PMI RESEARCH & DEVELOPMENT

PMI Tobacco Heating System (THS 2.2) Menthol

Module 2.7.4 Adapted – Summary of Clinical Safety

May 2013

TABLE OF CONTENTS

Listing of Tables

ABBREVIATIONS

1-OHP	1-hydroxypyrene
2-NA	2-aminonapththalene
3-HPMA	3-hydroxypropylmercapturic acid
4-ABP	4-aminobiphenyl
AAMA,	N-acetyl-S-(2-carbamoylethyl)-L-cysteine
AE	Adverse events
ALT	Alanine transaminase
AUC	Area under curve
BA	Bioavailability
BMI	Body mass index
BoExp	Biomarkers of Exposure
BP	Blood pressure
CC	Conventional cigarette
CFR	Code of federal regulations
C_{max}	Maximum concentration
CNS	Central nervous system
CO	Carbon monoxide
CoHb	Carboxyhaemoglobin
COHb	Carboxyhaemoglobin
CPD	Cigarettes per day
CRP	C-reactive protein
CTP	Center for tobacco products

CYP	CytochromeP450
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EHCSS	Electrically heated cigarette smoking system
FTC	Federal Trade commission
GAMA	N-(R/S)-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine
HDL	High density lipoprotein
HPHC	Harmful and Potentially Harmful Constituents
hs-CRP	High sensitive-C-reactive protein
ICF	Informed consent form
INR	International Normalized Ratio
IRB	Institutional Review Board
LAD	Left anterior descending
mCC	Menthol conventional cigarette
MCEQ	Modified cigarette evaluation questionaire
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenyl mercapturic acid
MNSW	Minnesota nicotine withdrawal scale
MRTP	Modified Risk tobacco product
NEQ	Nicotine Equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol)
NS	Non smoker
o-tol	o-toluidine

PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Pulse rate
QSU	Questionnaire of smoking urges
RBC	Red blood cell
SA	Smoking abstinence
SAE	Serious adverse events
SD	Standard deviation
SOC	System organ class
S-PMA	S-phenylmercapturic acid
THS	Tobacco heating system
T_{max}	Time to reach maximum concentration
WBC	White blood cell

2.7.4 SUMMARY OF CLINICAL SAFETY

2.7.4.1 Exposure to the Investigational Product

Clinical studies assessing tobacco products are different from those assessing pharmaceutical drugs. Unlike drugs, the dose of tobacco-derived aerosol is not fixed. It is determined by the smoking pattern of each individual smoker. Therefore, the number of cigarettes smoked per day, smoking topography, consumer's satisfaction and preferences, as well as inhalation intensity, determine overall daily exposure. Unless otherwise specified in the specific Clinical Study Protocol, smokers in the studies presented have consumed the investigational tobacco product (EHCSS JLI, THS 1.0 or THS 2.1) *ad libitum*.

The clinical studies presented here were designed to evaluate the intrinsic performance of the MRTP (e.g., exposure reductions, smoker health profile) for comparing MRTP to CC in adult, healthy smokers.

The present summary of clinical safety describes final safety data from nine clinical trials:

Two clinical studies were performed with THS 2.1 and seven clinical studies were performed with its predecessors - THS.1.0 (5 studies) and the EHCSS Series JLI (2 studies). Data derived from the predecessors are considered supportive. The studies were conducted in Europe, Asia, and the US during the years 2002 – 2012.

This data presented in this summary of clinical safety are based on two separate datasets and data extracted from three clinical study reports.

1. Datasets were derived from:

    a. Two clinical studies with THS 2.1
    (Study numbers ZRHX_EX_01 and ZRHX_PK_02)

    b. Four clinical studies with THS 1.0.
    (SPA 04-01, SPA 05-01, SPA 05-03 and CS 06-02), and

2. Clinical study reports provided data from:

    a. Two studies with EHCSS Series JLI (EHCSS JLI-01-02 and EHCSS JLI 02-02)

    b. One study with THS 1.0 (EHCK6 01-03).

PMI currently does not have possession of the original datasets for the safety data reported from three clinical study reports (EHCSS JLI-01-02, EHCSS JLI 02-02, EHCK6 01-03). The studies summarized here based on the clinical study report prepared by PMI's former affiliate Philip Morris USA.

2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

In nine clinical studies with THS 2.1, THS 1.0, or EHCSS Series JLI a total number of 1089 subjects were randomized, 104 subjects exposed to EHCSS JLI, 389 subjects exposed to THS 1.0, and 48 subjects exposed to THS 2.1 after randomization. Four serious adverse events (SAEs) were reported in subjects using EHCSS Series JLI and three SAEs in subjects using the THS 1.0.

Only one SAE in study CS 06-02 was judged to be related to the investigational product by the investigator (Section 2.7.4.2.1.3). No SAEs were reported for subjects exposed to THS 2.1.

No safety or tolerability concerns emerged during these studies.

Table 1 provides a general overview of the number of studies included in this safety summary, exposure duration, number of subjects exposed as well as SAE and adverse event (AE) count for pooled EHCSS JLI, THS 1.0, and THS 2.1 clinical studies.

Table 1 - Exposure to EHCSS Series JLI, THS 1.0, THS 2.1 and Adverse Events

Product Tested	No. Studies	Exposure Duration	Subjects (exposed)	No. SAE[1] (JLI/THS 1.0/THS 2.1)	No. SAE (CC)	No. AE (JLI/THS1.0/THS 2.1)	No. AE (CC)	Total No. AEs
EHCSS Series JLI	2	Up to 1 year	JLI 104 CC: 73	4	0	232	149	389
THS 1.0	5	Up to 3 months	THS 1.0: 385 CC: 295	3	0	287	161	448
THS 2.0	0	-	-	-	-	-	-	-
THS 2.1	2	Up to 6 days	THS2.1: 48 CC: 48	0	0	28	29	57

(1) Note: One SAE was considered related to the investigational product

The majority of the recorded AEs were mild in severity. Five severe AEs were recorded in the studies with EHCSS Series JLI. Seven severe AEs were recorded in CS-0602. In studies with THS 2.1, no severe AEs were recorded. All 57 AEs in clinical studies ZRHX_PK_02 and ZRHX_EX_01 were considered either mild or moderate. Overall, the majority of AEs in all studies were judged to be non-related to the study product or study procedures.

2.7.4.1.1.1 Methods used to evaluate safety

All AEs occurring from the time of the first exposure to the investigational or reference product to the end of the safety follow up period were recorded. The investigator assessed the relationship with the tested product and study procedures using the following categorization:

The maximum intensity of each AE reached was assigned to one of the following categories:

(mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

(moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

(severe) = An AE which prevents normal, everyday activities (such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy).

Safety variables assessed in the nine clinical studies were vital signs, clinical laboratory assessments, ECG, and physical examination. Solicited and unsolicited symptoms as well as SAEs were collected, analyzed and described.

In all studies, the verbatim reports of AEs were reviewed by a physician and the signs and symptoms were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®). Every verbatim term was matched with the appropriate Preferred Term. The incidences of AEs were recorded. Adverse events occurring between the time of first exposure to the tested product and end-of-study were to be followed up until resolved or stabilized.

Serious adverse events

In all clinical studies included in this summary, any SAE reported or observed during the study after signature of the ICF until the end of the safety follow-up period whether or not attributable to the investigational product, to any reference product, other medication or to any study procedures, or any SAE related to the product and spontaneously reported after the safety follow up was to be reported by the Investigator or other study site staff within 24 hours after first awareness by any party involved in the study to the Sponsor. In addition, the respective IRB had to be notified of these reports as well.

A SAE was defined as any untoward medical occurrence that results in death, is life threatening, results in disability/ incapacity, requires in-patient hospitalization or prolongation of existing hospitalization or is a congenital anomaly/birth defect in the offspring of a study subject. In addition, important medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above were to be considered serious (examples of such events are: invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization). The nature of each SAE, date and time of onset, outcome, and relationship to the investigational product was recorded.

Additionally, SAEs that were related to study participation (e.g., procedures, invasive tests, change of prior therapies) or related to concurrent medication were collected and recorded from the time the subject consented to participate in the study until termination of his/her participation.

2.7.4.1.1.2 Narratives of studies conducted

Narratives of clinical studies included in this summary are presented below. Section 2.7.4.1.2 provides a detailed summary of the overall extent of exposure to the investigational and reference products.

A summary table of the number of subjects exposed by study arm is provided in Table 2. Table 3, Table 4, and Table 5 provide a tabulated overview of the clinical studies presented below.

