 2015 and 2016. PMI is now further moving to the next stage of its assessment program, on risk characterization, which includes perception and behavior assessment (PBA) studies.

Perception and Behavior (Ambulatory)

Perception and Behavior and Assessment (PBA) studies are planned to evaluate:

-The effect on tobacco use behavior among adult smokers, i.e. the likelihood that adult smokers will switch from CC to THS 2.2, use THS 2.2 in conjunction with CC or switch back to CC.

-The effect on tobacco use initiation among adult non-smokers, i.e. the likelihood that adult never smokers and adult former smokers will initiate use of THS 2.2.

-The effect on consumer understanding and perceptions, i.e. the effect the communication will have in terms of enabling the public to comprehend the information concerning modified exposure/risk claims and the effect the communication will have on the public

perception about the health risks of using THS 2.2 in comparison to CC, NRTs and cessation.

The purpose of the THS-PBA-07-US Actual Use Study is to investigate how US adult daily smokers of CC actually use the THS 2.2 product in a close to real-world conditions environment. This actual use study of THS 2.2 involves an assessment of subject-reported stick-by-stick usage behavior consumption of THS 2.2 tobacco sticks and of CC to describe the proportion of subjects who start using THS 2.2, switch from CC to THS 2.2, use THS 2.2 in conjunction with CC or switch back to CC. Study participants will be able to continue consuming CC and other tobacco products ad libitum throughout the study periods. The study will be conducted with both variants of THS 2.2, i.e. menthol and non-menthol.

2.2 The Tobacco Heating System

The development of Electrically Heated Cigarette Smoking System (EHCSS) started in the 1990s, and since then, PMI has continuously leveraged and improved the principle of heating versus burning tobacco in order to substantially reduce the exposure to HPHCs with THS. These developments have been ongoing through different versions and were focused on continuous improvement in order to achieve:

1. Increased reduction of HPHCs by reducing and controlling the heating temperature.
2. Improved taste to the point where smokers are prepared to accept the candidate MRTP as a replacement for CC.
3. Improved convenience in use and handling.

Table 2 Evolution of the Electrically Tobacco Heating System Development

Name of the Product	Development and Commercial Status	Key Characteristics	Improvements	Aerosol Chemistry
EHCSS Series JLI	Middle of 1990s. The EHCSS Series JLI was test marketed in Richmond (USA) in 2002 as Accord® and in Osaka, Japan in 2002 as Oasis®	Energy control of the heating blades External Tobacco Stick heating Tobacco Stick design using coated cast leaf tobacco Usage limited to 8 puffs per Stick Peak temperature of the tobacco material ~ 550°C	Substantially reduced CO delivery compared to CC Sidestream smoke significantly reduced compared to CC	↓HPHC yield relative to CC
EHCSS Series K6 (also referred to as THS 1.0)	EHCSS Series K6 (THS 1.0) was test marketed in Australia and Switzerland in 2006	Change from Series JLI: Addition of a highly activated carbon filter	Improved consumer acceptability compared with the earlier versions Reduced yields of GVP HPHCs compared to EHCSS Series JLI	↓HPHC yield relative to CC
THS 2.0	Development timing 2007-2010. No commercial or marketing activity	Temperature control of the heating blade Internal THS Tobacco Stick heating THS Tobacco Stick design using shredded cast leaf tobacco Usage limited to 6 minutes Heating blade temperature of 375°C Significant device size reduction and introduction of a two-piece system including a Charger and Holder	Overall reduction of HPHC delivery compared to THS 1.0 Consumer acceptability improved (taste and ergonomics)	↓HPHC yield relative to CC ↓HPHC yield relative to THS 1.0

Name of the Product	Development and Commercial Status	Key Characteristics	Improvements	Aerosol Chemistry
THS 2.1	Development in 2011	Changes from THS 2.0: Introduction of blend FR1 [1] THS Tobacco Stick design using crimped cast leaf tobacco	Increased manufacturing consistency Improved consistency of sensory experience	↓HPHC yield relative to CC Comparable HPHC yield to THS 2.0
THS 2.2	Development from 2011	Changes from THS 2.1: Optimized heater blade temperature profile and [redacted] compared to THS 2.1	Improved puff by puff consistency and sensory satisfaction compared to THS 2.1	↓HPHC yield relative to CC Comparable HPHC yield to THS 2.0 and 2.1
		Change of tobacco blend from FR1 to Dorado II [2]. Blends demonstrated to be equivalent through a comparability protocol [14].	Blend sustainability for commercial manufacturing	Aerosol chemistry directly comparable to former blend, but very minor changes in the Tobacco Plug composition, aerosol fractions and Bill of Material

[1] Blend FR1 was used in THS versions described in the IB editions 1, 2 and 3

[2] Blend Dorado II was used in THS versions described in the IB edition 4 and 5

The concept that lowering the temperature can effectively reduce the levels of HPHCs was confirmed early in tests using the first versions of the THS technology. It was also shown that such reduction in HPHCs leads to lower levels of BoExp in smokers who switched to THS and was instrumental to the decision to further develop the EHCSS.

A significant design change was made with the introduction of a two piece system of a Charger and Holder with THS 2.0, which is expected to have better user acceptance than the somewhat bulky, single piece THS 1.0 device. The temperature control and optimization was achieved through heating the THS Tobacco Stick internally instead of externally and optimal electronic control of the heating blade temperature, [redacted]

3 DESCRIPTION OF THE PRODUCT

THS 2.2 has three distinct components, which perform different functions during use:

- A THS Tobacco Stick, which contains the tobacco plug.
- A Holder into which the THS Tobacco Stick is inserted.
- The Charger which is used to recharge the Holder after each use.

These three components are shown in Figure 1.

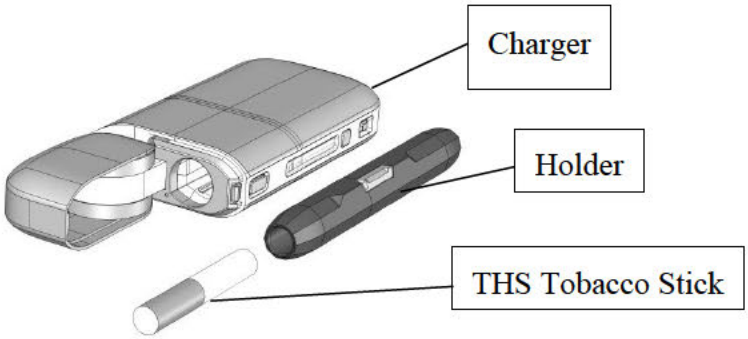

Figure 1 The Three Components of THS 2.2

3.1 The Product Components

3.1.1 The Holder

The Holder comprises 4 major components (Figure 2):

- The Casing.
- The Heater element, which is a glass-coated metallic resistive element through which electricity is passed to create the heating (heating blade).
- Control Electronics, which ensure the temperature control of the heating element and continuously measure the element temperature, allowing overheating to be detected and inhibited.
- A Battery, which stores sufficient power for a single THS Tobacco Stick use.

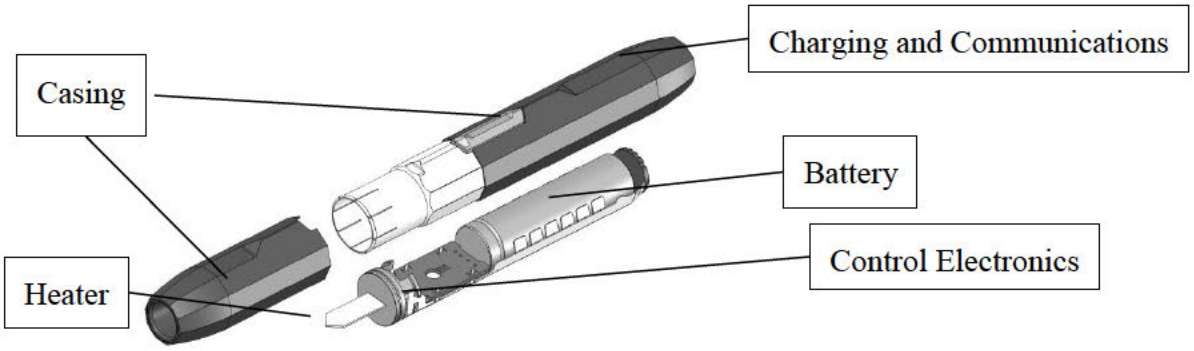

Figure 2 An Exploded View of the Holder Showing the Component Parts and Assemblies

3.1.2 The Charger

The Charger (Figure 3) is designed to be portable (approximately the size of a pack of CC) and to recharge the Holder. The Electronics regulate both the charging of the Holder battery from the Charger battery and the charging of the Charger battery from an external power source.

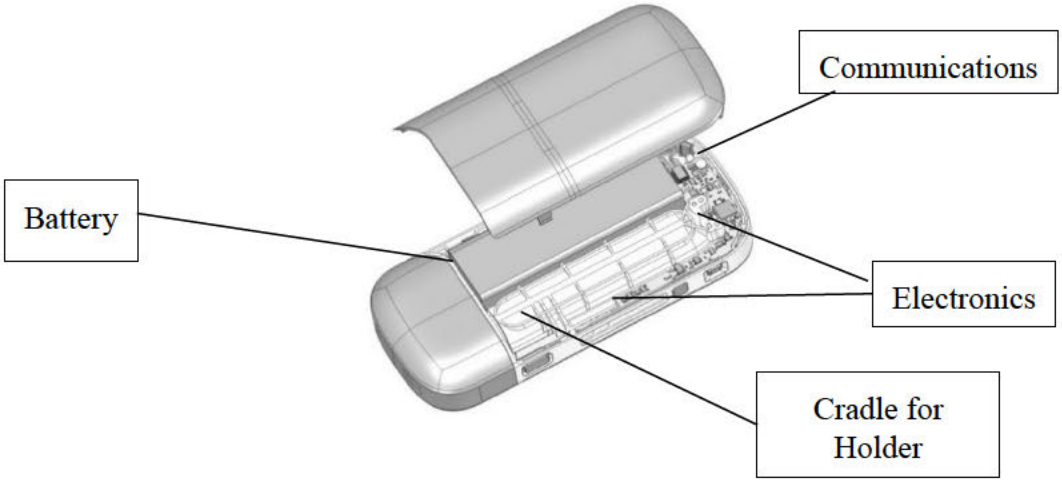

Figure 3 An Exploded View of the Charger

3.1.3 The THS Tobacco Stick

The THS Tobacco Stick is similar in basic design to a CC, but is shorter, contains less tobacco material and has an additional filter section. The THS Tobacco Stick comprises a number of elements (Figure 4):

- A Tobacco Plug manufactured from crimped, cast-leaf tobacco. Glycerin is added to the cast-leaf to facilitate aerosolization.
- A Hollow Acetate Tube which acts as a mechanical spacer between the tobacco plug and the first filter.
- A Polymer-Film Filter, which reduces primarily phenol.
- A low-density cellulose acetate Mouth Piece Filter.
- The Outer and Tipping Papers (standard papers used in CC).
- The Mouth Piece Filter.

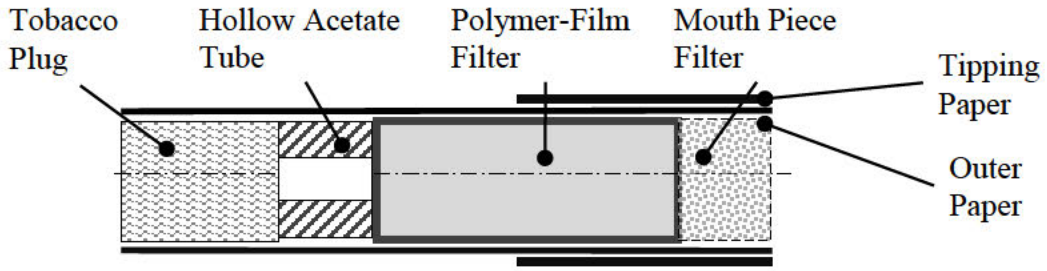

Figure 4 A Cross-Sectional Diagram of the THS Tobacco Stick

3.1.3.1 Bill of Materials

The THS Tobacco Stick is made up of elements that include those used in CCs and some new elements which have been developed specifically for the THS Tobacco Stick. All materials have been evaluated with regards to their toxicological potential and have been approved for use.

The overall composition of the THS Tobacco Stick is as shown in Table 3.

Table 3 Bill of Materials for the THS Tobacco Stick

Component	Approximate % of Total Error! eference source not found.	Average Weight (mg/THS Tobacco Stick) Error! Reference ource not found.	Comment
Tobacco Plug	40%	313.5	Specification is ± 30mg
Hollow Acetate Tube	10%	81	Calculated from bulk weighing
Polymer-film Filter	37%	295.7	Specification is ± 30mg
Mouth Piece Filter	7%	53	Calculated from bulk weighing
Outer Paper	3%	27.6	Calculated from known paper size and average density
Tipping Paper	2%	18.2	Calculated from known paper size and average density
Adhesives	1%	5.7	Estimate
Total	100%	794.7	

[1] Values in this table are representative. They may slightly vary from batch to batch.

The average weights in the bill of materials may slightly differ from batch to batch. Only batches within specifications are released for use.

3.1.3.2 The Tobacco Plug

The tobacco plug is made from the materials shown in Table 4. Nicotine content is 5.6 to 6.4 mg per Tobacco Stick.