Table 2- Summary of Subjects Exposed in presented Clinical Studies

Study	THS 2.1	CC	EHCSS JLI	THS 1.0	THS 1.0 Menthol	Abstinence	EHCSS K3	Total	Design
PK-02	28(1)	28						28	X-over
EX-01	20 (2)	20						40	//
CS06-02		79		237				316	//
SPA05-03		56			28	16		100	//
SPA05-01		56		28		16	28	128	//
SPA04-01		64		32		32	32	160	//
EHCJLI-01-02		40	40			20		100	//
EHCJLI-02-02		33	64					97	//
EHCK6/01/03		40		60		20		120	//
TOTAL	**48**	**416**	**104**	**357(3)**	**28(3)**	**104**	**60**	**1089**	

(1) Note: 28 subjects were randomized into the study and are presented in this safety summary. Five additional subjects were exposed to the THS2.1 at Admission during a product trial of up to 3 THS Tobacco Sticks, however, were not randomized in the study. The five subjects were are not included in the safety summary presented here .Two of those five subjects experienced in total three adverse events, all mild in nature.

(2) Note: 20 subjects randomized to CC were exposed to THS2.1 at Admission (product trial of up to 3 THS Tobacco Sticks).

(3) Note: A total of 385 subjects (THS 1.0 and THS 1.0 menthol) exposed to THS1.0.

Table 3 - Summary of Nicotine PK with Single-Use Exposure

Study ID	Study Objective	Study Design	Subjects (no. [M/F], [nicotine level ≤ 0.6/ > 0.6])		C_{max} [ng/mL]	t_{max} [min]	$AUC_{(0-t)}$ [ng hr /mL]
ZRHX-PK-02 (UK)	Pilot relative BA study comparing the absorption of nicotine from THS 2.1 and CC	Open, randomized, cross-over, single use and ad-libitum	28 (1) [14/14 M/F; 12/16 nicotine ≤ 0.6 / > 0.6]	THS 2.1/CC	8.4/11.9	8/8	17.7/22.8

(1) Note: 5 subjects who were exposed to the product in a product trial at Admission, however, were not randomized.

Table 4 - Summary of Nicotine PK with Ad-libitum Exposure

Study ID	Study Objective	Study Design	Subjects (no. [M/F], [nicotine level ≤ 0.6/ > 0.6])		C_{peak} [ng/mL]	t_{peak} [hr]	C_{trough} [ng/mL]	$C_{(avg)}$ [ng /mL]
ZRHX-PK-02 (UK)	Pilot relative BA study comparing the absorption of nicotine from THS 2.1 and CC	Open, randomized, cross-over, single use and ad-libitum	28(1) [14/14 M/F; 12/16 nicotine ≤ 0.6 / > 0.6]	THS 2.1/CC	14.9/24.0	12.9/10.5	4.1/12.3	----
ZRHX-EX-01 (PL)	Pilot exposure reduction study comparing THS 2.1 and CC, including nicotine PK assessments during Day 5	Open, randomized, parallel-arm, ad-libitum	39 (2) [19/20 M/F; 22/17 nicotine ≤ 0.6 / > 0.6]	THS 2.1/CC	24.0/25.5	14.0/15.9	-----	12.9/13.7

(1) Note: 5 subjects who were exposed to the product in a product trial at Admission, however, were not randomized. (2) Note: original sample size of 40 subjects was reduced because of one mis-randomized subject

Table 5 - Summary of Exposure Reduction Studies

Study ID (location, study period)	Study Design	Study &product, regimen	# Subj by arm randomized/ completed	Duration	Gender M/F CC baseline 10-19/>19cig/day	Primary Endpoints
EHCJLI/01/02 (US, 14 March 2002)	Randomized, open, parallel	EHCJLI/01/02 A single-center, randomized, open-label, forced switching, controlled clinical study to evaluate the short term exposure to smoke constituents of the EHCSS ACCORD JLI to Marlboro LIGHTS (11 mg FTC tar yield) and Merit ULTIMA (1 mg FTC tar yield) cigarettes in adults smokers during controlled smoking.	EHCSS JLI exposed subjects:40 Total subjects: 100	Exposure duration: 8 days	Male/Female: 50/50 Not Available	Reductions (45% to 85% at day 8) in total daily levels of all biomarkers of exposure were observed upon switching for 8 days from Marlboro LIGHTS to EHCSS ACCORD JLI. Reduction were statistically greater in both EHCSS ACCORD JLI groups compared to the Merit ULTIMA groups for nicotine equivalents, free NNAL, total NNAL, 3-HPMA, S-PMA, 1-OHP and mutagenicity. Total Daily levels of all biomarkers of exposure generally remained stable throughout the study in the Marlboro LIGHTS group. COHb $AUC_{(7-23)}$ was reduced > 80% by Day 3 in EHCSS ACCORD JLI Uncontrolled and CONTROLLED smoking groups as compared to smoking Marlboro LIGHTS at Baseline. At Day 1, 3 and 8, COHb $AUC_{(7-23)}$ in both EHCSS ACCORD JLI smoking groups were statistically similar to

Table 5 - Summary of Exposure Reduction Studies

Study ID (location, study period)	Study Design	Study &product, regimen	# Subj by arm randomized/ completed	Duration	Gender M/F CC baseline 10-19/>19cig/day	Primary Endpoints
						that in the no smoking group.
EHCJLI/02/02 (US, 31 May 2002)	Randomized, multicenter (2 centers), open, parallel design	A 12-Month, Randomized, Controlled Study to Evaluate the Exposure to Smoke Constituents of an Electrically Heated Cigarette Smoking System (EHCSS ACCORD JLI) in Healthy Adult Smokers compared to adult smokers who continue to smoke Marlboro ULTRA LIGHTS (1 to 7 mg tar FTC) or Merit ULTIMA (1 to 3 mg tar FTC).	EHCSS JLI exposed subjects:64 Total subjects: 97	Exposure duration: 12 months	Male/Female: 45/52 Baseline CC consumption: -EHCSS/JLI: 24.3 ± 9.9 - Marlboro ULTRA LIGHTS: 23.3 ± 6.8	Compared to Baseline while smoking cigarettes with 1 to 7 mg tar delivery (FTC), overall least squares mean 24h urine nicotine equivalents and 3-HPMA and plasma cotinine decreased by about 16% to 35% in subjects who switched to EHCSS ACCORD® JLI for 52 weeks in their normal life setting. These least squares mean percent reductions were statistically significantly different from the changes from Baseline in the Marlboro ULTRA LIGHTS group

Table 5 - Summary of Exposure Reduction Studies

Study ID (location, study period)	Study Design	Study &product, regimen	# Subj by arm randomized/ completed	Duration	Gender M/F CC baseline 10-19/>19cig/day	Primary Endpoints
EHCK6/01/03 (US, 19 June 2003)	Randomized, open, parallel	THS 1.0 (Tar: 5mg FTC, Nicotine 0.4mg FTC), Marlboro LIGHTS (Tar: 10mg FTC, Nicotine 0.8mg FTC) Marlboro LIGHTS (Tar: 6mg FTC, Nicotine 0.5mg FTC). Controlled smoking	THS 1.0 exposed subjects:60 Total subjects: 120	Exposure duration: 8 days	Male/Female: 57/63 CC baseline 10-19 / >19cig/day: 60/60	COHb, 3HPMA • Compared to Baseline while smoking Marlboro 10mg, at Day 8, least squares mean daily urine 3-HPMA, nicotine equivalents, 1-OHP and mutagenicity were reduced by about 40% to 50% in subjects who switched to THS 1.0. • Compared to Baseline while smoking Marlboro 10mg, at Day 8, least squares mean evening COHb, daily urine total NNAL, S-PMA and MHBMA were reduced by about 64% to 77% in subjects who switched to THS 1.0
SPA04-01 (UK, 26 October 2004)	Randomized, open, parallel	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)	THS 1.0 exposed subjects:32 Total subjects: 160	Exposure duration: 8 days	Male CC consumption at baseline 10-19 / > 19 cig/day: 40/40 Female CC consumption at baseline 10-19 / > 19 cig/day: 40/40	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.