Table 4 Tobacco Plug Composition

Component	Approximate % of Total [1]	Average Weight [1] (mg)
Tobacco	64%	201.5
Glycerin (pharmaceutical grade)	17 %	52.3
Water	12%	36.1
Wrapper	2.5%	7.71

Component	Approximate % of Total [1]	Average Weight [1] (mg)
Guar (food grade, E412)	2.5%	7.85
Fibers	1.67%	5.23
Propylene Glycol	0.81%	2.55
Ethanol	<< 1.0%	traces
Flavors	0.075%	0.236
Total	100%	313.5

[1] Values in this table are representative. They may slightly vary from batch to batch

The average weights in the Tobacco Plug composition may slightly differ from batch to batch. Only batches within specifications are released for use.

3.1.3.3 Aerosol Fractions Determined by International Organization for Standardization (ISO) and Health Canada Methods

Many countries require cigarette manufacturers to print the per cigarette yields of tar, nicotine, and carbon monoxide (CO) on the outside of the packaging. Per cigarette/Tobacco Stick tar, nicotine, and carbon monoxide yields are normally determined by standardized test methods. The most widely used test method is ISO 4387. PMI has developed a modified version of this method, which improves the determination of tar in products with high water content, which is typical for heated tobacco products [15]. Another method is the more intensive smoking method, Health Canada Intense (HCI) [16].

Table 5 lists ISO and HCI reported values:

Table 5 Reported Aerosol Fractions for the THS Tobacco Sticks

Constituent (mg/THS Tobacco Stick)	ISO [1]	Health Canada Intense regime [2]
Tar/NFDPM [3]	3	10.5
Nicotine	0.4	1.30
Carbon monoxide	1	0.5

[1] International Organization for Standardization ISO machine-smoking regimen. The analytical method has been modified to avoid inaccuracies as a result of condensation from high water-content aerosols.

[2] Health Canada Intense machine-smoking regimen (55 mL puff volume, 2-second puff duration, 30-second inter-puff interval) [16]. Data collected 11/11/2014, product reference CONS.01938.RD(2)/B-13063, blend Dorado II.

[3] NFDPM: nicotine free dry particulate matter

3.2 Product Use

To use THS 2.2, the THS Tobacco Stick is inserted into the Holder. The heating of the THS Tobacco Stick is initiated by pressing the button on the Holder and an LED indicates when the initial heating process is complete.

Once initial heating is complete, the product is used in much the same way as a CC:

- The user draws air through the THS Tobacco Stick.
- This initiates the use heating cycle, which follows a puff-by-puff heating profile designed to provide a consistent user experience throughout use.
- The Holder and THS Tobacco Stick can deliver up to 14 puffs over a period of approximately 6 minutes.
- Once this cycle is complete, the Holder must be recharged and a new THS Tobacco Stick must be used.

In use, the Holder/THS Tobacco Stick combination can be held and used in a manner very similar to a CC. Detailed user manuals are provided to study sites and subjects.

3.3 Product Stability

Stability tests have been performed under three sets of 12 month storage conditions. The conditions are a) 60% relative humidity (RH), 22°C, b) 35% RH, 30°C, and c) 75% RH, 30°C. The levels of nicotine, tar, carbon monoxide, glycerin, 29 other HPHCs and 3 flavor markers were measured as well as aerosol droplet size characteristics, the basic physical characteristics of the THS Tobacco Stick, and a qualitative sensorial assessment. (b) (4) [redacted]. Under condition b) the TPM fell below the expected level after 7 months. Water and glycerin showed a consistent reduction with time, but remained within specification as did all other measurements. (b) (4) [redacted]. At 6 months the TPM level was below expectation, and after 9 months the glycerin was below specification. Other parameters showed some variation but remained within specification [17].

The conclusion is that under normal usage conditions the THS Tobacco Sticks show some variation, but deliveries of HPHCs and general performance remain consistent over a period of 12 months.

4 NON-CLINICAL STUDIES

As described in section 1.1, the THS product consists of a THS Tobacco Stick and a THS Tobacco Stick Holder that is a separate component in which the THS Tobacco Stick is inserted in order to heat it and generate an inhalable aerosol. The initial step in the toxicological assessment process is the qualification of the materials and ingredients used in the manufacturing of the THS Tobacco Stick disclosed in the bill of material (Table 3). The qualification of the materials used in the Holder, the packaging materials and the indirect materials used in the manufacturing process are also included in the toxicological assessment process. The materials and ingredients mentioned above were toxicologically assessed and approved for their intended use.

The next step consists of the toxicological assessment of the aerosol generated from the heated THS Tobacco Stick on puffing. The endpoints for the *in vitro* part of the aerosol assessment include cytotoxicity and genotoxicity. For cytotoxicity, the neutral red uptake (NRU) assay is used, while for genotoxicity, gene mutation induced by the aerosol in bacterial and mammalian cells are evaluated with the Ames and the mouse lymphoma assay (MLA), respectively. The *in vivo* toxicological assessment includes a 90-day aerosol inhalation study in rats.

The main studies conducted for non-clinical evaluation of THS 2.2 are summarized in Table 6.

Table 6 Non-Clinical Assessment of THS 2.2

Test System	Smoke Generation Regimen	THS Tobacco Sticks Tested	Study Report Number
Smoke chemistry	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	RLS-ZRH-2012-252
NRU	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/CAST LEAF – CL/Flavor/Reynaldo	RLS-ZRH-2012-249
Ames	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/CAST LEAF – CL/Flavor/Reynaldo	RLS-ZRH-2013-15
MLA	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	RLS-ZRH-2012-315
90-Day inhalation study	Health Canada Intense (HCI)	ZRH/C3/F Reform 1/Cast Leaf – CL/Flavor/Reynaldo	15006

4.1 Constituent Analysis of the THS Aerosol

The following criteria have been used consistently through the THS development program for the selection of scientifically meaningful HPHC aerosol to be monitored:

1. Priority toxicants in tobacco smoke as listed by regulatory bodies, or proposed by cognizant authorities (Food and Drug Administration (FDA) [4], World Health Organization (WHO) [18], Health Canada [19]).
2. HPHCs with established BoExp in human (smoke/aerosol constituents or metabolites).
3. HPHCs which are predominantly formed below 400°C.
4. HPHCs which are predominantly formed above 400°C.

4.1.1 Reduction of HPHCs in THS 2.2 vs. 3R4F

Heating instead of burning tobacco excludes many constituents from forming as a result of tobacco combustion. By only heating the tobacco, the number and concentration of HPHCs in the aerosol are further reduced as compared to the 3R4F reference cigarette. University of Kentucky 3R4F reference cigarette (ISO tar 7.8 mg; nicotine 0.74 mg; CO 10.7 mg) serves as an international standard for research purposes and provides a basis for comparing data collected in various laboratories. The 3R4F reference cigarettes are the third production run and are considered to be representative of the US market cigarettes [20].

The constituents generated under HCI by THS 2.2 aerosol are qualitatively and quantitatively significantly reduced compared to the HPHCs measured for 3R4F reference cigarette on an equal nicotine basis (Figure 5).

4.1.2 Product and Design Evolution

With THS 1.0, THS Tobacco Sticks were heated up to 500 °C, and subsequent developments enabled lowering the temperature for the THS 2.2 system to no more than 350 °C. When compared to its predecessors, THS 2.2 showed on a nicotine equivalent basis, similar or reduced levels of HPHCs in the generated aerosol.

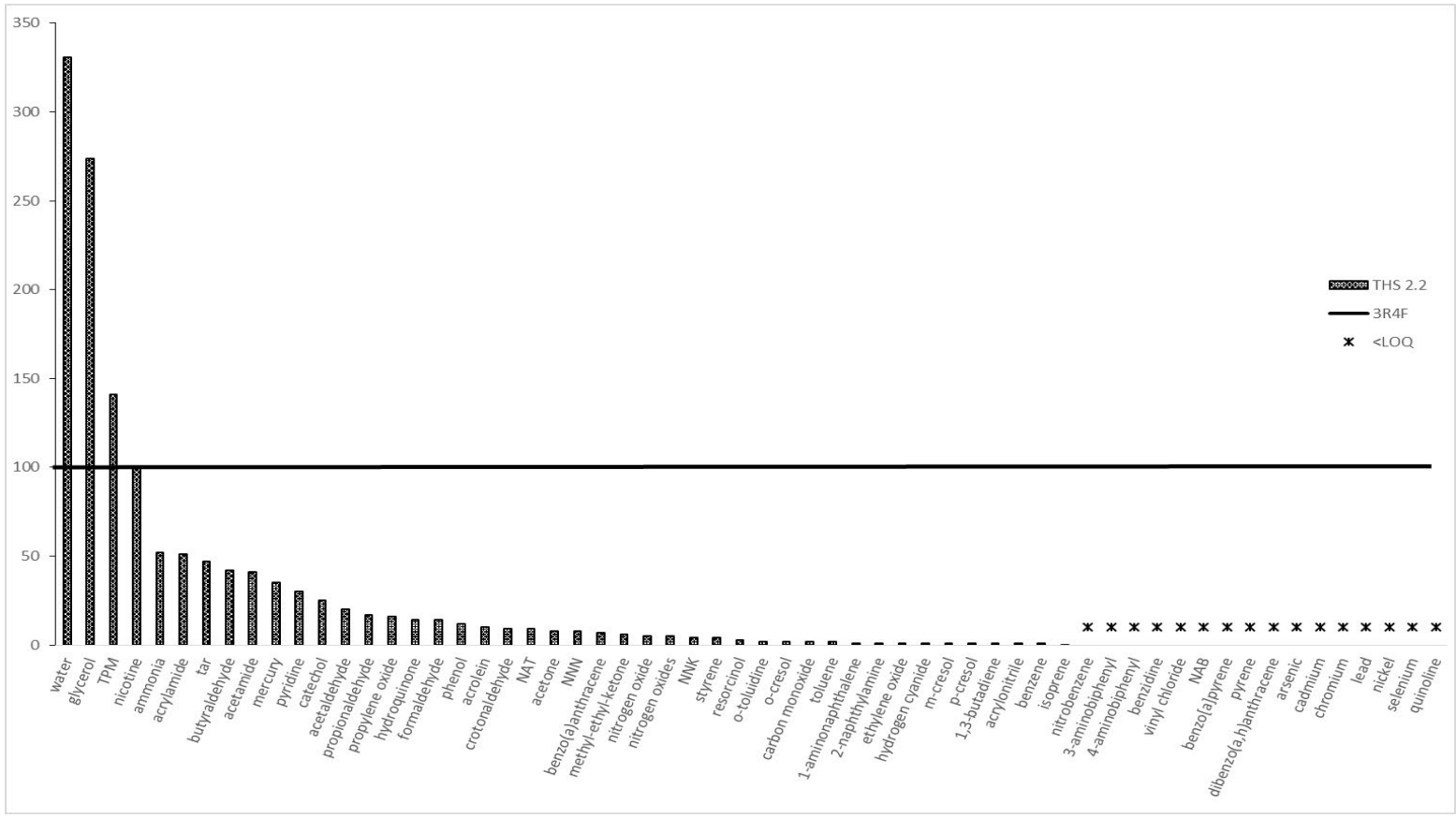

Figure 5 Comparison of Constituents of THS 2.2 to those from 3R4F, on a per mg Nicotine Basis (Constituents of 3R4F Set to 100%)

4.2 *In Vitro* Toxicology

4.2.1 Neutral Red Uptake Assay

The neutral red uptake *in vitro* cytotoxicity assay (NRU) has been widely used and accepted by the chemical and pharmaceutical industry, and by regulatory authorities, as a screening method to determine the cytotoxicity of compounds [21, 22]. It is known to be responsive to both the particle phase of CC smoke and to the GVP [23], and it can discriminate between different CC tobacco types [24, 25]. The assay is a well-established, reproducible, and standardized short-term test that responds to cytotoxic compounds in a dynamic range of five orders of magnitude [26].

On an equal nicotine basis, the cytotoxicity of TPM and GVP for THS 2.2 was lower than that from 3R4F reference cigarette when smoked under Health Canada Intense (HCI) machine-smoking regimen conditions (Figure 6).

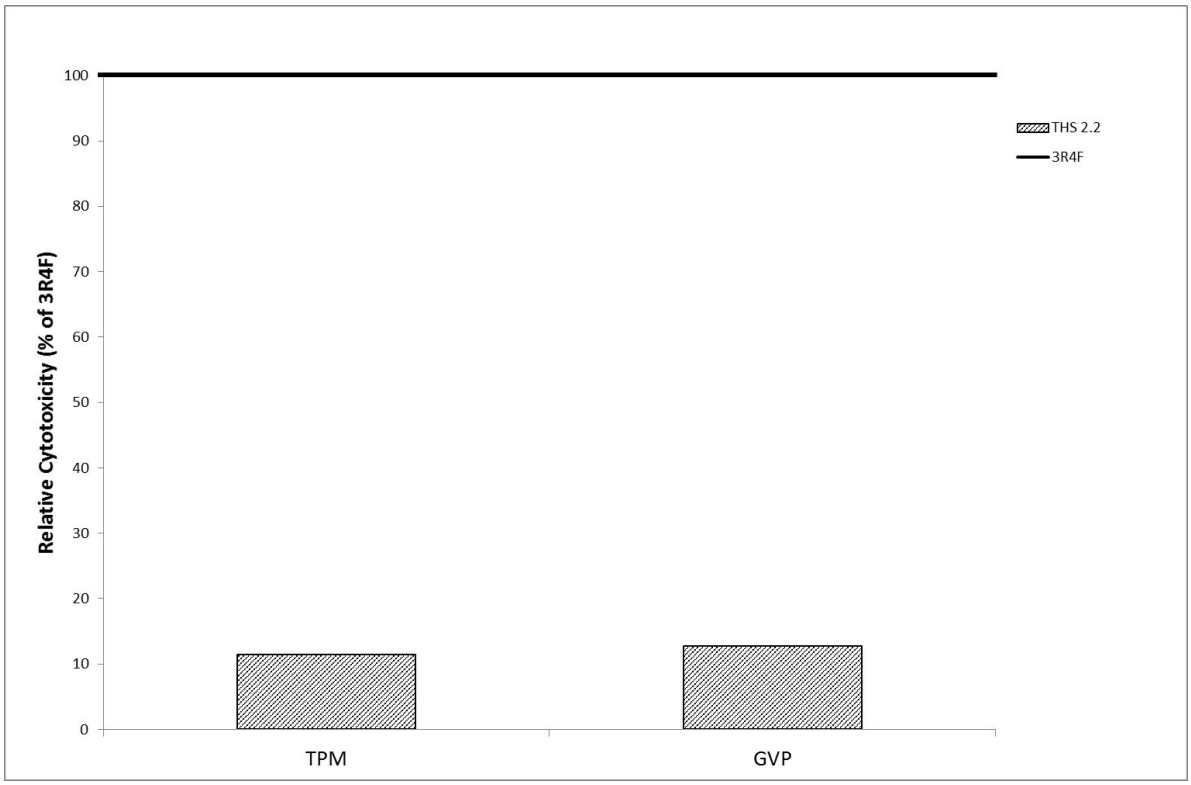

Figure 6 Relative cytotoxicity in Neutral Red Uptake Assay of TPM and GVP of THS 2.2 compared to 3R4F smoked under HCI, on an Equal Nicotine Basis

4.2.2 Genotoxicity Studies

4.2.2.1 Bacterial Reverse Mutation Test

The Salmonella reverse mutation assay (Ames assay) is recommended both by the Organisation for Economic Co-operation and Development (OECD) and International Conference on Harmonization (ICH), as part of the standard testing battery for genotoxicity [27, 28]. The Ames test can detect and discriminate the mutagenic activity of different types of CC [23, 29] with different filter ventilation, filter efficiency, and paper porosity [30], and different tobacco types and CC smoke fractions [31]. The Ames assay is sensitive to TPM from CC smoke, but the sensitivity depends on the strain and the presence or absence of a metabolic activation system (S9). The strains that are the most sensitive toward TPM are TA98, TA100 and TA1537 with S9 (TA98>TA100>TA1537). TA98, TA100 and TA1537 without S9 and TA1535 with S9 show only marginal response. TA102 with and without S9 and TA1535 without S9 are not responsive to TPM [32].

The TPM (up to 2.5 mg/plate) and the GVP (up to 3.0 mg/plate) from THS 2.2 did not show any mutagenic activity in the different strains tested in presence or absence of S9 (data not shown). The TPM (from 50 µg/plate) and the GVP (from 200 µg/plate) from 3R4F were however reported as mutagenic in absence and presence of S9.

4.2.2.2 Mouse Lymphoma TK Assay

The mouse lymphoma TK assay (MLA) is recommended both by the OECD [33] and ICH [27], as part of the standard testing battery for genotoxicity. MLA measures the induction of forward mutations at the tk-locus in L5178Y/tk+/-3.7.2C mouse lymphoma cells. The response to TPM is in general very low, only up to a 3- to 5-fold increase over the background mutant frequency [34, 35], but the assay can nevertheless discriminate the mutagenic activity of different tobacco types [36].

On a nicotine equivalent basis, the relative mutagenicity of TPM and GVP from THS 2.2 was substantially lower than 3R4F with or without metabolic activation (S9) (Figure 7).

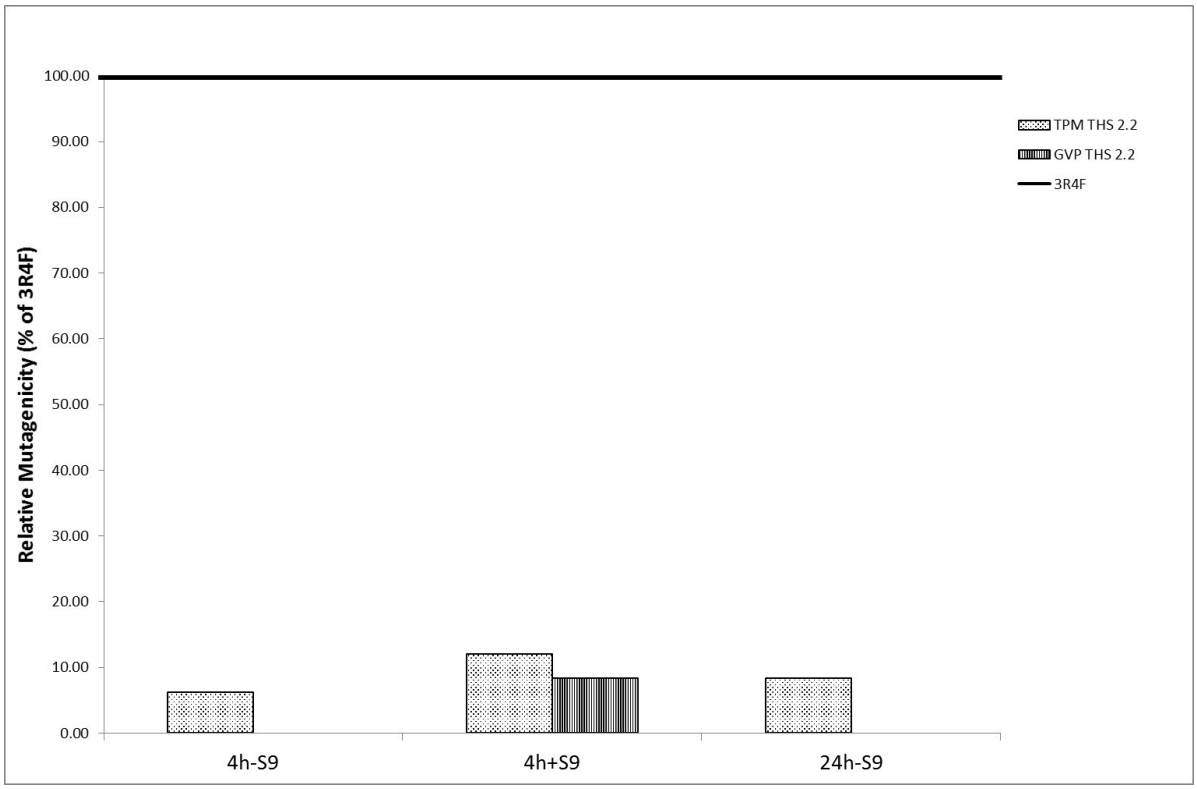

Figure 7 Relative Mutagenicity in MLA of TPM and GVP of THS 2.2 Compared to 3R4F Smoked Under HCI, on an Equal Nicotine Basis, with and without S9 Metabolic Activation

4.3 *In Vivo* Toxicology

4.3.1 90-Day Rat Inhalation Study

Previous studies showed that a 90-day rat inhalation study is a suitable model for the detection of diluted mainstream smoke-related changes in systemic toxicity and histopathology of the respiratory tract [29, 37, 38]. The inhalation toxicity of THS 2.2 was investigated after sub-chronic exposure to the mainstream aerosol. The biological activities of the THS 2.2 aerosol were compared with those of 3R4F. The toxicological activity was determined in basic conformity with OECD guideline 413 with regard to the following parameters: body weight, food consumption, ophthalmologic changes, clinical observations, clinical chemical and hematological parameters, gross pathological observations, organ weights, and histopathological changes in the respiratory tract [39].

Measurement of aerosol HPHCs showed lower content of formaldehyde, acrolein, acetaldehyde and carbon monoxide in the THS 2.2 exposure chambers when compared to the 3R4F ones, thus validating the experimental paradigm.

The generated aerosol was reproducibly inhaled by the animals, as indicated by the measured BoExp COHb, and the urinary nicotine and selected BoExp [3-hydroxypropylmercapturic acid -HPMA-, S-phenylmercapturic acid -SPMA-, 2-cyanoethylmercapturic acid -CEMA- and the sum of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone plus its glucuronide conjugates -total NNAL-, for acrolein, benzene, acrylonitrile and NNK respectively]. Data showed a good correlation between measured BoExp and HPHC concentrations in the test atmospheres.

The overall evaluation of the data, summarized in Table 7, indicates that exposure to THS 2.2 aerosol induces less inflammation and fewer degenerative changes to the respiratory tract organs and does not result in additional hazards to those presented by smoking CC.

Table 7 Systemic Toxicity and Histopathology of Male and Female Rats Exposed to Mainstream Smoke from 3R4F and Mainstream Aerosol form THS 2.2 in a 90-Day Inhalation Study

Findings [1]	3R4F	THS 2.2
Death	No death related to exposure up to 23 µg/L nicotine in test atmosphere	No death related to exposure up to 50 µg/L nicotine in test atmosphere.
Body weight	Reduced body weight gain.	Reduced body weight gain but less pronounced compared to 3R4F.
Organ weight	Dose-dependent increase of lung, larynx and trachea weight. Increase of liver weight at 23 µg/L nicotine. Increase of adrenal gland weight. Dose-dependent decrease of thymus and uterus weight.	Increase in lung, larynx and trachea weight less pronounced when compared to 3R4F. Increase of liver weight at 23 and 50 µg/L nicotine. Increase of adrenal gland weight. Decrease in thymus weight less pronounced than 3R4F. Dose-dependent decrease of uterus weight.
Respiratory physiology	Dose-dependent reduction in respiratory minute volume.	No change in respiratory minute volume.
Lung inflammation	Dose-dependent increase in immune cell counts present in bronchoalveolar lavage.	Minimal increase in immune cell counts present in bronchoalveolar lavage.
Clinical Chemistry	Dose-dependent increase in liver enzymes.	Dose-dependent increase in liver enzymes.

Findings [1]	3R4F	THS 2.2
Histopathology	Nose: Reserve cell hyperplasia of the respiratory epithelium. Squamous epithelial metaplasia of the respiratory epithelium and olfactory epithelium. Ulceration and atrophy of olfactory epithelium. Larynx: Squamous epithelial metaplasia at base and distal base of epiglottis. Hyperplasia of squamous epithelium of vocal folds. Epithelial thickness at the floor of the larynx and at the lower medial region of vocal cords. Tracheal ring and bifurcation: Reserve cell hyperplasia. Goblet cell hyperplasia at tracheal epithelium. Lung: Presence of macrophages with and without yellow pigmentation in the alveolar lumen. Presence of neutrophilic granulocytes in the alveolar lumen. Goblet cell hyperplasia at the main bronchus.	Significantly decreased histopathological changes compared to 3R4F.

[1] Study was performed in rats according to OECD TG 413 (2009); 90-day inhalation period, exposure for 6 h/d, 5 d/wk. Groups: sham, low, medium and high nicotine both for CC and THS 2.2. Three groups (sham, high CC and high THS 2.2) were kept for a 42 days post-inhalation period.

In conclusion, the exposure to the mainstream aerosol from THS 2.2 did not cause additional toxicity when compared to the smoke from the 3R4F reference cigarette. Moreover, the overall biological activity of the THS 2.2 aerosol with respect to the toxicity on respiratory tract organs was significantly decreased in comparison to 3R4F cigarette.

4.4 Conclusions

By heating instead of burning tobacco, the aerosol composition of the THS Tobacco Stick becomes less complex, and measured HPHCs are either substantially reduced or undetectable. It is, however, acknowledged that not all possible HPHCs in CC are known and can be analytically measured.

Even if the contribution of single constituents to induction of smoking related disease is not known and needs to be further investigated, it is nevertheless reasonable to assume that exposure to a less complex mixture and a substantial reduction in the measured HPHCs is likely to lead to a reduced toxicological hazard compared to CC smoke.

THS 1.0 and 2.1 were improved in design and features for consumer use, and the heating profile was further optimized and controlled and the heating temperature decreased. These changes resulted in even greater reductions in some of the HPHCs in THS 2.2 compared to former versions, leading to reduced *in vitro* cytotoxicity and genotoxicity in standard, internationally recognized biological assays.

Furthermore, the 90-day inhalation studies in rats revealed less toxicological effects in the respiratory tract from exposure to THS 2.2 than exposure to CC.

In summary, the results of chemical, in *vitro* and *in vivo* toxicological assessment of THS 2.2 and consistent results throughout the evolution of the THS support the conclusion that adult smokers in clinical studies will not be exposed to new or increased hazard compared to continuous CC use.

5 PRODUCT EXPERIENCE IN CURRENT SMOKERS

Several clinical studies with THS have been conducted by PMI and Philip Morris USA[1] from 2004 to 2008. Extensive data are available for THS 1.0, the EHCSS Series K6, and its predecessors, EHCSS Series E4 and EHCSS Series JLI. The clinical experience ranges from short-term studies in confinement to long-term studies in an ambulatory setting (Table 9).

In 2012, PMI conducted two exploratory clinical studies; one short-term PK/PD and one Reduced Exposure with THS 2.1 (see sections 5.1.1 and 5.2.1).

The version 2.2 of THS is considered mature to the extent that sensorial qualities of the product and possible user acceptance are judged high by PMI. The decision was made to put THS 2.2 into a comprehensive assessment program including clinical and PBA studies for generation of qualifying evidence suitable for submission as new MRTP to regulatory agencies, the scientific community and risk assessment policy makers. PMI's phased approach includes first assessing THS 2.2 in relatively short-term studies and then gradually expanding the duration and resemblance to actual use in real world conditions in the global clinical THS development program.