Table 5 - Summary of Exposure Reduction Studies

Study ID (location, study period)	Study Design	Study &product, regimen	# Subj by arm randomized/ completed	Duration	Gender M/F CC baseline 10-19/>19cig/day	Primary Endpoints
		cigarettes in adults smokers during controlled smoking				
SPA05-01 (JP, 2 August 2005)	Randomized, open, parallel	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	THS 1.0 exposed subjects: 28 Total subjects: 128	Exposure duration: 8 days	Male CC consumption at baseline 10-19 / > 19 cig/day: 41/48 Female CC consumption at baseline 10-19 / > 19 cig/day: 23/16	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 (AAMA, GAMA, 2-NA were minimally reduced in subjects using THS 1.0 as compared to subjects smoking CC at the end of exposure.
SPA05-03 (JP, 26 June 2006)	Randomized, open, parallel	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	THS 1.0 menthol exposed subjects: 28 Total subjects: 100	Exposure duration: 6 days	Male CC consumption at baseline 10-19 / > 19 cig/day: 26/35 Female CC consumption at baseline 10-19 / > 19 cig/day: 24/15	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 cell 16-kDa protein, , was not significantly

Table 5 - Summary of Exposure Reduction Studies

Study ID (location, study period)	Study Design	Study &product, regimen	# Subj by arm randomized/ completed	Duration	Gender M/F CC baseline 10-19/>19cig/day	Primary Endpoints
		Lark Menthol (1 mg TIOJ Tar Yield) cigarettes in adult smokers during controlled smoking				different between groups.
CS06-02 (PL, 23 October 2007)	Randomized, open, parallel	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.	THS 1.0 exposed subjects: 237 Total subjects: 316	Exposure duration: 35 days	Male CC consumption at baseline 10-19 / > 19 cig/day: 51/110 Female CC consumption at baseline 10-19 / > 19 cig/day: 56/98	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.
ZHRX-EX-01 (PL, 22 June	Randomized, open, parallel	THS 2.1, CC Ad-libitum	THS 2.1 exposed subjects:20	Exposure duration: 5	Male CC consumption at baseline 10-19 / > 19	COHb, 3HPMA, MHBMA, S-PMA

Table 5 - Summary of Exposure Reduction Studies

Study ID (location, study period)	Study Design	Study &product, regimen	# Subj by arm randomized/ completed	Duration	Gender M/F CC baseline 10-19/>19cig/day	Primary Endpoints
2012)			Total subjects:40	days	cig/day: 9/10 Female CC consumption at baseline 10-19 / > 19 cig/day: 11/10	

Note: Controlled smoking= Smoking is limited to one product with no minimum daily number. On the Acclimation Day, the maximum daily number is limited to 20% above the subject's usual daily maximum number according to the subject's smoking history; the maximum daily number on subsequent study days is limited to the number actually smoked on the Acclimation Day. On each day, smoking opportunities offered at equal intervals between 07:00 and 23:00 only, and on each day after the Acclimation Day, the total daily cigarettes smoked are evenly divided over the day

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

Tested Product: EHCSS JLI

DESIGN

A randomized, open-label, forced-switching, controlled, parallel design conducted at a single research center to evaluate the short term exposure to smoke constituents of an Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers during controlled smoking.

OBJECTIVES

To measure biomarkers of exposure in adult smokers switching from Marlboro Lights to an ECHSS for a period of 8 days under Controlled Smoking conditions and to determine if Carboxyhemoglobin (biomarker estimating the biological effective dose) was at least 80% lower in adult smokers of EHCSS ACCORD® JLI as compared to adult smokers of Marlboro LIGHTS cigarettes.

POPULATION

One hundred subjects (50 males and 50 females), healthy adult volunteers who indicated they were Marlboro Lights smokers for at least 4 weeks prior to study initiation, smoking 10 to 30 cigarettes per day for 12 months prior to study initiation were randomized. Ninety-seven subjects completed the study.

SAFETY RESULTS

There were no deaths, SAEs, or other significant AEs in this study.

A total of 121 AEs were reported by 46 of the 100 subjects (46%) during the trial. Headache was the most common AE reported during this study, reported in 17 of 100 subjects overall (17%). The remaining AEs were reported by 9 or fewer subjects (≤ 9%) each. All AEs were either mild or moderate in severity.

One subject withdrew from the study due to AEs. There was no detailed information reported on the AEs leading to the withdrawal of the subject from the study. The Investigator considered all AEs to be unrelated to the investigational product. The analysis of AEs for this study is based on the study report.

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

Tested Product: EHCSS JLI

DESIGN

A randomized, open-label, controlled, parallel design conducted at two research centers to evaluate the exposure to smoke constituents of an EHCSS in healthy adult smokers

OBJECTIVES

Compare biomarkers of exposure in adult smokers switching from cigarettes with 1 to 7 mg tar delivery, Federal Trade Commission (FTC) method, to an EHCSS for a period of 12 months to adult smokers who continue[§] to smoke Marlboro ULTRA LIGHTS or Merit ULTIMA.

POPULATION

Ninety-seven healthy adult male and female smokers between 25 and 65 years of age who smoked non-menthol cigarettes with 1 to 7 mg tar delivery (FTC), with daily cigarette consumption between 10 and 40 were randomized to either the EHCSS JLI or the Marlboro ULTRA LIGHTS group in a 2:1 ratio. 82 subjects (37 males and 45 females) completed the study. All 97 randomized subjects were included in the demographics and safety analyses.

Subjects were adult smokers of manufactured, non-menthol cigarettes, smoking between 10 and 40 cigarettes per day for 10 years or more, with 50% of the subjects having smoked for 20 or more years prior to study initiation. Subjects indicated they had smoked any brand of cigarettes with greater than 3 and up to 7 mg tar delivery (FTC), or any brand of cigarettes with 1 to 3 mg tar delivery (FTC), exclusively for at least 12 weeks prior to study initiation.

SAFETY RESULTS

Four SAEs (neck pain, headache, and two episodes of appendicitis) occurred in the EHCSS JLI group (all were considered unrelated to the investigational product).

Two subjects discontinued the study due to AEs (urticaria and appendicitis which were both considered unrelated to the investigational product). Serious AEs and AEs leading to study discontinuation are discussed further in the Analysis of Adverse Events section of this report (Section 2.7.4.2.1) and in Section 2.7.4.3.4 Withdrawal. A total of 268 AEs were reported by 65 (67%) of the 97 subjects during the trial. Headache was the most common AE during this

study, reported by 27 (28%) of 97 subjects. All AEs were mild or moderate in severity, with the exception of the severe AEs of hand fracture, jaw fracture, headache, toothache, and vomiting. All AEs of severe intensity occurred in the EHCSS JLI group and were considered unlikely or unrelated to the study "Treatment."

The Investigator considered 34 of the 268 AEs (13%) to be possibly or probably related to the investigational product. All remaining AEs in this study were considered to be unlikely or unrelated to the investigational product."

EHCK6/01/03 - A Randomized, Controlled Study Comparing the Short Term Exposure to Smoke Constituents of the EHCSS K6 to Marlboro LIGHTS and Marlboro ULTRA LIGHTS in Adult Smokers During Controlled Smoking.

Tested Product: THS 1.0

DESIGN

This research study utilized a randomized, open-label, controlled, forced-switching, parallel design conducted at a single research centre comparing the Short Term Exposure to Smoke Constituents of the THS 1.0 (EHCSS K6) to Marlboro LIGHTS and Marlboro ULTRA LIGHTS in Adult Smokers during Controlled Smoking

OBJECTIVES

To assess changes in COHb and urine 3-HPMA (biomarker of exposure) from Baseline to Day 8 in adult Marlboro LIGHTS smokers who were randomly assigned to continue smoking Marlboro LIGHTS, to stop smoking, or to switch to THS 1.0 or Marlboro ULTRA LIGHTS.

POPULATION

One-hundred twenty self-affirmed Marlboro Lights adult smokers with a daily cigarette consumption of 10 to 30 cigarettes/day with neither gender constituting more than 60% of the total were randomized into 1 of 4 parallel groups with 20 subjects in the Marlboro Lights group, 20 subjects in the Marlboro Ultra Lights group, 60 subjects in the THS 1.0 group, and 20 subjects in the No-Smoking group.

SAFETY RESULTS

There were no deaths, SAEs, or other significant AEs in this study.

A total of 76 AEs were reported by 45 (38%) of the 120 subjects during the trial. Headache was the most common AE reported during this study, reported in 19 (16%) of 120 subjects overall. The remaining AEs were reported by 8 or fewer subjects (≤7%) each. All AEs were mild or moderate in severity. No subjects discontinued the study due to an AE. The Investigator considered an AE of wheezing in the Marlboro LIGHTS group to be possibly related to study treatment and considered all the remaining AEs to be unlikely or unrelated to study treatment.

SPA 04-01 - 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 adult smokers during controlled smoking

Tested Product: THS 1.0

DESIGN

The study was performed at a single research center according to a randomized, open-label, controlled, parallel group design. Eligible subjects were to be randomized to 5 study groups (32 subjects per group).

OBJECTIVE

The objective of the study was to investigate the changes in biomarkers of exposure in Marlboro (M6) cigarette (6 mg ISO tar yield) adult smokers who have been randomly assigned to switch to THS 1.0 (EHCSS K6), EHCSS-K3 (K3), or Phillip Morris One (PM1) cigarettes (1 mg ISO tar yield), to continue smoking M6, or to stop smoking. Primary objectives of this study were to assess the changes from baseline (Day 0) to Day 8 in COHb (1700 hour) Urinary excretion of *S*-PMA.

POPULATION

Adult healthy volunteers, smokers of Marlboro 6 mg ISO tar cigarettes, N=160 of either gender and of Caucasian origin were to be enrolled in this study.

SAFETY

Safety assessments included AE recording, blood pressure, pulse rate, electrocardiogram (ECG), and clinical laboratory tests.

SAFETY CONCLUSIONS

Overall, 53 subjects (33.1%) reported one or more AEs (88 AE episodes in total) after enrollment in the study. The number of subjects reporting AEs per study group were 13 (40.6%), 4 (12.5%), 9 (28.1%), 16 (50.0%), and 11 (34.4%) subjects for study groups THS 1.0, K3, M6, PM1, and NS respectively. The majority of the AEs reported were of mild severity, and all except two (PM1: 1 subject with dyspepsia and vomiting) were judged to be not related to the products. No AE was categorized severe.

The overall most common system organ classes (SOCs) reported were nervous system disorders (20 subjects, 12.5%), gastrointestinal disorders (19 subjects, 11.9%), and respiratory, thoracic, and mediastinal disorders (10 subjects, 6.3%). Clinically significant

increases in transaminase levels, not related to study products or procedures were reported for 4 subjects (THS 1.0, K3, M6, and NS groups). Clinically significant abnormalities in vital signs or ECG assessments were not reported during the course of this study.

Overall, there were no trends related to the study products observed in the AE reports, in clinical laboratory, vital signs, ECG, and physical examinations.

There were no withdrawals due to AEs and no occurrences of SAEs in this study.

SPA 05-01 - 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

Tested Product: THS 1.0

DESIGN

This was a randomized, open-label, controlled, parallel-group study which was conducted at a single research centre in Japan.

OBJECTIVE

The objective of the study was to investigate the differences in biomarkers of exposure in adult smokers smoking Marlboro cigarettes (M6J) at baseline (Day 0) who were then randomly assigned to switch to THS 1.0 (EHCSS K6), K3, or Lark1J or to continue smoking M6J, or to stop smoking.

POPULATION

One-hundred twenty-eight (39 women, 89 men) healthy smokers of Japanese origin were randomized to the 5 study groups (THS 1.0: 28; K3: 28, M6J: 28; Lark1J: 28; NS: 16). Mean age was 23.5 years. The average daily cigarette consumption during the run-in period was 19 cig/day. Smoking history duration was <10 years for most subjects.

SAFETY RESULT

Twelve AEs were reported by 9 subjects. All AEs were of mild intensity and none was severe or product-related. Ten AEs concerned abnormal laboratory values (increase in the activity of hepatic aminotransferases, in blood bilirubin concentration or leukocyte count; presence of leukocytes in the urine) and 2 AEs were disorders of the reproductive system (dysmenorrhea). The AEs resolved rapidly or improved without specific treatment (except analgesics for dysmenorrhea).

The changes observed in laboratory variables were minor, occurred in all study groups and were without clinical significance. Blood urea nitrogen increased in all groups, urine pH tended to decrease in some subjects.

There were no notable changes in vital signs, ECG, or physical examinations.

There were no withdrawals due to AEs and no occurrences of SAEs in this study.

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

Tested Product: THS 1.0

DESIGN

This was a single-center, randomized, open-label, controlled, parallel-group study.

OBJECTIVE

The objective of this study was to investigate the differences in biomarkers of exposure in adult smokers smoking Marlboro menthol cigarettes (M4MJ) at study baseline (Day 0) who were then randomly assigned to switch for 6 days to either THS 1.0 Menthol (EHCSS K6M menthol) cigarettes (5 mg tar; 0.3 mg nicotine; 1 mg CO) smoked using the THS 1.0, to the low-tar Lark1MJ menthol cigarettes (1 mg tar; 0.1 mg nicotine), to continue to smoke M4MJ cigarettes (4 mg tar; 0.3 mg nicotine) or to stop smoking (NS). The daily allotment of cigarettes was fixed for each individual based on the median cigarette consumption during the run-in period.

POPULATION

A total of 100 Japanese smoking subjects (10-30 manufactured cigarettes per day) were included. Mean age was 23.9 years.

SAFETY CONCLUSIONS

Three AEs were reported by three subjects. All AEs were of mild or moderate intensity and none was severe or product-related. Two AEs were disorders of the reproductive system (painful menses) or of the nervous system (post-traumatic headache) and one AE concerned abnormal laboratory values (proteinuria). The AEs resolved rapidly without specific treatment (except analgesics for painful menses and post-traumatic headache).

The changes observed in laboratory variables were minor, occurred in all study groups, and were without clinical significance. Mean ALT activity increased in all groups, while urine pH tended to decrease in some subjects. There were no notable changes in vital signs, ECG, or physical examinations.

Urinalysis revealed only sporadic cases of presence of blood, ketones, leukocyte esterase, nitrite, and proteins in the urine. Transient proteinuria was reported as an AE for one subject. Slight increases in mean BP and PR and decrease in body weight were noted in all study groups, which were probably secondary to the practical conditions of the study. No individual case of hypertension was observed, however, ECG recordings revealed no abnormality in any subject.

Thus, evaluation of safety and tolerability of smoking detected no obvious untoward effect on health of subjects in this study.

There were no withdrawals due to AEs and no SAEs in this study.

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.

Tested Product: THS 1.0

DESIGN

Single-center, randomized, open-label controlled study, two study arms (THS 1.0 [EHCSS K6] and CC) A 1-month, single-center, randomized, open-label, controlled clinical study to compare biomarkers of cardiovascular risk in smokers of electrically heated cigarettes and smoker of conventional cigarettes

OBJECTIVE

To compare high sensitivity C-reactive protein (hs-CRP) blood concentration and white blood cell (WBC) count in subjects smoking THS 1.0 for 1 month versus subjects continuing to smoke conventional cigarettes.

POPULATION

A total of 316 healthy, Caucasian, subjects, aged 30 to 60, smoking for at least 10 years 10 to 30 commercially available conventional cigarettes with 3 to 10 mg tar yield were randomized to THS 1.0 and CC study arms.

SAFETY

Physical examination (including weight and height), blood pressure, pulse rate, electrocardiogram (ECG), chest X-ray, clinical laboratory tests, medical history, AEs, and concomitant medication. Women only: urine pregnancy test.

A similar percentage of subjects reported adverse events during the K6 and CC study arms at 53% and 58%, respectively. Of the total of 225 and 74 adverse events reported for the K6 and CC study arms, respectively, a total of 4% of adverse events were considered to be related to the K6 investigational product and no adverse events considered related to the conventional cigarettes.

In total, three SAEs were reported. Two SAEs were reported for the safety population, both of which occurred after the end of the study following the K6 study arm. Subject 0336 experienced a deep vein thrombosis on Day 49, which resolved after 6 days. This event was considered related to the investigational product due to cigarette smoking being a known risk factor for this condition Subject 0058 experienced a post-traumatic splenic injury on Day 85,

which resolved after 13 days. A further SAE of acute myocardial infarction occurred prior to randomization and the subject (Subject 0609) did not enter the study.

A total of seven adverse events reported for the safety population were severe and included increased triglyceride levels on two occasions by one subject, and single episodes of toothache, ischialgia, post-traumatic spleen injury and arterial hypertension during the K6 study arm and a single episode of menstruation pain during the CC study arm. None of these severe adverse events were considered related to the investigational products. One subject from the safety population was withdrawn due to adverse events. Subject 0459 (a male) was withdrawn during the CC study arm due to a moderate adverse event of influenza, which occurred on Day 13 and resolved after 8 days.

There were no apparent differences in any of the clinical laboratory values, vital signs, ECG parameters, or physical examinations during the study.

ZRHX-EX-01 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..

Tested Product: THS 2.1

DESIGN

A single-center randomized, controlled, open-label, 2-arm, parallel group *ad libitum* smoking study comparing the use of THS 2.1 cigarettes and CC to evaluate the exposure to selected smoke constituents in smokers switching from CC to THS 2.1 cigarettes as compared to those continuing to smoke CC.

OBJECTIVE

The aim of this exploratory study was to evaluate the effect of a new candidate modified risk tobacco product (CANDIDATE MRTP), Tobacco Heating System (THS) 2.1, on selected biomarkers of exposure (BoExp) compared to conventional cigarettes (CC). In addition, the subjective effects (urge to smoke and withdrawal symptoms) were explored and initial information on safety when using THS cigarettes was collected. The preliminary results obtained in this exploratory study will serve to gain knowledge on product performance and variability of the selected endpoints to optimize study design and sample size for future clinical studies.

POPULATION

A total of 40 female or male, healthy Caucasian, smokers with a smoking history of at least three years of consecutive smoking prior to Screening and a minimum of 10 non-mentholated CC per day with a maximum yield of 1 mg nicotine ISO/CC during the four weeks prior to Screening were randomized to the THS 2.1 and CC study arms. All 40 subjects completed the study.