PMI conducted four confirmatory clinical studies in 2013 and 2014 with non-menthol THS 2.2, including smoking abstinence and/or NRT as points of reference and CC as a comparator to THS 2.2 [5, 7, 9, 10], in Japan and Europe. These studies aimed at assessing the PK of nicotine and reduced exposure to HPHCs both in confined conditions. The conduct phase of all studies is completed and data are currently being compiled and analyzed. Results will be reported when clinical study reports will be completed.

All clinical studies were conducted in accordance with the Declaration of Helsinki which was effective at the time of each conducted study.

[1] PMI and Philip Morris USA Inc. are unaffiliated companies after Altria Group, Inc. completed the spin-off of Philip Morris International Inc. to shareholders of Altria Group, Inc. on March 28, 2008.

5.1 PK/PD

5.1.1 PK/PD with THS 2.1

An exploratory clinical study was conducted in the UK from May to September 2012 (ZRHX-PK-02; NCT01780688) [40]. It was a randomized, crossover study comparing plasma nicotine profiles of THS 2.1 and CC. Twenty-eight adult smokers completed the study.

The shape of plasma nicotine concentration-time curves was similar for the two products, with a lower nicotine absorption following single use of THS 2.1 as compared to CC. Following single use, the extent of nicotine absorption ($AUC_{0\text{-last}}$) was 23% (90% CI: 15%, 30%) lower on average for THS 2.1 than for CC. Similarly, the maximum nicotine concentrations (C_{max}) were 30% (90% CI: 18% to 40%) lower, on average, following single use of THS 2.1 compared to CC. Time to peak plasma concentration (t_{max}) was not different between both products (see Figure 8).

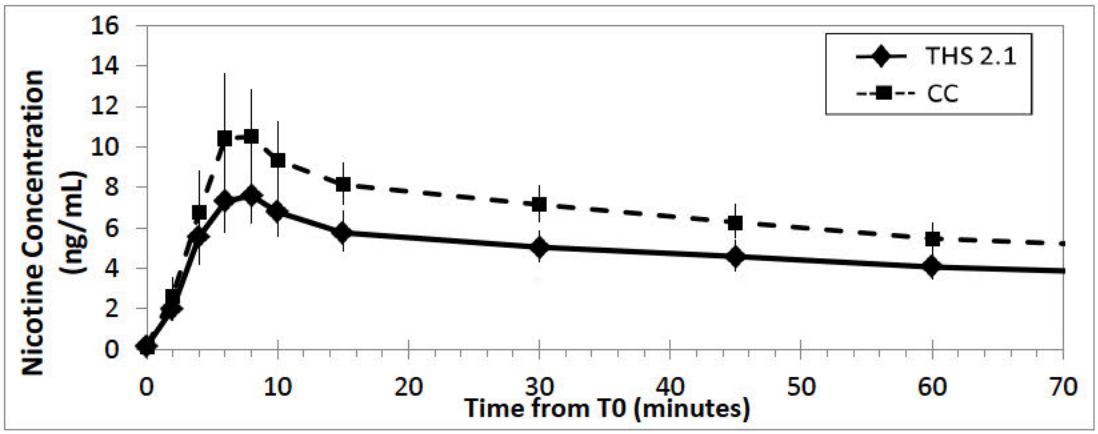

Figure 8 Nicotine Plasma Concentration Curves over Time (Presented as Mean and Confidence Interval)

Subjective and pharmacodynamic effects of product use were assessed using the brief questionnaire of smoking urges (QSU-brief). After 24 hours of smoking abstinence a single use of CC or THS 2.1 resulted to in a 40% reduction of the urgent desire to smoke (see Figure 9).

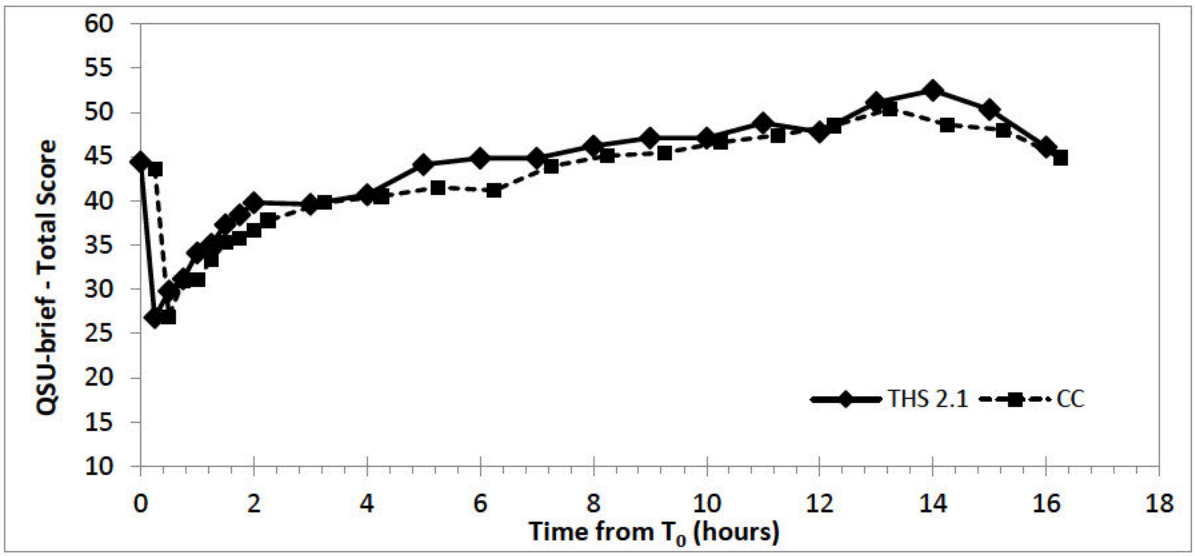

Figure 9 QSU-brief Total Score after Single Use of THS 2.1 and CC

5.2 Reduced Exposure

The FDA Center for Tobacco Products (CTP) has established an abbreviated list of 18 HPHCs [41] to be measured in smoke based on:

1. Availability of analytical methods.
2. Coverage of several chemical classes.
3. Representative sample of the FDA established full list of 93 HPHCs to be measured in smoke representing five key risks:
   a. Carcinogen.
   b. Cardiovascular toxicant.
   c. Respiratory toxicant.
   d. Reproductive and development toxicant.
   e. Addiction potential.

PMI has established validated analytical methods to measure BoExp to 14 of the 18 HPHCs in the abbreviated list of 18 HPHCs [4]. These BoExp represent 10 out of 13 chemical classes of compounds considered to be present in smoke as listed by the FDA and seven out of nine compounds mentioned by the WHO as HPHCs recommended to be lowered in cigarette smoke [18]. The BoExp assessed in PMI clinical studies cover all five major risks stipulated by FDA.

Table 8 summarizes results obtained from the one-week Reduced Exposure study conducted with THS 2.1 and similar studies done with THS 1.0 with exposure durations of between 5 and 35 days.

There is a consistent reduction of BoExp in smokers who switch from CC to THS.

Table 8 Biomarkers of Exposure after Switching to THS - Percentage Change from Baseline CC Use

	HPHC (Organ Class Toxicity)		Acrolein (RT, CT)	Pyrene Surrogate for PAH	NNK (CA)	Benzene (CA, CT, RDT)	CO (RDT, CT)	1,3-Butadiene (CA, RT, RDT)	4-Aminobiphenyl (CA)	o-Toluidine (CA)	Crotonaldehyde (CA)	2-Aminonaphtha-lene (CA)	Acrylonitrile (CA, RT)	NNN (CA)
Product Version	**Study**	**Duration**	**3-HPMA[1]**	**1-OHP[2]**	**Total NNAL[3]**	**S-PMA[4]**	**COHb[5]**	**MHBMA[6]**	**4-ABP[7]**	**o-TOL[8]**	**3-HMPMA[9]**	**2-NA[10]**	**CEMA[11]**	**Total NNN[12]**
THS 2.1	ZRHX-EX-01	Day 5	-64%	-59%	-61%	-88%	-75%	-80%	-45%	-23%	N/M	-84%	-85%	-81%
THS 1.0	SPA04-01	Day 8	-36%	-63%	-55%	-79%	-70%	-54%	N/M	-62%	-53%	N/M	N/M	N/M
	SPA05-01	Day 8	-24%	-67%	-52%	-76%	-54%	-55%	-49%	-68%	-41%	-15%	N/M	N/M
	SPA05-03 *	Day 5/6	-28%	-68%	-55%	-83%	-57%	-19%	-41%	-53%	-59%	-12%	N/M	N/M
	CS06-02	Day 35	-2.63%	-36%	-49%	-48%	-55%	-29%	-43%	-30%	N/M	-43%	N/M	N/M

(1) 3-Hydroxypropyl-mercapturic acid; (2) Total 1-hydroxypyrene, (3) Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, (4) S-Phenyl-mercapturic acid, (5) Carboxyhemoglobin, (6) Monohydroxybutenyl-mercapturic acid, (7) 4-Aminobiphenyl, (8) o-Toluidine, (9) 3-Hydroxy-1-methylpropyl-mercapturic acid, (10) 2-Aminonaphthalene, (11) 2-Cyanoethylmercapturic acid, (12) Total N-nitrosonornicotine; Organ class toxicity [4]

AD: addictive; CA: carcinogen; CT: cardiovascular toxicant; RDT: reproductive and developmental toxicant; RT: respiratory toxicant

BoExp for addiction potential (AD) "Nicotine" and its metabolites is measured in each study

N/M: Not measured in this study

* This version of THS 1.0 was with menthol

5.2.1 Reduced Exposure Study with THS 2.1

An exploratory clinical study was conducted in Poland from May to September 2012 (ZRHX-EX-01; NCT01780714) [42]. It was a randomized, open-label, 2-arm, parallel group *ad libitum* smoking study comparing the use of THS Tobacco Sticks and CC. Subjects were confined in a controlled environment for nine days. Forty adult smokers completed the study.

At the end of the study, on day 5, the urinary concentration of BoExp adjusted for creatinine, with the exception of *o*-toluidine (-25.03%) decreased from baseline by at least 47.03% (4-ABP) and up to 85.05% (CEMA) (Figure 10). Differences between the two arms were statistically significant and were seen within 24-hours of starting use of THS 2.1. The lower than expected reduction of o-toluidine was investigated and contamination by the sampling plastic material was identified as the potential cause.

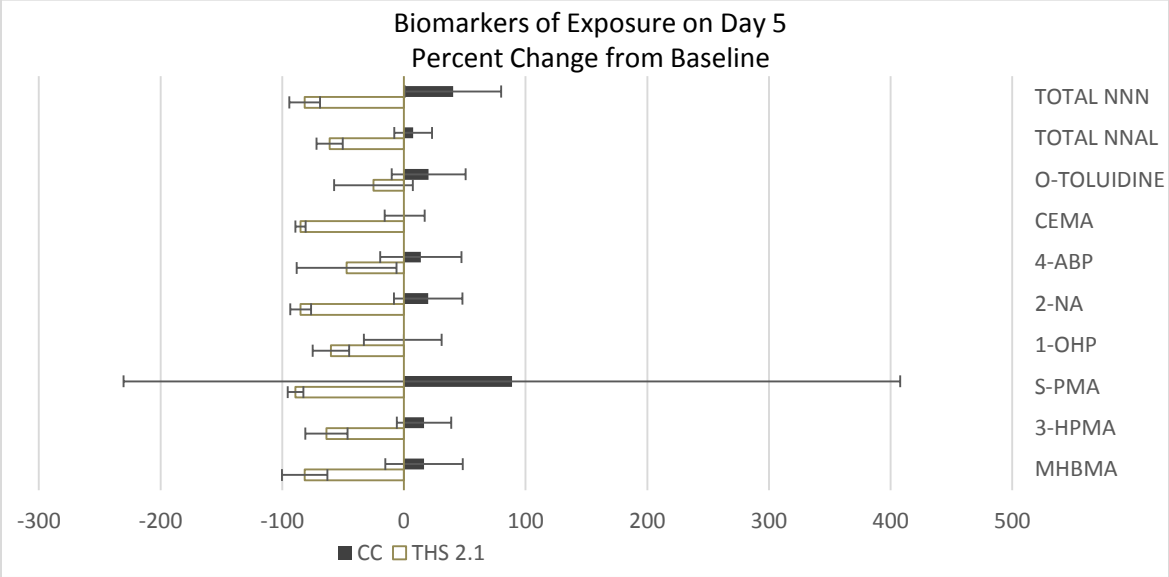

Figure 10 Changes in Biomarkers of Exposure in THS 2.1

At the end of the study on day 5, the percentage of COHb in blood decreased by 75% for the THS 2.1 arm and increased by 7.5% from baseline for the CC arm.

Cigarette Consumption:

Average cigarette consumption increased by 27.1% from Day 1 to Day 5 for THS 2.1 (from 21 to 27 THS Tobacco Sticks on average) and by 12.9% for CC (from 18 to 20 CC on average) from Day 1 to Day 5 (Figure 11).

Nicotine Equivalents (NEQ):

Excretion of nicotine and its metabolites in urine are well-established tobacco-specific BoExp to nicotine [43]. On a quantitative basis, the measured concentration of the molar sum of nicotine, cotinine, trans-3'-hydroxycotinine, and their respective glucuronide conjugates, expressed as NEQ in 24-h urine, provides an estimate of up to ~85% of total nicotine uptake and excretion in smokers [44].

Mean NEQ value at baseline and at Day 5 were within the same range for THS 2.1 (from 12.12 at baseline to 12.26 mg/g creatinine at Day 5) and slightly increased for CC (from 12.43 at baseline to 14.23 mg/g creatinine at Day 5) (Figure 11). The estimated median nicotine uptake at the end of the study was 1.01 mg nicotine per CC (range 0.75 – 2.01 mg) and 0.74 mg nicotine per THS Tobacco Stick (range 0.43 – 1.24 mg).