Randomization quotas were used to ensure that each gender and smoking stratum (10-19 CC/day vs. >19 CC/day) represented at least 40% of the study population.

SAFETY

No serious or severe AEs were reported and no withdrawal from the study due to an AE. Overall, there were 18 AEs reported after randomization in 14 subjects. 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.

The assessment of cough showed that the overall number of subjects who experienced a regular need to cough was l0 out of 20 subjects enrolled in THS 2.1 arm. 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.

ZRHX-PK-02 A single-center, open-label, randomized, controlled, crossover study to explore the nicotine pharmacokinetic (PK) profile and safety of Tobacco Heating System (THS) 2.1 compared to conventional cigarettes (CC) following single and *ad libitum* use in smoking, but otherwise healthy subjects.

Tested Product: THS 2.1

DESIGN

A single-center, open-label, randomized, controlled, two-period, two-sequence, crossover study to explore the nicotine PK and safety of THS cigarettes compared to CC following single use in smoking, but otherwise healthy subjects.

OBJECTIVE

The goal of this exploratory study was to evaluate the pharmacokinetic (PK) profile of nicotine for a new modified risk tobacco product THS 2.1 and for conventional cigarettes (CC). In addition, the subjective effects (urge to smoke and withdrawal symptoms) related to the use of these products were explored. Another goal of the study was to collect initial information on safety when using THS cigarettes.

POPULATION

A total of 28 female or male, healthy Caucasian, smokers with a smoking history of at least three years of consecutive smoking prior to Screening and a minimum of 10 non-mentholated CC per day with a maximum yield of 1 mg nicotine ISO/CC during the four weeks prior to Screening were enrolled in the study and randomized.

Subjects were current smokers who did not plan to quit smoking in the next 3 months however were ready to accept interruptions of smoking for up to two consecutive days.

Randomization quotas were used to ensure that each gender and smoking stratum (ISO nicotine levels ≤0.6 mg vs. >0.6 mg ≤ 1 mg) represented at least 40% of the study population.

SAFETY

No serious or severe AEs were reported and there were no withdrawals from the study due to an AE took place. Overall, there were 39 AEs reported in 17 of the 28 subjects randomized. More AEs were reported during the first study period (30 AEs in 16 subjects), than the second study period (nine AEs in five subjects). 11 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.

A total of six presyncope events were experienced by five subjects (one subject after THS 2.1 exposure and four subjects after CC use). The investigator suggested allowing a light breakfast before product use in future studies to prevent such events. This was included in the protocol for Clinical Study ZRHR_PK_06.

The assessment of cough showed that the number of subjects who experienced a regular need to cough was low (≤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.

2.7.4.1.2 Overall Extent of Exposure

A detailed description of the population exposed and assessed in the studies presented in this Clinical Safety Summary is provided in this section.

2.7.4.1.2.1 EHCJLI 01/02

(Study arms: Marlboro LIGHTS, EHCSS JLI, Merit ULTIMA)

Maximum cigarette consumption allowed in the controlled smoking group was capped 20% above of the maximum daily consumption as reported in the smoking history. Maximum cigarette consumption allowed in the uncontrolled smoking group was capped 60 cigarettes per day.

Compared to Baseline when subjects smoked Marlboro Lights, average daily cigarette consumption increased by 51 % in the EHCSS JLI uncontrolled group at Day 8. In the EHCSS JLI controlled smoking Marlboro Lights and Merit Ultima groups, daily cigarette consumption remained stable from Baseline through Day 8, consistent with controlled smoking conditions.

Detailed data on exposure on a daily basis is not reported in the clinical study report and therefore not available for reporting here.

2.7.4.1.2.2 EHCJLI 02/02

(Study arms: Marlboro ULTRA LIGHTS and EHCSS JLI)

At Baseline while subjects smoked their current brand of cigarettes with 1 to 7 mg tar (FTC), the difference between the “Treatment” groups in cigarette consumption during the 24-hour confined clinic visits was not statistically significant.

Over all 52 weeks, both groups had an increase in study-assigned cigarette consumption during the 24-hour confined clinic visits compared to Baseline. In both groups, cigarette consumption increased from Baseline to Week 2, decreased at Week 4, remained fairly stable

through Week 26, and then increased at Weeks 39 and 52. The increase in the EHCSS JLI group (LS mean of 97%) was statistically significantly greater than in the Marlboro ULTRA LIGHTS group (LS mean of 26%).

Table 6 summarizes the mean exposure in the one week studies by study arm.

Table 6 - Mean Exposure in 1-Week THS 1.0 Study EHCSS JLI 02/02

Exposure	Study EHCSS 02/02 (US)	
	Marlboro ULTRA LIGHTS Mean±SD (no.)	EHCSS JLI Mean±SD (no.)
Baseline(CC only)	23.3 ± 6.8	24.3 ± 9.9
At week 2	30.0 ± 10.2	40.1 ± 15.7
At week 4	31.0 ± 13.0	45.1 ± 21.5
At week 26	27.4 ± 11.7	42.3 ± 21.4
At week 52	36.6 ± 16.0	63.4 ± 36.8

2.7.4.1.2.3 EHCK6 01/03

(Study arms: Marlboro LIGHTS, Marlboro ULTRA LIGHTS, THS 1.0)

The maximum daily number of cigarettes was limited to 20% above the subject's usual daily maximum number according to the subject's smoking history (up to 30 cigarettes per day) on the Acclimation Day. The maximum daily number on subsequent study days was limited to the number actually smoked on the Acclimation Day.

Mean cigarette consumption observed in all smoking groups from Day 1 through Day 8, consistent with controlled smoking conditions were on average as follows:

- 17.5 ± 4.1 at Baseline for THS and 17.7 ± 5.5 at Day 8
- 17.0 ± 4.2 at Baseline for Marlboro LIGHTS and 18.6 ± 4.7 at Day 8
- 16.9 ± 4.1 at Baseline for Marlboro ULTRA LIGHTS and 18.2 ± 4.2 at Day 8

The Marlboro Lights and Marlboro Ultra Lights groups smoked, on average, about 1 cigarette (about 6%) less at Baseline than they did on Day 1 through Day 8. All groups smoked about 3 fewer cigarettes per day at Baseline than they did on the Acclimation Day.

Table 7 presents an overview of the mean daily exposure during this study by study arm.

Table 7 - Mean Exposure in 1-Week THS 1.0 Study EHCK6/01/03

Exposure	Study EHCK6/01/03 (US)		
	Marlboro 10mg Mean±SD (no.)	Marlboro 6mg Mean±SD (no.)	THS 1.0 Mean±SD (no.)
Baseline (CC only)	16.9 ± 4.1	17.0 ± 4.2	17.5 ± 4.1
At 1-Day	17.9 ± 3.4	18.3 ± 4.5	17.6 ± 5.0
At 5-Day	17.0 ± 4.4	17.7 ± 4.9	17.1 ± 5.4
At 6-Day	17.6 ± 4.0	17.9 ± 4.8	17.3 ± 5.7
At 8-Day	18.2 ± 4.2	18.6 ± 4.7	17.7 ± 5.5

2.7.4.1.2.4 SPA 04-01

(Study arms: Marlboro LIGHTS, Marlboro ULTRA LIGHTS, THS 1.0)

Maximum cigarette consumption allowed in this study was capped at the mean daily cigarette consumption as reported in the smoking history.

The number of cigarettes smoked decreased slightly from Day 0 to Day 8 in all smoking groups. There were no differences in cigarette consumption between the smoking groups on Day 0 or Day 8. The average number of puffs reached nearly the technically possible maximum of 8 puffs on all days in both EHCSS groups.

Table 8 and Table 9 present an overview of the mean daily and cumulative exposure during this study by study arm.

2.7.4.1.2.5 SPA 05-01

(Study arms: CC (Marlboro), EHC K3, THS 1.0)

Maximum cigarette consumption allowed in this study was capped at 120% (rounded to the nearest whole number) of the median daily cigarette consumption as determined from the 7-day diary during the run-in period, with a maximum of 30 cigarettes per day.

Mean cigarette consumption at baseline (Day 0) was about 17 cigarettes (slightly greater with THS 1.0 than with M6J). Cigarette consumption decreased slightly on Day 1 in the four smoking groups. It progressively increased afterwards and regained approximately the initial level at Day 8.At Day 0, about one third of subjects in the K3, THS1.0, and M6J groups smoked 10-14 cigarettes/day, one third 15-19 cigarettes/day and one third 20 or more cigarettes/day. In the Lark1 and NS groups, a slightly greater proportion smoked 15-19 cigarettes/day (~43%). At Day 8, the proportion of subjects smoking less than 15 cigarettes/day had decreased in the THS1.0, K3, and M6 groups (especially in the K3 group), while the proportion of subjects smoking 20 or more cigarettes/day had slightly increased in all smoking groups.

Table 8 and Table 9 present an overview of the mean and cumulative exposure during this study by study arm.

2.7.4.1.2.6 SPA 05-03

(Study arms: CC (Marlboro), THS 1.0)

Maximum cigarette consumption allowed in this study was based on the subjects median daily cigarette consumption as determined from the 7-day diaries completed during the run-in period: for the subjects who had exhibited a median daily cigarettes consumption of 10-19 cigarettes, the individual allotment was defined as the median daily cigarette consumption + 2 with a maximum of 19 cigarettes; for those who had exhibited a median daily consumption of 20-30 cigarettes, the individual allotment was defined as the median daily cigarette consumption + 2 with a maximum of 30 cigarettes

Mean cigarette consumption at baseline (Day 0) was about 17 cigarettes and remained unchanged throughout the randomized smoking period in all smoking groups. At Day 0, the majority of subjects smoked 15-19 cigarettes/day, with a slightly greater proportion in the THS 1.0 Menthol and MM4 groups. At Day 6, the proportion of subjects smoking 20-24 cigarettes/day had increased in the THS 1.0 Menthol and LM1 groups (especially in the THS 1.0 Menthol group), while it had slightly decreased in the M4MJ group

The number of cigarettes smoked per day during the study was summarized by study group and study day by means of descriptive statistics and frequency tables according to the classification.

Table 8 and Table 9 present an overview of the mean daily and cumulative exposure during this study by study arm.

Table 8 - Mean Daily Exposure in 1-Week or longer THS 1.0 Studies (SPA 04-01, SPA 05-01, SPA 05-03)

Exposure	Study SPA 04-01 (UK)			Study SPA 05-01 (JP)			Study SPA 05-03 (JP)	
	CC [1] Mean±SD (no.)	K3 Mean±SD (no.)	THS 1.0 Mean±SD (no.)	CC [2] Mean±SD (no.)	K3 Mean±SD (no.)	THS 1.0 Mean±SD (no.)	CC [3] Mean±SD (no.)	THS 1.0 [4] Mean±SD (no.)
Baseline (CC only)	17.7±3.9 (n=64)	17.9±3.8 (n=32)	17.7±3.4 (n=32)	17.4±4.5 (n=56)	17.2±4.1 (n=28)	17.7±5.1 (n=28)	17.2±4.5 (n=56)	17.0±4.4 (n=28)
At 1-Day	16.9±4.2 (n=64)	15.9±3.8 (n=32)	15.5±4.8 (n=32)	16.7±4.0 (n=56)	16.4±3.7 (n=28)	16.5±5.0 (n=28)	17.3±4.3 (n=56)	17.0±4.3 (n=28)
At 5-Day	16.9±4.2 (n=62)	16.9±3.9 (n=32)	16.8±4.3 (n=30)	16.5±4.1 (n=55)	16.9±3.8 (n=28)	17.2±5.4 (n=28)	17.3±4.4 (n=56)	17.5±4.8 (n=28)
At 6-Day	16.8±4.2 (n=62)	16.5±4.0 (n=32)	16.3±4.5 (n=30)	16.5±4.1 (n=55)	16.8±3.7 (n=28)	17.3±5.3 (n=28)	17.4±4.3 (n=56)	17.6±5.1 (n=28)
At 8-Day	17.1±4.5 (n=62)	17.1±3.9 (n=31)	16.8±4.3 (n=30)	17.2±4.3 (n=55)	18.1±4.0 (n=27)	18.0±5.3 (n=28)	NA	NA

Note: CC: conventional cigarette. THS 1.0: Tobacco heating System 1.0 (previously named K6). K3: previous version of THS 1.0. Non Compl: subjects randomized to THS 1.0 not fully compliant to the product (i.e., smoking CC in addition or substitution of THS 2.1). NA: not applicable
Note: (1) Pooled data of exposure to M6 (32 subjects) and PM1 (32 subjects) conventional cigarettes
Note: (2) Pooled data of exposure to M6 (28 subjects) and Lark1 (28 subjects) conventional cigarettes
Note: (3) Pooled data of exposure to MM4 (28 subjects) and LM1 (28 subjects) conventional cigarettes
Note: (4) the mentholated version of THS 1.0 was tested in SPA-05-03

Table 9 - Mean Cumulative Exposure in 1-Week or longer THS 1.0 Studies (SPA 04-01, SPA 05-01, SPA 05-03)

Exposure	Study SPA04-01 (UK)			Study SPA05-01 (JP)			Study SPA05-03 (JP)	
	CC [1] Mean±SD (no.)	K3 Mean±SD (no.)	THS 1.0 Mean±SD (no.)	CC [2] Mean±SD (no.)	K3 Mean±SD (no.)	THS 1.0 Mean±SD (no.)	CC [3] Mean±SD (no.)	THS 1.0 [4] Mean±SD (no.)
At 1-Day	16.9±4.2 (n=64)	15.9±3.8 (n=32)	15.5±4.8 (n=32)	16.7±4.0 (n=56)	16.4±3.7 (n=28)	16.5±5.0 (n=28)	17.3±4.3 (n=56)	17.0±4.3 (n=28)
At 5-Day	84±20.9 (n=62)	81.3±17.7 (n=32)	80.9±21.7 (n=30)	83.3±20.7 (n=55)	82.7±18.7 (n=28)	85.3±26.2 (n=28)	86.4±21.1 (n=56)	86.1±23.4 (n=28)
At 6-Day	100.8±24.9 (n=62)	97.8±21.1 (n=32)	97.2±26.0 (n=30)	99.9±24.6 (n=55)	99.5±22.2 (n=28)	102.6±31.2 (n=28)	103.9±25.3 (n=56)	103.8±28.4 (n=28)
At 8-Day	135±33.6 (n=62)	131.6±28.9 (n=31)	130.8±33.8 (n=30)	133.7±32.7 (n=55)	133.9±29.6 (n=27)	138.3±41.7 (n=28)	NA	NA

Note: CC: conventional cigarette. THS 1.0: Tobacco heating System 1.0 (previously named K6). K3: previous version of THS 1.0. Non Compl: subjects randomized to THS 1.0 not fully compliant to the product (i.e., smoking CC in addition or substitution of THS 2.1). NA: not applicable
Note: (1) Pooled data of exposure to M6 (32 subjects) and PM1 (32 subjects) conventional cigarettes
Note: (2) Pooled data of exposure to M6 (28 subjects) and Lark1 (28 subjects) conventional cigarettes
Note: (3) Pooled data of exposure to MM4 (28 subjects) and LM1 (28 subjects) conventional cigarettes
Note: (4) the mentholated version of THS 1.0 was tested in SPA-05-03

2.7.4.1.2.7 CS 06-02

(Study arms: CC (Marlboro), THS 1.0)

The baseline (Week -1) daily cigarette consumption of conventional cigarettes was similar for subjects subsequently randomized to the THS 1.0 and CC study arms, with a mean of 25 CPD. For the THS 1.0 study arm, the subjects' daily cigarette consumption increased from baseline to a mean of 33 CPD in Week 1, and increased further to a mean of 40 CPD in Week 5. This overall increase of 21% in CPD was made up of increases of 21%, 23%, and 43% for the subjects who smoked 10-19, 20-30, and >30 CPD at baseline, respectively, with the average CPD at the end of study being 34, 43, and 53, respectively. This increasing trend for the THS study arm was also consistent throughout the sub-groups for age and gender. For the CC arm there was no apparent change in daily cigarette consumption, with an overall mean across Weeks 1 to 5 of 23 CPD.

Table 10 presents an overview of the mean and cumulative exposure during this study by study arm.

Table 10 - Mean Daily and Weekly Exposure in 5-Week THS 1.0Study CS06-02

Exposure Period	THS 1.0 Mean±SD [% compliance] (1) (no.)	CC Mean±SD (no.)
Baseline (CC only) (2)	25±6 (n=236) (4)	25±6 (n=77)(4)
Week 1	33±5 [99.0%] (n=236)	24±1 (n=77)
Week 2	37±1 [100.0%] (n=236)	24±1 (n=75)
Week 3	36±5 [100.0%] (n=236)	23±2 (n=75)
Week 4	36±4 [99.9%] (n=235)	23±1 (n=75)
Week 5	40±2 [99.9%] (n=235)	23±1 (n=75)
Weeks 1-5 (3)	38±3 [99.8%] (n=236)	23±1 (n=77)

Note: CC: conventional cigarette. THS 1.0: Tobacco heating System 1.0. NA: Not applicable
Note: (1) Compliance = (Number of THS 1.0 cigarettes per week / Total number of cigarettes per week) * 100
Note: (2) Subjects smoked CC for Week -1 visit, data are summary of available data (less than 1 week)
Note: (3) Summary across Weeks 1 to 5 (during randomization period)
Note: (4) Data presented as published in the clinical study report for the full analysis set with 236 and 38 subjects in the THS 1.0 and CC arms, respectively.