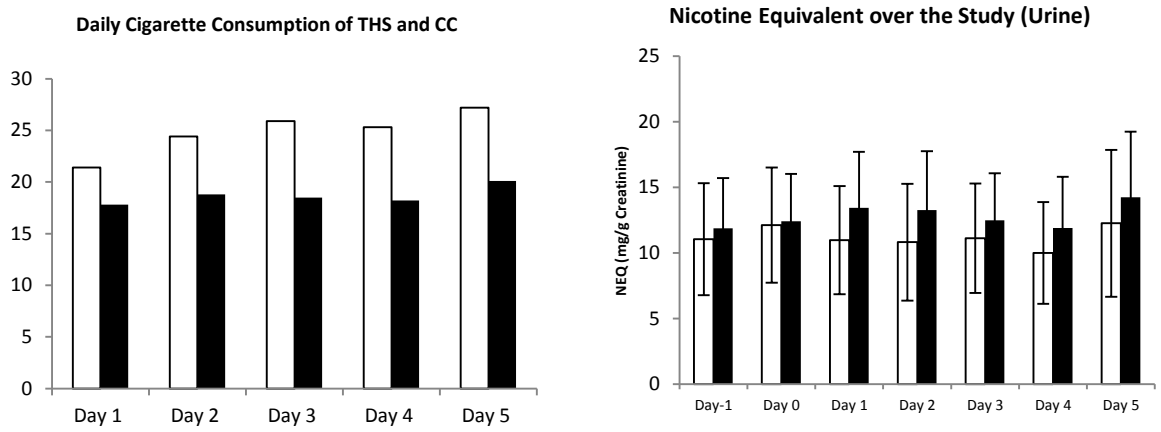

Figure 11 Cigarette Consumption and NEQ (mg/g Adjusted for Creatinine)

(□ THS 2.1; ■ CC)

The increased consumption of THS Tobacco Sticks reflects an adaptation process due to switching from CC to THS 2.1, which has a calculated lower median nicotine uptake per THS Tobacco Stick compared to CC. Also, different sensorial characteristics compared to the subjects' preferred CC brand contributed to the change in consumption pattern. Adaptation effects and consumption are currently being assessed in studies with longer duration (4 to 12 weeks) in an ambulatory, real world environment.

5.3 Other Relevant Clinical Findings

Clinical studies conducted jointly by PMI and Philip Morris USA[1] up to 2008 with an earlier version of THS, the Electrically Heated Cigarette Smoking System (EHCSS), in Europe, Asia,

Africa, and in the US showed reductions in exposure to selected HPHCs present in both GVP and TPM of mainstream smoke in subjects who used the EHCSS, as compared to subjects continuing to smoke CC, in confined and ambulatory conditions.

Chemical analysis of smoke from EHCSS-JLI showed lower yields of formaldehyde and several reported HPHCs and a decrease in the CO yield [45]. Clinical evaluations also confirmed reduced exposure to selected HPHCs and reduced excretion of mutagenic material in urine [46, 47]. Further clinical evaluations concluded that switching from CC to the second-generation EHCSS-JLI improved prognostic markers for cardiac disease assessed by symptom-limited spiro-ergometry [48], heart rate and rate-pressure-product parameters [49] after three days of product switching.

Importantly, a 12-month randomized, parallel-group study in 97 adult male and female smokers of CC evaluated BoExp and cardiovascular risk factors after switching to EHCSS-JLI. There was a rapid and sustained reduction in all measured BoExp after switching to EHCSS. These reductions in exposure were associated with statistically significant and pathophysiological favorable changes in several cardiovascular risk factors, including white blood cell count, urine 11-dehydrothromboxane B2, and high-density lipoprotein cholesterol [47].

Table 9 presents the main conclusions from studies performed with former versions of THS 2.2.

[1] PMI and Philip Morris USA Inc. are unaffiliated companies after Altria Group, Inc. completed the spin-off of Philip Morris International Inc. to shareholders of Altria Group, Inc. on March 28, 2008.

Table 9 Conclusions from Selected Clinical Studies with EHCSS Series E4, EHCSS Series JLI and THS 1.0 (EHCSS Series K6)

Product	Study Title	Study Setting	Conclusions
EHCSS Series E4	**EHCE4/01/01** A single-center study to evaluate the short term exposure to smoke constituents of an electrically heated smoking system in adult smokers during controlled smoking [46, 50-53]	**EHCSS Series E4 exposed subjects:** 40 **Total subjects:** 110 **Exposure duration:** 8 days **Location:** USA This study evaluated BoExp (CO, COHb, nicotine, and urine mutagenicity) under controlled smoking conditions when adult smokers of one CC brand (CC1) were switched to an EHCSS or a low-tar CC (CC2) or no-Smoking (NS).	Compared to baseline, BoExp on Day 8 decreased by 53% to 93% ($p < 0.0001$) for EHCSS Series E4 groups and 18% to 39% ($p < 0.02$) for CC2. Environmental tobacco smoke arising from the smoking activities of the different study groups was measured in the air of a separate smoking room over 1-hour periods. Concentrations of respirable suspended particulates in both EHCSS Series E4 groups were about 90% lower than in the CC1 and CC2 groups, similar to the 95% reduction in the NS group. CO was undetectable in the EHCSS Series E4 and NS groups. Seventy-four subjects (67%) experienced at least one adverse event (AE) during the study. Headaches of mild to moderate intensity were the most common reported event across all study groups. None of the reported events was considered as a likely study-related event by the investigator. No clinically significant changes were observed for hematology, clinical chemistry, and urinalysis investigations for any of the study groups.
EHCSS Series JLI	**EHCJLI/01/02** A single-center study to evaluate the short term exposure to smoke constituents of an electrically heated cigarette smoking system in adult smokers during controlled smoking [54-56]	**EHCSS Series JLI exposed subjects:** 40 **Total subjects:** 100 **Exposure duration:** 8 days **Location:** USA This study evaluated eight BoExp (urine nicotine and five major metabolites, expressed as NEQ; plasma cotinine; total NNAL, total 1-OHP; COHb; 3-HPMA; S-PMA; and urine mutagenicity).	After 8 days of smoking EHCSS Series JLI, BoExp decreased by 43% to 85% compared to baseline.

Product	Study Title	Study Setting	Conclusions
EHCSS Series JLI	**EHCJLI/02/02** A 12-month, randomized, controlled study to evaluate the exposure to smoke constituents of an electrically heated cigarette smoking system in healthy adult smokers [47, 57-59]	**EHCSS Series JLI exposed subjects:** 64 **Total subjects:** 97 **Exposure duration:** 12 months **Location:** USA This study evaluated BoExp and cardiovascular risk markers. Smokers were either switched to EHCSS Series JLI or continued smoking CC for 12 months. BoExp and cardiovascular risk markers were measured at 0.5, 1, 2, 3, 4, 5, 6, 9, and 12 months.	There was a rapid and sustained reduction in all BoExp after switching to the EHCSS Series JLI, with statistically significant reductions from baseline in NEQ (–18%), plasma cotinine (–16%), total NNAL (–73%) total 1-OHP (–53%), urine mutagenicity (–52%), hemoglobin adducts of 4-ABP) (–43%), COHb $AUC_{7\text{-}23h}$ (–80%), and 3-HPMA (–35%). These reductions in exposure in the EHCSS Series JLI group were associated with statistically significant and pathophysiological favorable changes in several cardiovascular risk markers, including white blood cell count (WBC) (–0.78 × 103/µL), hemoglobin (–0.16 g/dL), hematocrit (–0.44%), urine 11-dehydrothromboxane B2 (–374 ng/24 h), and high-density lipoprotein (HDL) cholesterol (+5 mg/dL). Sixty-five of the 97 subjects (67%) reported at least 1 AE over the 12-month study period, with headache being the most commonly experienced AE. No product-related trends were noted in the AEs, physical examinations (including vital signs and larynx examination), clinical chemistry, urinalysis, or electrocardiogram findings.
THS 1.0 (EHCSS Series K6)	**FARMOVS 310/2002** A randomized controlled, crossover study assessing the exercise performance in adult smokers comparing electrically heated cigarettes, conventional cigarettes, and no-smoking (NS) [49]	**THS 1.0 exposed subjects:** 18 **Total subjects:** 18 **Exposure duration:** 9 days (3 days to THS 1.0) **Location:** South Africa	The effects of reduced smoke exposure on the prognostic parameters heart rate (HR) and rate–pressure-product (RPP) were investigated in smokers switching to THS 1.0 and NS. Exposure parameters declined from CC to THS 1.0 and to NS. Resting HR and RPP increased from NS to THS 1.0 and to CC. Chronotropic response/HR recovery were more pronounced in NS than in THS 1.0 and CC. RPP_{max} was similar in NS and THS 1.0 and lowest during CC. Exposure to THS 1.0 for 3 days improved the prognostic parameters HR and RPP in an apparently dose-dependent manner.

Product	Study Title	Study Setting	Conclusions
THS 1.0 (EHCSS Series K6)	**FARMOVS 127/2003** A pilot study to establish symptom-limited spiroergometry as a tool to distinguish between different exposure to cigarette smoke in adult smokers [48, 59, 60]	**THS 1.0 exposed subjects:** 18 **Total subjects:** 18 **Exposure duration:** 9 days (3 days to THS 1.0) **Location:** South Africa This study investigated whether the use of THS 1.0 or NS would improve exercise performance compared to continuing smoking CC. Randomization took place 3 days before performing symptom-limited spiro-ergometry.	Non-smoking (NS) and THS 1.0 vs. CC resulted in: - Less severe dyspnoea (NS, 44.4% [p < 0.01 vs. CC]; THS 1.0, 50% [p = 0.03 vs. CC]; CC, 88.9%) - Higher working capacity (NS, 2.92 ± 0.4 W/kg [p = 0.06 vs. CC]; THS 1.0, 2.92 ± 0.4 W/kg [p = 0.04 vs. CC]; CC, 2.86 ± 0.5 W/kg) - Higher peak oxygen uptake (NS, 2694 ± 466 ml O_2/min [p = 0.08 vs. CC]; THS 1.0, 2830 ± 606 mL O_2/min [p = 0.03 vs. CC]; CC, 2682 ± 492 ml O_2/min) All data indicate that exposure to THS 1.0 and NS for 3 days may improve cardiovascular function as detected by symptom-limited spiro-ergometry.
THS 1.0 (EHCSS Series K6)	**SPA04-01** A randomized, controlled study comparing the short term exposure to smoke constituents of the EHCSS-K6 and EHCSS-K3 to Marlboro (6 mg ISO tar yield) and Philip Morris One (1 mg ISO tar yield) cigarettes in adults smokers during controlled smoking [61, 62]	**THS 1.0 exposed subjects:** 32 **Total subjects:** 160 **Exposure duration:** 8 days **Location:** UK **Location:** Korea	The levels of COHb and S-PMA in smokers using THS 1.0 were statistically significantly lower after 8 days of exposure than in smokers continuing smoking CC. The levels of BoExp: total NNAL, total 1-OHP, 3-HPMA, o-tol, and MHBMA were reduced in the THS 1.0 group as compared to CC group. In the study, 88 AEs reported (53 subjects) were of mild severity with 12.5% of reported AEs in the THS 1.0 group. All of the AEs except two (CC group: dyspepsia and vomiting) were not judged product-related. No serious adverse events (SAEs) were reported.

Product	Study Title	Study Setting	Conclusions
THS 1.0 (EHCSS Series K6)	**SPA05-01** A randomized, controlled, study comparing the short-term exposure to smoke constituents of EHCSS-K6 and EHCSS-K3 cigarettes to *Marlboro* (6 mg TIOJ tar yield) and *Lark One* (1 mg TIOJ Tar yield) cigarettes in adult smokers during controlled smoking [63]	**THS 1.0 exposed subjects:** 28 **Total subjects:** 128 **Exposure duration:** 8 days **Location:** Japan	BoExp COHb, S-PMA, total 1-OHP, MHBMA, o-tol, 4-ABP and total NNAL, 3-HPMA, were markedly reduced, excretion of mutagenic material in urine was moderately reduced and N-acetyl-S-(2-carbamoylethyl)-L-cysteine [AAMA], N-(R,S)-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine [GAMA], and 2-NA were minimally reduced in subjects using THS 1.0 as compared to subjects smoking CC at the end of exposure. In the study, all of the 12 AEs (9 subjects) were of mild intensity and none was serious or product-related. No SAEs were reported.
THS 1.0 (EHCSS Series K6)	**SPA05-03** A randomized, controlled study comparing the short term exposure to smoke constituents of the menthol version of EHCSS-K6 cigarettes to Marlboro Menthol (4 mg TIOJ Tar Yield) and Lark Menthol (1 mg TIOJ Tar Yield) cigarettes in adult smokers during controlled smoking [63]	**THS 1.0 menthol exposed subjects:** 28 **Total subjects:** 100 **Exposure duration:** 6 days **Location:** Japan	The study was to determine BoExp to 12 selected HPHCs in cigarette smoke, excretion of mutagenic material in urine, and serum Clara cell 16-kDa protein, an indicator of lung epithelial injury. The mean decreases from baseline to Day 5/6 were statistically significant ($p < 0.05$) for exposure to 10 of 12 HPHCs including the primary endpoint (CO) and urinary excretion of mutagenic material in the THS 1.0 menthol group (-12.3% to -83.4%). Serum Clara (Club) cell 16-kDa (CC-16) protein was not significantly different between groups. Three subjects (3%) reported an AE after randomization (5 AEs). None of the AEs were judged to be related to the study cigarettes or study procedures. All AEs resolved rapidly. Hematology examinations showed no notable changes during the study. Urinalysis revealed only sporadic cases of the presence of blood, ketones, leukocyte esterase, nitrite, and proteins in urine. There were no withdrawals due to an AE, and no occurrence of a SAE.