2.7.4.1.2.8 ZRHX_PK_02

(Study arms: CC, THS 2.1)

In ZHRX-PK-02, all subjects received the IP according to the randomization scheme.

The actual CC consumption during ad libitum use was summarized by exposure and study day (Day 2 and Day 5 only).

Table 11 and Table 12 present an overview of the mean and cumulative exposure during this study by study arm.

2.7.4.1.2.9 ZRHX_EX_01

(Study arms: CC, THS 2.1)

In ZHRX-EX-01 All subjects received the IP according to the randomized scheme.

Details of the subjects' daily consumption at Day 1 and Day 5 of THS cigarettes or CC, including total number of cigarettes smoked are listed by subject in Table 11. The number of cigarettes consumed during the study is summarized in Table 12. In the CC study arm, the mean number of cigarettes consumed daily also increased from Day 0 (18.2 cig/day) to Day 5 (20.1 cig/day). Comparable trends were observed with median numbers of cigarettes smoked. Subjects in the THS 2.1 study arm smoked more cigarettes throughout the study than those in the CC study arm.

Table 11 and Table 12 present an overview of the mean and cumulative exposure during this study by study arm.

Table 11 - Mean Daily Exposure in THS 2.1 Studies

	Study ZHRX-PK-02 (UK)		Study ZHRX-EX-01 (PL)	
Exposure	**THS 2.1 [(1)] Mean±SD (no.)**	**CC Mean±SD (no.)**	**THS 2.1 [(2)] Mean±SD (no.)**	**CC Mean±SD (no.)**
Baseline (CC only)	NA	NA	18.9±4.6 (n=20)	18.2±4.1 (n=20)
At 1-Day	10.9±3.6 (n=28)	16.7±3.6 (n=28)	21.4±7.4 (n=20)	17.8±3.1 (n=20)
At 5-Day	NA	NA	27.2±9.2 (n=20)	20.1±3.3 (n=20)

Note: CC: conventional cigarette. THS 2.1: Tobacco heating System 2.1. NA: Not applicable
Note: (1) 28 out of the 33 subjects in the safety population participated to each product specific ad-libitum use day after the single-use day
Note: (2) 20 out of the 22 subjects associated to THS 2.1 in the safety population in participated to the 5-days exposure

Table 12 - Mean Cumulative Daily Exposure in THS 2.1 Studies

	Study ZRHX-PK-02 (UK)		Study ZRHX-EX-01 (PL)	
Exposure	**THS 2.1 [(1)] Mean±SD (no.)**	**CC Mean±SD (no.)**	**THS 2.1 [(2)] Mean±SD (no.)**	**CC Mean±SD (no.)**
At 1-Day	10.9±3.6 (n=28)	16.7±3.6 (n=28)	21.4±7.4 (n=20)	17.8±3.1 (n=20)
At 5-Day	NA	NA	124±37.1 (n=20)	93.3±15.6 (n=20)

Note: CC: conventional cigarette. THS 2.1: Tobacco heating System 2.1. NA: Not applicable
Note: (1) 28 out of the 33 subjects in the safety population participated to each product specific ad-libitum use day after the single-use day
Note: (2) 20 out of the 22 subjects associated to THS 2.1 in the safety population in participated to the 5-days exposure

2.7.4.1.3 Demographic and Other Characteristics of Study Population

A detailed description of baseline demographics and subject characteristics in the studies presented in this Clinical Safety Summary is provided in this section.

2.7.4.1.3.1 EHCJLI 01/02

Subject demographics are presented in Table 13. Of the 130 subjects enrolled, 100 subjects were randomly assigned to one of the 5 study groups, with 20 subjects per study arm (Marlboro Light, Merit Ultima, EHCSS JLI – Controlled Smoking, EHCSS JLI – Uncontrolled Smoking, and No smoking [NS]).

Ninety-seven percent of the randomized subjects were Caucasian. There was balance between the genders across the study (50% male and female) and within each study arm. The mean age was 34 years with a standard deviation of 11 years (range: 21 to 63 years). The BMI was 24.6 kg/m^2 (range: 17.9 to 33.2 kg/m^2). During the Acclimation day (Day -2) the average number of cigarettes smoked was approximately 20 cigarettes (range: 12 to 29 cigarettes). There were no significant differences between the study groups in the demographic characteristics.

Table 13 - Summary of Demographics and Baseline Characteristics in the EHCJLI/01/02 Study

Characteristic	Marlboro LIGHTS (N=20)	Merit ULTIMA (N=20)	EHCSS JLI Controlled (N=20)	EHCSS JLI Uncontrolled (N=20)	No Smoking (N=20)	Overall (N=100)
Age – yr	37.3±11.0	30.3±9.5	35.0±12.0	30.4±9.2	34.6±13.0	33.5±11.0
Male sex – no. (%)	9 (45%)	10 (50%)	10 (50%)	10 (50%)	11 (55%)	50 (50%)
Body-mass index - kg/m^2	23.9±2.8	24.3±4.0	25.0±2.3	25.0±3.5	24.7±1.6	24.6±2.9
Race –no. (%)						
Caucasian/White	20 (100%)	19 (95%)	20 (100%)	19 (95%)	19 (95%)	97 (97%)
Asian/Japanese	0	0	0	0	1 (5%)	1 (1%)
Black	0	0	0	1 (5%)	0	1 (1%)
Hispanic	0	1 (5%)	0	0	0	1 (1%)
	0					
Daily consumption - cpd	20.3±4.2	19.1±5.5	20.3±4.0	19.6±4.1	20.3±4.1	19.9±4.3

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)

2.7.4.1.3.2 EHCJLI 02/02

The subject demographics are presented in Table 14. Of the 115 enrolled subjects 97 were randomly assigned to one of the two study groups. Thirty-three subjects were assigned to the Marlboro Ultra Light study arm and 64 were assigned to the EHCSS JLI arm.

Sixty-nine percent of the randomized subjects were Caucasian. There was balance between the genders across the study (46.4% male vs. 53.6% female) and within each study arm. The mean age was 42 years with a standard deviation of 9.4 years (range: 25 to 64 years). The BMI was 25.6 kg/m^2 (range: 19 to 32 kg/m^2). During the 24-hour urine collection period (prior to randomization) the self-reported average number of cigarettes smoked was 24.3 cigarettes (range: 8 to 50 cigarettes) in the EHCSS JLI arm vs. 23.3 cigarettes (range: 8 to 45 cigarettes) in the Marlboro Ultra-Light arm. At Baseline there were no significant differences between the study groups in the demographic characteristics.

Table 14 - Summary of Demographics and Baseline Characteristics in the EHCJLI/02/02 Study

Characteristics	EHCSS-JLI (N=64)	Marlboro Ultralights (N=33)	Overall (N=97)
Age – yr	41.3±9.1	42.9±10	41.8±9.4
Male sex – no. (%)	29 (45.3%)	16 (48.5%)	45 (46.4%)
Body-mass index - kg/m^2	25.3±2.9	26.1±3.3	25.6±3.0
Race – no. (%)			
Black	1 (1.6%)	0 (0.0%)	1 (1.0%)
Caucasian/White	61 (95.3%)	32 (97.0%)	93 (95.9%)
Hispanic	2 (3.1%)	1 (3.0%)	3 (3.1%)
Daily consumption - cpd	24.3±9.9	23.3±6.8	-
Smoking history – no. (%)			
10 to 15 yr	14 (21.9%)	6 (18.2%)	20 (20.6%)
16 to 19 yr	16 (25.0%)	4 (12.1%)	20 (20.6%)
20 to 29 yr	19 (29.7%)	15 (45.5%)	34 (35.1%)
30+ yr	15 (23.4%)	8 (24.2%)	23 (23.7%)

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)

2.7.4.1.3.3 EHCK6 01/03

The subject demographics are presented in Table 15. Of the 136 subjects that were enrolled, 120 were randomly assigned to one of the four study groups, with 20 subjects assigned to each of the Marlboro LIGHT, Marlboro ULTRA-LIGHT, and Smoking Abstinence arms, and 60 assigned to the THS 1.0 arm.

Ninety-four percent of the randomized subjects were Caucasian. There was balance between the genders across the study (47.5% male vs. 52.5% female) and within each study arm. The mean age was 32 years with a standard deviation of 10 years (range: 21 to 60 years). The BMI was 24.9 kg/m^2 (range: 18 to 33 kg/m^2). During the acclimation day (Day -2) the average number of cigarettes smoked was approximately 20 cigarettes (range: 12 to 30 cigarettes). Overall, a smoking history of 10 years or more was reported by 60 subjects (58%) participating in the study. The mean Fagerström score of all 120 subjects was 4.5 (range: 1 to 8). There were no significant differences between the study groups in the demographic characteristics.