Product	Study Title	Study Setting	Conclusions
THS 1.0 (EHCSS Series K6)	**CS06-02** A 1 month, single-center, randomized, open-label, controlled clinical study to compare biomarkers of cardiovascular risk in smokers of EHCSS-K6 and smokers of CC. [62]	**THS 1.0 exposed subjects:** 237 **Total subjects:** 316 **Exposure duration:** 35 days **Location**: Poland	There were no statistically significant differences between THS 1.0 and CC arms for high sensitive C-reactive protein (hs-CRP) and WBC at the end of study (35 days), even though there was slight reduction from baseline in the THS 1.0 study arm. At the end of the study, the THS 1.0 group had higher levels of HDL cholesterol, decreased levels of 11-dehydrothromboxane B2, red blood cells (RBC), hematocrit, and hemoglobin levels, as compare to CC group consistent with changes expected upon smoking cessation. This was not statistically significant. At the end of the study (35 days), the levels of the BoExp: COHb, o-tol, 2-NA, 4-ABP, total NNAL, total 1-OHP, NEQ were lower THS 1.0 than CC arms although an increase in cigarette consumption was observed. Overall, 299 AEs were reported for 316 subjects in this study with 52.7% in the THS 1.0 group. A total of 4% of AEs were considered to be related to the THS 1.0 product and no AEs were considered related to CC. Two SAEs were reported.
THS 1.0 (EHCSS Series K6)	**EHCK6/01/03** A clinical study to compare changes in spot urine and 24-hour urine collections of selected biomarkers of exposure in adult smokers switching from *Marlboro Ultra Lights* to the electrically heated cigarette smoking system (EHCSS-K) [64-67]	**THS 1.0 exposed subjects:** 60 **Total subjects:** 120 **Exposure duration:** 8 days **Location:** US	After switching from Marlboro Lights at baseline to THS 1.0 for 8 days, levels of 3-HPMA, COHb, total NNAL, MHBMA, total 1-OHP, S-PMA, and urine mutagenicity were reduced (>50%). Hematology parameters were not significantly different between the THS 1.0 group and the other groups when compared to the Marlboro Lights cigarette. A total of 76 AEs were reported by 45 subjects with 56% of the subjects being randomized to the THS 1.0 group. No SAEs were reported.

Product	Study Title	Study Setting	Conclusions
THS 1.0 (EHCSS Series K6)	**EHCK6/02/04** A 12-week, randomized, controlled, pilot study to evaluate exposure to smoke constituents of the electrically heated cigarette smoking system (EHCSS-K) in adult smokers [64]	**THS 1.0 exposed subjects:** 60 **Total subjects:** 90 **Exposure duration:** 12 weeks **Location:** US	After 12 weeks of exposure, BoExp NEQ, 3-HPMA, total NNAL, and S-PMA were reduced in subjects randomized to THS 1.0 compared to subjects randomized to CC. From Baseline to Week 12, there was a statistically significant decrease in mean hemoglobin, hematocrit, and RBC in the THS 1.0 group, compared to the CC group. There were no statistically significant differences between the groups in absolute change from baseline to week 12 for WBC or platelet counts. A total of 216 AEs were reported by 67 subjects with 62% of the AEs in the THS 1.0 group. All AEs were considered mild or moderate and not product-related. No SAEs were reported.
THS 1.0 (EHCSS Series K6)	**RESWBC-1008-06** A randomized, controlled, crossover study comparing heart rate variability in adult smokers of EHCSS-K, conventional cigarettes, and no-smoking [68, 69]	**THS 1.0 exposed subjects:** 30 **Total subjects:** 30 **Exposure duration:** 12 weeks **Location:** US Studies have indicated that increased variability in the heart's inter-beat interval is physiologically desirable. This study assessed the difference in heart rate variability derived from the 24-hour ECG following different exposures of smoking CC, using THS 1.0, or NS for 3 days each.	Heart rate variability tended to increase with reduced HPHCs exposure.

5.4 Adverse Events

In total, around 655 subjects were exposed to THS 1.0 and its earlier development versions, namely EHCSS-K4 and EHCSS-JLI and 68 subjects were exposed to THS 2.1 in clinical studies. Four serious adverse events (SAEs) were reported in subjects using EHCSS Series JLI and three SAEs in subjects using THS 1.0. No SAEs were reported for subjects exposed to THS 2.1.

For THS 2.2, more than 400 subjects were exposed until April 2015. No SAEs were reported for subjects exposed to non-menthol THS 2.2 in the four clinical studies conducted with THS 2.2 [5, 7, 9, 10].

5.4.1 EHCSS Series JLI

More than 100 subjects were exposed to EHCSS JLI. Four SAE were reported in studies with EHCSS Series JLI (cervical neck pain, headache, and two episodes of appendicitis), all four in the Clinical Study EHCJLI/02/02 [70]. Three hundred and eighty-nine (389) adverse events were reported.

The SAEs occurred in the EHCSS Series JLI group and were all considered unrelated to the investigational or comparison product.

One subject was discontinued from the study due to hospitalization. Three SAEs resolved with sequelae. One SAE remained unchanged at the end of the study (cervical neck pain).

One subject experienced the SAE of neck pain (verbatim term "cervical neck pain"). At check-in the subject reported that she had been involved in a motor vehicle accident before the study and was diagnosed with an acute cervical sprain. During the study she was hospitalized for surgery to correct a disc problem.

One subject experienced the SAE of severe headache. At that time, the subject reported that she had been in the hospital overnight due to severe headache and underwent a spinal tap to rule out meningitis. The cerebrospinal fluid evaluation was without finding. The Investigator considered the SAE to be unrelated to the investigational or comparison product and the SAE resolved without sequelae.

5.4.2 THS 1.0

More than 500 subjects were exposed to THS 1.0. In total, three SAEs were reported in the THS 1.0 clinical studies, and 696 adverse events. All three SAEs occurred in the Clinical Study CS06-02 [71] with one SAE prior to randomization and no THS use:

1) One SAE was an acute myocardial infarction during screening period and was not randomized into the study.

2) The second SAE was a post-traumatic splenic injury not related to the investigational or comparison product.

3) The third SAE was an upper extremity deep vein thrombosis (DVT), which occurred one week after the study end, in a male subject in the THS 1.0 study arm. The subject had a 20-year smoking history with a mean consumption of 25 CC per day. The event was resolved but required chronic treatment for thrombosis prevention. The investigator considered the event to be moderate in severity and related to the investigational product.

5.4.3 PK/PD Study with THS 2.1

No serious or severe AEs were reported. Table 10 provides a summary of events as recorded in the short term PK/PD clinical study ZRHX-PK-02 (NCT01780688) performed in 2012 [40].

Table 10 Summary of Most Frequent AEs in Clinical Study ZRHX-PK-02

	THS 2.1 (N=33)		CC (N=28)	
Preferred Term	**No. Events**	**No. Subjects**	**No. Events**	**No. Subjects**
Subjects with any AEs	26	14	16	10
Headache	5	5	2	2
Dizziness	4	4	2	2
Nausea	4	4	5	5
Presyncope	1	1	5	4

No subjects were discontinued from the study due to an AE. Overall, there were 42 AEs reported in 19 of the 33 subjects in the safety population. More AEs were reported during the first study period (30 AEs in 16 subjects) than the second study period (nine AEs in five subjects). Fourteen subjects experienced AEs following THS 2.1 exposure and 10 subjects following CC exposure. The most frequently reported AEs were nausea, headache, dizziness, and presyncope. Other AEs included constipation, cold sweat and dermatitis contact, chest discomfort, fatigue, hyperhidrosis, vomiting and ear pain.

A total of six presyncope events were experienced by five subjects (one subject after THS 2.1 exposure and four subjects after CC use). It was suggested by the investigator that a light breakfast be allowed before product use in future studies to prevent such events.

The assessment of cough showed that the number of subjects who experienced a regular need to cough was low in both arms of the study (≤ 7 subjects during each single use day). No clinically relevant findings were reported in the hematology, clinical chemistry, urine analysis, vital signs, ECG, and spirometry exams.

5.4.4 Reduced Exposure Study with THS 2.1

No serious or severe AEs were reported. Table 11 provides a summary of events as recorded in the most recent Reduce Exposure clinical study ZRHX-EX-01 (NCT01780714) conducted in 2012 [42].

Table 11 Summary of Most Frequent AEs in Clinical Study ZRHX-EX-01

	THS 2.1 (N=20)		CC (N=20)	
Preferred Term	**No. Events**	**No. Subjects**	**No. Events**	**No. Subjects**
Subjects with any AEs	5	4	13	10
Blood triglycerides increased	0	0	2	2
Increased COHb	0	0	2	2
Oropharyngeal pain	1	1	1	1
Nasopharyngitis	1	1	1	1

No subjects were discontinued from the study due to an AE. Overall, there were 18 AEs reported in 14 subjects after randomization. Four subjects experienced five AEs during the THS 2.1 exposure and ten subjects experienced 13 AEs during CC exposure. The most frequently reported AEs were increased blood triglycerides and oropharyngeal pain. Other AEs reported were hiccups, constipation, hyperbilirubinaemia, nasopharyngitis and pharyngeal erythema.

The assessment of cough showed that the overall number of subjects who experienced a regular need to cough was 10 out of 20 subjects, almost equally distributed between CC and THS 2.1 arms.

No notable differences in the assessment of cough impact, cough intensity or assessment of sputum production were observed between study arms. No clinically relevant findings were reported in the hematology, clinical chemistry, urine analysis, vital signs, ECG, and spirometry exams.

5.4.5 THS 2.2

More than 400 subjects had been exposed to THS 2.2, for 1 to 8 days until April 2015. No SAEs were reported for THS 2.2.Based on available human safety data (adverse events) from the four clinical studies conducted with THS 2.2 [5, 7, 9, 10], there are no safety signals suggesting new or increased risks associated with THS 2.2 use in adult smokers compared to CC. All results and AEs will be assessed after completion of the clinical study reports and reported in this IB.

5.5 Market Experience

iQOS is the new brand name under which PMI has chosen to commercialize the Tobacco Heating System (THS). iQOS was introduced with pilot launches in Nagoya, Japan and Milan, Italy in November 2014. Aggregate safety data on the consumers' experience will be reported once available.

5.6 Conclusions

The results of clinical studies conducted with THS 1.0 and its predecessors showed a consistent reduction of BoExp to HPHCs, substantiating, in combination with the results of the non-clinical assessment, a successful implementation and evolution of the principle of heating vs. burning tobacco to reduce exposure to HPHCs.

THS 2.1 tested in clinical studies showed further reduction of measured HPHCs to a level close to that described for smoking cessation [72]. In other studies, testing former versions of THS 2.2, namely CS06-02 and EHCJLI/02/02 [70, 71], the reduced exposure was also associated with favorable biological changes on selected biological parameters (e.g., 11-dehydrothromboxane B2, HDL).

A PK/PD exploratory study with the THS 2.1 (ZRHX-PK-02) [40] indicated that the THS 2.1 is close to CC in terms of nicotine PK profile and overall exposure to nicotine resulting in a reduction of the urge to smoke comparable to CC after single use. This is an important indicator towards potential product acceptance for smokers willing to switch from CC to THS 2.2. Pending data of four clinical studies conducted in 2013 and 2014, including smoking abstinence or NRT use, will generate further information on THS 2.2, both in terms of PK/PD response and in terms of changes in clinical risk endpoints. Clinical studies with THS revealed no safety concern for the versions tested in these studies. In summary, the clinical study results support the ongoing comprehensive clinical assessment program with THS 2.2.

6 GUIDANCE FOR THE INVESTIGATOR

6.1 Target Populations

The target population for THS 2.2 is adult smokers.

6.2 Use of Product

To use THS 2.2, the consumer inserts the THS Tobacco Stick into the Holder to pre-heat it. Thereafter, the aerosol is inhaled by placing the lips on the THS Tobacco Stick mouthpiece and drawing air through the THS Tobacco Stick. Subjects need to be informed about the correct use of the product and the associated main unit. Once the Holder is switched on, the user can puff for approximately six minutes (although approximately 20 seconds of this six-minute period is for heating). The THS 2.2 Holder may warm up slightly when in use. A detailed user manual will be provided at the study sites and to subjects.

6.3 Product Variants

The THS 2.2 Holder, Charger and accessories are currently available in one format only. THS Tobacco Sticks are available in non-menthol and menthol options. This Investigator's Brochure describes the non-menthol variant of the THS Tobacco Sticks.

6.4 Warnings and Precautions

Although aerosol chemistry showed that heating instead of burning tobacco reduces the HPHCs compared to CC, given the current state of knowledge of THS 2.2 it has not been demonstrated that THS 2.2 reduces the risk of developing smoking-related diseases compared to CC.

Cigarette smoking causes cancer, pulmonary diseases, cardiovascular diseases, and many other related diseases. Smoking cessation has multiple benefits and is, by far, the best way to reduce any risks of developing such diseases.

Based on the results of the exploratory clinical studies on nicotine absorption and exposure with THS 2.1, it can be expected that THS 2.2 is similar to CC with regard to nicotine levels when used *ad libitum*. Due to sensorial and technological differences between THS 2.2 and CC, smokers may adapt their product use behavior and consume more THS Tobacco Sticks than CC, without increase in overall nicotine exposure (section 5.2.1). Confinement setting may also have an influence on product use behavior, explaining an increase both in THS 2.2 and CC use.

A smoker using THS 2.2 may experience transient symptoms suggesting mild nicotine over-exposure such as stimulatory effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, decreased ability to concentrate), gastric acid secretion, and vomiting center. Individuals who experience adverse events (suggesting excessive stimulant effects) should be instructed to reduce their intensity of product use by increasing the interval between the use of a new THS Tobacco Stick, and/or by decreasing the number of puffs and/or the intensity of puffing.

6.5 Adverse Events

Table 12 provides a summary of the total THS product safety profile as recorded in clinical studies. More details are provided in section 5.4. Based on available human safety data (adverse events) from the four clinical studies conducted with THS 2.2 [5, 7, 9, 10], there are no safety signals suggesting new or increased risks associated with THS 2.2 use in adult smokers compared to CC.

Table 12 THS Exposure and Adverse Events

THS Version	No. Studies	Exposure	Subjects (exposed to THS)	No. SAEs	No. AE
EHCSS JLI	3	Up to 1 year	307 (144)	4 SAEs	389
THS 1.0	9	Up to 1 month	980 (511)	3 SAEs	696
THS 2.1	2	Up to 6 days	73 (68)	0 SAEs	60

6.6 Smoke – Drug Interactions

It is established that smoking accelerates the metabolism of many drugs, particularly those primarily metabolized by CYP1A2. The CYP1A2 enzyme-inducing effects of cigarette smoke are thought to be related to exposure to polycyclic aromatic hydrocarbons and other combustion products [73]. Levels of these HPHCs are significantly lower in THS as compared to CC. The results of the ZRHX-EX-01 study (reduction of CYP1A2 activity of about 25% compared to Baseline) suggest that CYP1A2 activity will decrease with THS 2.2 use after five days. The magnitude of this effect appears to be similar to that observed following smoking cessation [74]. Therefore, smokers treated with theophylline, clozapine, olanzapine, ropinirole or any other drug primarily metabolized by CYP1A2 may need adjustment in the dosage regimen of these drugs with narrow therapeutic index

6.7 Abuse and Dependence

Given current product knowledge, there is no reason to expect changes in abuse and dependence compared to that observed for CC.

6.8 Known Effects of Nicotine Overdose

Nicotine poisoning may occur from accidental ingestion, especially by small children, of one or more THS Tobacco Sticks, which are part of THS 2.2. Toxic effects of nicotine develop rapidly following acute overdose. Oral nicotine doses above 60 mg are probably lethal in adult humans. The gastric absorption of nicotine from tobacco taken by mouth is delayed because of slowed gastric emptying and the acidic environment in the stomach. As a result, vomiting caused by the central effect of the initially absorbed fraction may remove much of the tobacco remaining in the gastrointestinal tract. Signs and symptoms of acute nicotine intoxication include nausea, hyper-salivation, abdominal pain, vomiting, diarrhea, perspiration, headache, dizziness, hearing and visual disturbances, mental confusion, and marked weakness. Other subsequent conditions may also occur such as syncope, prostration, dyspnoea, seizures, hypotension, and a weak, rapid, and irregular pulse. Lethal doses rapidly produce seizures. Death may occur within a few minutes following severe nicotine overdose, usually as a result of respiratory failure secondary to paralysis of respiratory muscles [75].

Acute nicotine intoxication generally requires symptomatic and supportive care. There is no specific antidote for nicotine intoxication. If vomiting has not occurred following acute ingestion, the stomach should be emptied immediately by inducing emesis or by gastric lavage. Because acute nicotine intoxication can result in seizures, activated charcoal should be administered following gastric lavage and/or emesis to decrease absorption of nicotine. Alkaline solutions should be avoided. Treatment is supportive and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation [76].

6.9 Summary of Non-Clinical Studies

The non-clinical assessment of THS consisted of evaluating the toxicological risk associated with the use of this alternative product for tobacco consumption by adult smokers.

Aerosol chemistry showed that heating instead of burning tobacco reduces the HPHCs compared to CC.

In vitro studies demonstrated a decreased biological activity of THS generated aerosol compared to CC smoke. The cytotoxicity (NRU assay) was reduced by more than 80% in THS 2.2 compared to CC. The genotoxic activity in bacterial cells (Ames assay) and in mammalian cells (MLA) was decreased. No genotoxic activity could be detected in bacterial cells (Ames) with THS 2.2. The genotoxic activity in mammalian cells (MLA) was decreased between 80% and 90% with THS 2.2 in comparison to CC.

In vivo 90-day inhalation study performed with THS 2.2 demonstrated their lower toxicity compared to the exposure to CC.

The non-clinical assessment performed with THS, including the THS 2.2 version, supports the conclusion that subjects in the 6-month exposure ambulatory study will not be exposed to increased or new hazards when compared to continued smoking of CC.

6.10 Summary of Clinical Studies

PMI and Philip Morris USA conducted a number of clinical studies in Europe, Asia, Africa and the United States with various versions of heated tobacco systems, namely EHCSS K4, EHCSS JLI and THS 1.0 from 2004 to 2008. In addition, PMI conducted two exploratory clinical studies with THS 2.1 in Europe in 2012.

In total, 655 subjects were exposed to THS 1.0 and its predecessor versions in clinical studies. As presented in Table 8, those studies showed incremental reductions in exposure to selected HPHCs in subjects who used THS technology as compared to subjects who continued to smoke CC, under both controlled and ambulatory conditions.

In 2012, two studies were performed by PMI with THS 2.1 in a total of 68 subjects. The first study, a PK/PD Study (ZRHX-PK-02) suggested that the nicotine PK profile of THS 2.1 and related total exposure to nicotine is close to CC. The results of this study and the QSU brief evaluation, together, indicate that THS 2.1 was able to reduce craving to a level comparable to CC. It might be assumed that THS 2.2 would be an acceptable substitute of CC for adult smokers.

The second study, a 5-day exposure study in confinement (ZRHX-EX-01), showed a reduction of BoExp in the range of 47% to 90% compared to baseline CC smoking. With the exception of *o*-toluidine (see section 5.2.1), those results are in alignment with results from previous studies with THS. For some BoExp, levels of reduction were close to those observed when subjects cease smoking. The relatively lower reduction of o-toluidine of just 25% from baseline was most likely due to contamination by the sampling plastic material. The lower nicotine plasma concentration after single use of THS 2.1 compared to CC was not associated with an adaptation of smoking behavior. Subjects consumed more THS Tobacco Sticks during ad libitum use than CC, however with no difference in nicotine, cotinine or nicotine equivalents levels compared to CC, but did have reduced levels of biomarkers of exposure.

The clinical studies conducted so far with THS 2.2 in more than 400 subjects have not revealed any SAE. The conduct phases of the PK/PD and the reduced exposure studies are now completed, and results will be reported when the clinical study reports will be completed.

In conclusion, the clinical studies revealed no safety concerns to preclude adult smokers from using THS. Study results from THS 1.0 and the more recent versions THS 2.1 and THS 2.2, support proceeding with the comprehensive assessment program for THS 2.2 with long-term

ambulatory and actual use studies. Data from four clinical studies conducted in 2013 and 2014 are expected to provide further evidence of reduced exposure to HPHCs and potentially of reduced health risk. A 6-month exposure study (followed by a 6-month extension study) is expected to show mid-term changes to biological and functional risk markers linked to tobacco related diseases that are not likely to be seen in a shorter period. The planned PBA study will investigate how adult CC smokers in the U.S. actually use the THS 2.2 product in a close to real-world conditions environment and will provide a perspective on the risk characterization of this product. The exposure response and PBA studies will be conducted in 2015 and 2016.

7 REFERENCES

[1] Family Smoking Prevention and Tobacco Control Act. Pub L. No 111-31, 123 Stat. 1776 (June 22, 2009).

[2] Borgerding M, Klus H. Analysis of complex mixtures – Cigarette smoke. Exp Toxicol Pathol. 2005; 57:43-73.

[3] Royal College of Physicians (RCP). Harm reduction in nicotine addiction: helping people who can't quit. A report by the Tobacco Advisory Group of the Royal College of Physicians. 2007 ISBN 978-1-86016-319-7.

[4] U.S. Department of Health and Human Services. Docket No. FDA-2012-N-0143: harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Fed Regist. 2012; 77(64):20034-7.

[5] Philip Morris Products S.A. A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of THS 2.2 following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine gum [ZRHR-PK-02-JP]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01959607 NLM Identifier: NCT01959607.

[6] Philip Morris Products S.A. A single-center, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of THS 2.2 Menthol following single use in smokers compared to menthol conventional cigarettes and nicotine gum [ZRHM-PK-05-JP]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01967706 NLM Identifier: NCT01967706.

[7] Philip Morris Products S.A. Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 (THS 2.2)[ZRHR-PK-01-EU]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01967732 NLM Identifier: NCT01967732.

[8] Philip Morris Products S.A. A single-center, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of THS 2.2 Menthol following single use in smokers compared to menthol conventional cigarettes and nicotine nasal spray [ZRHM-PK-06-US]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01967719 NLM Identifier: NCT01967719.

[9] Philip Morris Products S.A. A controlled, 3-arm parallel group study to demonstrate reductions in exposure to smoke constituents in smoking subjects switching to THS 2.2 or to smoking abstinence, compared to smoking conventional cigarettes for 5 days in

confinement [ZRHR-REXC-04-JP]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01970982 NLM Identifier: NCT01970982.

[10] Philip Morris Products S.A. A randomized, controlled, open-label, 3-arm parallel group, single center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the THS 2.2 or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement (ZRHR-REXC-03-EU). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01959932 NLM Identifier: NCT01959932.

[11] Philip Morris Products S.A. A randomized, controlled, multi-center study to demonstrate reductions in exposure to selected smoke constituents in smokers switching to THS 2.2 Menthol or smoking abstinence compared to smoking menthol conventional cigarettes, for 90 days [ZRHM-REXA-07-JP]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01970995 NLM Identifier: NCT01970995.

[12] Philip Morris Products S.A. Reduced exposure study using the Tobacco Heating System 2.2 (THS 2.2) Menthol for 91 days in confinement and ambulatory [ZRHM-REXA-08-US]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 Dec 02]. Available from: http://clinicaltrials.gov/show/NCT01989156 NLM Identifier: NCT01989156.

[13] Philip Morris Products S.A. Evaluation of biological and functional changes in healthy Smokers after switching to THS 2.2 for 26 weeks [ZRHR-ERS-09-US]. In: ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US) 2015- [cited 2015 Mar 30] Available from: https://clinicaltrialsgov/ct2/show/NCT02396381?term=NCT02396381&rank=1 NLM Identifier: NCT02396381.

[14] Philip Morris Products S.A. *Unpublished on file data:* Investigation report to Dorado-II-Ron comparability report. 2014.

[15] Ghosh A, Jeannet C. An improved Cambridge Filter pad extraction methodology to obtain more accurate water and "tar" values: in situ Cambridge filter pad extraction methodology. Beiträge zur Tabakforschung. 2014; 26(2):38-49.

[16] Health Canada, Tobacco Control Programme. Determination of "Tar", nicotine and carbon monoxide in mainstream tobacco smoke. T-115. 1999.

[17] Philip Morris Products S.A., Campelos P, Hadju Schenk R. *Unpublished on file data:* Report - Zurich finished product qualification (9A199D). WBS J-1002RDA0016. 2014.

[18] WHO Study Group, Ashley DL, Burns D, Djordjevic M, Dybing E, Gray N, Hammond SK, Henningfield J, Jarvis M, Reddy KS, Robertson C, Zaatari G. The scientific basis of tobacco product regulation: second report of a WHO study group. World Health Organ Tech Rep Ser. 2008; (951):1-277, 1 p following

[19] Health Canada. Consolidation - Tobacco reporting regulations. DORS/2000-273. 2013.

[20] Chepiga TA, Morton MJ, Murphy PA, Avalos JT, Bombick BR, Doolittle DJ, Borgerding MF, Swauger JE. A comparison of the mainstream smoke chemistry and mutagenicity of a representative sample of the US cigarette market with two Kentucky reference cigarettes (K1R4F and K1R5F). Food Chem Toxicol. 2000; 38(10):949-62.

[21] National Institute of Health (NIH), National Toxicology Program (NTP), Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). Report of the International Workshop on in vitro methods for assessing acute systemic toxicity - NIH Publication No: 01-4499. 2001.

[22] Babich H, Borenfreund E. Cytotoxic and morphological effects of phenylpropanolamine, caffeine, nicotine, and some of their metabolites studied In vitro. Toxicol In Vitro. 1992; 6(6):493-502.

[23] Tewes FJ, Meisgen TJ, Veltel DJ, Roemer E, Patskan G. Toxicological evaluation of an electrically heated cigarette. Part 3: genotoxicity and cytotoxicity of mainstream smoke. J Appl Toxicol. 2003; 23(5):341-8.

[24] Bombick DW, Putnam K, Doolittle DJ. Comparative cytotoxicity studies of smoke condensates from different types of cigarettes and tobaccos. Toxicol In Vitro. 1998; 12:241-9.

[25] Stabbert R, Voncken P, Rustemeier K, Haussmann HJ, Roemer E, Schaffernicht H, Patskan G. Toxicological evaluation of an Electrically Heated Cigarette. Part 2: Chemical composition of mainstream smoke. J Appl Toxicol. 2003; 23:329-39.

[26] Borenfreund E, Babich H, Martin-Alguacil N. Comparisons of two in vitro cytotoxicity assays - The neutral red (NR) and tetrazolium MTT tests. 1988.

[27] ICH S2 (R1). Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. 2011; Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S2_R1/Step4/S2R1_Step4.pdf (Accessed on 17 July 2014).

[28] OECD (Organization for Economic Co-operation and Development). Guidelines for the testing of chemicals: bacterial reverse mutation test [test 471]. Avialble from: http://wwwoecdorg/chemicalsafety/risk-assessment/1948418pdf. 1997.

[29] Roemer E, Teredesal A, Terpstra P, Vanscheeuwijck PM, Haussmann HJ, Philip Morris USA. The discriminative power of rat inhalation studies investigating the irritative property of inhalants. Poster presented at the Validity of Animal Models of

Human Respiratory Disease Conference, Santa Fe, NM, USA. 1998; Available from: http://legacy.library.ucsf.edu/tid/agp67e00/.

[30] Tewes FJ, Meisgen TJ, Gomm WA, Roemer E, Carchman RA. Cigarette parameters that influence the mutagenicity of mainstream smoke condensate. Poster presented at the 38th Society of Toxicology Meeting, New Orleans, LA, USA. 1999.

[31] DeMarini DM. Genotoxicity of tobacco smoke and tobacco smoke condensate. Mutat Res. 1983; 114:59-89.

[32] Roemer E, Tewes FJ, Meisgen TJ, Veltel DJ, Carmines EL. Evaluation of the potential effects of ingredients added to cigarettes. Part 3: in vitro genotoxicity and cytotoxicity. Food Chem Toxicol. 2002; 40:105-11.

[33] OECD (Organization for Economic Co-operation and Development). Guidelines for the testing of chemicals: in vitro mammalian cell gene mutation test [test 476]. 1997; Available from: http://www.oecd-ilibrary.org/docserver/download/9747601e.pdf?expires=1396856312&id=id&accname=guest&checksum=AF32E093BEC632C14B1E9CAED2C65968 (Accessed on 17 July 2014).

[34] Clive D, Johnson KO, Spector JF, Batson AG, Brown MM. Validation and characterization of the L5178Y/TK+/- mouse lymphoma mutagen assay system. Mutat Res. 1979; 59:60-108.

[35] Mitchell AD, Evans EL, Jotz MM, Riccio ES, Mortelmans KE, Simmon VF. Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: in vitro mutagenesis and DNA damage. Environment International. 1981; 5:393-401.

[36] Schramke H, Tewes FJ, Roemer E. Using the mouse lymphoma TK assay to compare the mutagenicity of mainstream smoke condensate from research cigarettes. Poster presented at the 41st Society of Toxicology Meeting, Nashville, TN, USA. 2002; Available from: http://legacy.library.ucsf.edu/tid/tcu80g00/pdf.

[37] Terpstra PM, Teredesai A, Vanscheeuwijck PM, Verbeeck J, Schepers G, Radtke F, Kuhl P, Gomm W, Anskeit E, Patskan G. Toxicological evaluation of an electrically heated cigarette. Part 4: subchronic inhalation toxicology. J Appl Toxicol. 2003; 23(5):349-62.

[38] Vanscheeuwijck PM, Teredesai A, Terpstra PM, Verbeeck J, Kuhl P, Gerstenberg B, Gebel S, Carmines EL. Evaluation of the potential effects of ingredients added to cigarettes. Part 4: subchronic inhalation toxicity. Food Chem Toxicol. 2002; 40(1):113-31.

[39] OECD (Organization for Economic Co-operation and Development). Guidelines for the testing of chemicals: subchronic inhalation toxicity: 90-Day Study [test 413]. 2009; Revised version available from: http://www.oecd-

ilibrary.org/docserver/download/9741301e.pdf?expires=1405584197&id=id&accname=guest&checksum=CEBC65DF6EC6726D2F404DED131DC3B9 (Accessed on 17 July 2014).

[40] Philip Morris Products S.A. A single-center, open-label, randomized, controlled, crossover study to explore the nicotine pharmacokinetic profile and safety of Tobacco Heating System (THS) 2.1 compared to conventional cigarettes following single and ad libitum use in smoking, but otherwise healthy subjects [ZRHX-PK-02]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013- [cited 2013 May 03]. Available from: http://clinicaltrials.gov/show/NCT01780688 NLM Identifier: NCT01780688.

[41] FDA (Food and Drug Administration). Guidance for industry and FDA staff - "Harmful and Potentially Harmful Constituents" in tobacco products as ssed in Section 904(e) of the Federal Food, Drug, and Cosmetic Act. 2011.

[42] Philip Morris Products S.A. A single-center, open-label, randomized, controlled, 2-arm parallel group study to evaluate the exposure to selected smoke constituents in smoking, but otherwise healthy subjects switching from conventional cigarettes to the Tobacco Heating System (THS) 2.1 [ZRHX-EX-01]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 -[cited 2013 May 03]. Available from: http://clinicaltrials.gov/show/NCT01780714 NLM Identifier: NCT01780714.

[43] Tricker AR. Biomarkers derived from nicotine and its metabolites: a review. Contributions to Tobacco Research. 2006; Vol 22:147-75.

[44] Benowitz NL, Jacob P, 3rd, Fong I, Gupta S. Nicotine metabolic profile in man: comparison of cigarette smoking and transdermal nicotine. J Pharmacol Exp Ther. 1994; 268(1):296-303.

[45] Roemer E, Stabbert R, Veltel D, Muller BP, Meisgen TJ, Schramke H, Anskeit E, Elves RG, Fournier JA. Reduced toxicological activity of cigarette smoke by the addition of ammonium magnesium phosphate to the paper of an electrically heated cigarette: smoke chemistry and in vitro cytotoxicity and genotoxicity. Toxicol In Vitro. 2008; 22(3):671-81.

[46] Roethig HJ, Kinser RD, Nelson BL, Oey J, Wang N. Short term clinical exposure evaluation of conventional and electrically heated cigarettes. Poster presented at the American College of Clinical Pharmacology Meeting, San Francisco, CA, USA. 2002.

[47] Roethig HJ, Feng S, Liang Q, Liu J, Rees WA, Zedler BK. A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2008; 48(5):580-91.

[48] Unverdorben M, der Bijl A, Potgieter L, Liang Q, Meyer BH, Roethig HJ. Effects of levels of cigarette smoke exposure on symptom-limited spiroergometry. Prev Cardiol. 2007.

[49] Unverdorben M, van der Bijl A, Potgieter L, Venter C, Munjal S, Liang Q, Meyer B, Rothig HJ. Effects of different levels of cigarette smoke exposure on prognostic heart rate and rate-pressure-product parameters. J Cardiovasc Pharmacol Ther. 2008; 13(175).

[50] Roethig HJ, Kinser RD, Lau RW, Walk RA, Wang N. Short-term exposure evaluation of adult smokers switching from conventional to first-generation electrically heated cigarettes during controlled smoking. J Clin Pharmacol. 2005; 45:133-45.

[51] Roethig HJ, Oey J, Nelson BL, Walk RA. Investigations of carboxyhemoglobin of adult smokers of conventional cigarettes and an electrically heated cigarette Poster presented at the 29th Annual Meeting of the Japanese Society of Toxicology, Nagoya, Japan. 2002.

[52] Roethig HJ, Gogova M, Mould D, Sarkar M. A population pharmacokinetic model for nicotine. Poster presented at the 32nd Annual Meeting of the American College of Clinical Pharmacology, Tampa, FL, USA. 2003.

[53] Lau RW, Hirnikel DJ, Roethig H-J, Philip Morris USA. Environmental tobacco smoke from conventional and electrically heated cigarettes. Poster presented at the Annual Meeting of ISEA/ISEE, BC, Vancouver, Canada. 2002; Available from: http://legacy.library.ucsf.edu/tid/khi96g00/pdf.

[54] Roethig HJ, Zedler BK, Kinser RD, Feng S, Nelson BL, Liang Q. Short-term clinical exposure evaluation of a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 2007; 47:518.

[55] Oey J, Kinser R, Feng CR, Nelson BL, Liang Q, Roethig H, Philip Morris USA. Clinical exposure evaluation of a new electrically heated cigarette smoking system. Poster presented at the 32nd American College of Clinical Pharmacology Meeting, Tampa, FL, USA. 2003.

[56] Oey J, Lau, R.W., Roethig, H.J. . Determination of environmental tobacco smoke from a second-generation electrically heated cigarette smoking system. Beitr Tabakforsch Intl. 2008; 23:1-7.

[57] Rees WA, Zedler BK, Roethig HJ, Kinser RD, Liang Q, Nelson BL, Philip Morris USA. A 12-month clinical evaluation of an electrically heated cigarette smoking system: biomarkers of exposure. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

[58] Zedler BK, Roethig HJ, Rees WA, Liang Q, Kinser RD, Nelson BL, Philip Morris USA. A 12-month clinical evaluation of an electrically heated cigarette smoking

system: biomarkers of potential harm. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

[59] Unverdorben M, van der Bijl A, Potgieter L, Liang Q, Sica D, Roethig H. Blood pressure monitoring in adult smokers comparing a conventional cigarette to an electrically heated cigarette smoking system. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

[60] Unverdorben M, van der Bijl A, Potgieter L, Liang Q, Roethig H. Spiroergometry in adult smokers comparing a conventional cigarette to an electrically heated cigarette smoking system. Poster presented at the American College of Clinical Pharmacology, Rockville, MD, USA, and at the Frontiers in Aerosol Dosimetry Research Conference, Irvine, CA, USA. 2005.

[61] Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol. 2012; 64(2 Suppl):S45-53.

[62] Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, Lindner D, Kulesza A, Magnette J. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 7: a one-month, randomized, ambulatory, controlled clinical study in Poland. Regul Toxicol Pharmacol. 2012; 64; (2 Suppl):S74-84.

[63] Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012; 64:S64-S73.

[64] Frost-Pineda K, Zedler BK, Oliveri D, Feng S, Liang Q, Roethig HJ. Short-term clinical exposure evaluation of a third-generation Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers. Regul Toxicol Pharmacol. 2008; 52:104-10.

[65] Oliveri D, Liang Q, Feng S, Kinser R, Roethig H, Zedler B, Philip Morris USA. A clinical study comparing the short term exposure to smoke constituents of a third generation EHCSS to conventional cigarettes in adult smokers. Poster presented at the American College of Clinical Pharmacology Meeting, Cambridge, MA, USA. 2006.

[66] Kapur S, Sarkar M, Muhammed R, Serafin R, Liang Q, Feng S, Roethig H, Philip Morris USA. Early morning urine void is an ideal alternative to 24 hour urine collection for determination of biomarkers of exposure in adult smokers. Poster presented at the American Society for Clinical Pharmacology and Therapeutics Meeting, Anaheim, CA, USA. 2007; Available from: http://legacy.library.ucsf.edu/tid/ifj30i00.

[67] Scherer G, Urban M, Hagedorn HW, Serafin R, Feng S, Kapur S, Muhammad R, Jin Y, Sarkar M, Roethig HJ. Determination of methyl-, 2-hydroxyethyl- and 3-cyanoethylmercapturic acids as biomarkers of exposure to alkylating agents in cigarette smoke. J Chromatogr B Analyt Technol Biomed Life Sci. 2010; (878):2520-8.

[68] Munjal S, Koval T, Muhammad R, Jin Y, Demmel V, Roethig HJ, Mendes P, Unverdorben M. Heart rate variability increases with reductions in cigarette smoke exposure after 3 days. J Cardiovasc Pharmacol Ther. 2009; 14(192).

[69] Koval T, Munjal S, Muhammad R, Jin Y, Roethig H-J, Mendes P, Unverdorben M, Philip Morris USA. White blood cell count in adult smokers declines with reduction in cigarette smoke exposure and after 3 days of no smoking. Poster presented at the American College of Clinical Pharmacology (ACCP), Philadelphia, PA, USA. 2008.

[70] Philip Morris USA. *Unpublished on file data:* [EHCJLI/02/02] A 12-month, randomized, controlled study to evaluate the exposure to smoke constituents of an electrically heated cigarette smoking system in healthy adult smokers. 2003.

[71] Philip Morris Products S.A. *Unpublished on file data:* [CS06-02] A 1-month, single-centre, randomised, open-label, controlled clinical study to compare biomarkers of cardiovascular risk in smokers of electrically heated cigarettes (EHCSS-K6) and smokers of conventional cigarettes. 2008.

[72] Carmella SG, Chen M, Han S, Briggs A, Jensen J, Hatsukami DK, Hecht SS. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers (Erratum in Chem Res Toxicol. 2012 Mar 19;25(3):763). Chem Res Toxicol. 2009; 22(4):734-41.

[73] Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. Clinical pharmacology & Therapeutics. 2008; 83(4).

[74] Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. Clin Pharmacol Ther. 2004; 76(2):178-84.

[75] Hibbs RE, Zambon AC. Goodman & Gilman's - The pharmacological basis of therapeutics. Brunton LL, Chabner Bae, Knollman Bae, editors. 12th ed.: McGraw-Hill; 2011. Agents acting at the neuromuscular junction and autonomic ganglia. p. 255-76.

[76] The Merck Manual for Health Care Professionals (online). Tobacco use. In: Health Care Professionals; Special Subjects. 2014- [cited 2014 Mar 14]; Available from: http://www.merckmanuals.com/professional/special_subjects/tobacco_use/tobacco.html?qt=nicotine.

8 SIGNATURE PAGE

Sponsor:	Philip Morris Products S.A., Research & Development Quai Jeanrenaud 5, Neuchâtel, Switzerland, 2000 Neuchatel, Switzerland
Product Name:	THS 2.2
Edition:	Edition 5
Version Number:	Final
Release Date:	27 April 2015
Previous Release Date:	24 November 2014

I, the undersigned, confirm that this Investigator's Brochure is accurate.

Signed: _____ Date: 27 Apr 2015

John Magnette, MD, FFPM, DiPharmMed

Manager Product Surveillance