Table 15 - Summary of Demographics and Baseline Characteristics in the EHCK6/01/03 Study

Characteristics	THS 1.0 (N=60)	Marlboro L 10mg (N=20)	Marlboro UL 6mg (N=20)	Smoking Abstinence (N=20)	Overall (N=120)
Age – yr	33.8 ± 12	31.7 ± 10	28.8 ± 7.4	30.7 ± 8.6	32.1± 10
Male sex – no. (%)	29 (48.3%)	9 (45.0%)	9 (45.0%)	10 (50.0%)	57 (47.5%)
Body-mass index - kg/m^2	25.0 ± 2.9	25.6 ± 3.0	25.0 ± 3.1	23.9 ± 2.7	24.9 ± 2.9
Race – no. (%):					
Asian/Japanese	0	0	1 (5.0%)	1 (5.0%)	2 (1.7%)
Caucasian/white	57 (95.0%)	20 (100%)	17 (85.0%)	19 (95.0%)	113 (94.2%)
Hispanic	2 (3.3%)	0	1 (5.0%)	0	3 (2.5%)
American Indian	1 (1.7%)	0	1 (5.0%)	0	2 (1.7%)
Daily consumption - cpd	20.2 ± 4.8	20.1 ± 4.8	19.7 ± 4.4	20.6 ± 4.7	20.2 ± 4.6
Smoking history – no. (%)					
up to 3 yr	3 (5.0%)	1 (5.0%)	0	1 (5.0%)	5 (4.2%)
4 to 9 yr	22 (36.7%)	7 (35.0%)	11 (55.0%)	5 (25.0%)	45 (37.5%)
10 to 15 yr	12 (20.0%)	7 (35.0%)	5 (25.0%)	6 (30.0%)	30 (25.0%)
16 to 19 yr	5 (8.3%)	1 (5.0 %)	1 (5.0%)	2 (10%)	9 (7.5%)
20 to 25 yr	11 (18.3%)	3 (15.0%)	3 (15.0%)	4 (20.0)	21 (17.5%)
26+ yr	7 (11.7%)	1 (5.0%)	0	2 (10%)	10 (8.3%)
FTND questionnaire score	4.5 ± 1.8	4.5 ± 1.7	4.4 ± 2.0	4.7 ± 1.5	4.5 ± 1.8

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)

2.7.4.1.3.4 SPA 04-01

Table 16 provides a summary of subjects' demographics by and across study groups including information about smoking category and the duration of smoking as assessed with the Smoking History Questionnaire.

All 160 subjects randomized were of Caucasian origin. The male/female proportions as well as the proportion of the smoking categories (10 - 19 and 20 - 25 cigarettes per day [CPD]) were exactly balanced (16/16) within all study groups. The mean age over all subjects was 28.7 years (range: 19 - 50 years). The mean BMI was 23.63 kg/m^2 (range: 18.6 - 30.0 kg/m^2) without considerable differences between the study groups.

Overall, a smoking history of 10 years or more was reported by 95 subjects (59.4%) participating in the study (THS 1.0: 17 subjects, 53.1%; both K3 and M6: 21 subjects, 65.6%; PM1: 20 subjects, 62.5%; NS: 16 subjects, 50%).

There was a tendency to a longer smoking history for smokers of 20 - 25 CPD in comparison to smokers of 10 - 19 cigs/day: 55 subjects (68.8%) smoking 20 - 25 CPD as compared to 40 subjects (50.0%) who smoked 10 - 19 cigs/day reported a smoking history of 10 years or more. This tendency was present in all study groups, except the M6 group where the smoking category was apparently not related to the smoking history.

The data summaries stratified by smoking category indicate that smokers of 20 – 25 CPD were slightly older than smokers of 10 - 19 CPD (30.0 vs.27.5 years, respectively). This overall tendency was present in all study groups except the M6 group, where the mean age was 31.3 vs. 30.6 years for smokers of 10 - 19 or 20 - 25 CPD, respectively. There were no relevant differences between males and females with respect to age, BMI, the duration of smoking, and the average daily cigarette consumption.

The mean Fagerström score of all 160 subjects was 5.2, with no relevant differences between the study groups. There was a general tendency to higher scores in smokers of 20 - 25 CPD (5.7) in comparison to smokers of 10 - 19 CPD (4.6). This difference can be explained by the structure of the questionnaire as a higher daily cigarette consumption increases the sum score. According to the classification of the Fagerström total score, overall 12 subjects (7.5%) fell into the lowest category of nicotine dependence (score 0 – 2), and overall 37 subjects (23.1%) fell into the highest category (score 7 - 10). Among the subjects classified into the highest dependence category, there were more smokers of 20 - 25 CPD (26 subjects; 32.5%) than smokers of 10 - 19 CPD (11 subjects; 13.8%). There were more males (22 subjects; 27.5%) than females (15 subjects; 18.8%) classified into the highest dependence category, but overall, there was no difference in the mean Fagerström score between male and female subjects (both 5.2)

Table 16 - Summary of Demographics and Baseline Characteristics in THS 1.0 Study SPA04-01

Characteristics	SPA04-01					
	EHCSS-K3 (N=32)	**THS 1.0 (N=32)**	**Marlboro 6mg (N=32)**	**Philip Morris 1mg (N=32)**	**Smoking Abstinence (N=32)**	**Overall (N=160)**
Age – yr	28.5±8.2	28.3±6.5	30.9±8.3	27.9±6.8	27.5±6.1	28.6±7.2
Male sex – no. (%)	16 (50.0%)	16 (50.0%)	16 (50.0%)	16 (50.0%)	16 (50.0%)	80 (50.0%)
Body-mass index - kg/m^2	23.7±2.7	23.7±3.0	23.1±2.7	24.0±3.1	23.8±2.9	23.6±2.9
Race – no. (%)						
Caucasian/white	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)	160 (100%)
Daily consumption – no. (%)						
10-19 cpd	16 (50.0%)	16 (50.0%)	16 (50.0%)	16 (50.0%)	16 (50.0%)	80 (50.0%)
20-25 cpd	16 (50.0%)	16 (50.0%)	16 (50.0%)	16 (50.0%)	16 (50.0%)	80 (50.0%)
Smoking History – no. (%)						
up to 3 yr	2 (6.3%)	1 (3.1%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	5 (3.1%)
4 to 9 yr	9 (28.1%)	14 (43.8%)	11 (34.4%)	11 (34.4%)	15 (46.9%)	60 (37.5%)
10 to 15 yr	12 (37.5%)	9 (28.1%)	9 (28.1%)	12 (37.5%)	11 (34.4%)	53 (33.1%)
16 to 19 yr	3 (9.4%)	2 (6.3%)	2 (6.3%)	3 (9.4%)	1 (3.1%)	11 (6.9%)
20 to 25 yr	3 (9.4%)	5 (15.6%)	4 (12.5%)	4 (12.5%)	3 (9.4%)	19 (11.9%)
26+ yr	3 (9.4%)	1 (3.1%)	6 (18.8%)	1 (3.1%)	1 (3.1%)	12 (7.5%)
Overall	32 (100%)	32 (100%)	32 (100%)	32 (100%)	32 (100%)	160 (100%)
FTND questionnaire score	5.4±1.9	5.0±1.5	5.0±2.1	5.3±1.5	5.1±1.9	5.2±1.8

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)

2.7.4.1.3.5 SPA05-01

Gender, age, BMI, and baseline cigarette consumption for subjects are presented in Table 17. All 128 subjects enrolled (89 men, 39 women) were randomly assigned to one of the 5 study groups: THS 1.0: 28 volunteers, K3: 28 volunteers, M6J: 28 volunteers, Lark1J: 28 volunteers, No smoking (NS): 16 volunteers.

All 128 subjects were of Japanese ethnic origin. There were about twice as many men as women in each group. Mean age was 23.5 years (range: 21-31 years) and very similar for women and men. Slightly less women than men were overweight or obese. During the run-in period (data from the 7-day diary), the proportion of men smoking 20 CPD or more slightly exceeded the proportion smoking less than 20 CPD, whereas the opposite was true for women.

Responses to the Fagerstrom questionnaire indicate that nicotine dependence was somewhat more pronounced among women than men in all study groups, and more pronounced in heavy than light cigarette consumers. Nearly half of the subjects had a score of 3-4 (slightly dependent). Only 11 subjects (7 women; 4 men) had high nicotine dependence scores (7-10) at the Fagerstrom questionnaire. The study groups were also comparable with regard to duration of smoking, while the majority of subjects (116, 90.6%) smoked for up to 9 years and only 12 subjects (9.4%) smoked for more than 9 years.

Data from the Smoking History Questionnaire also indicate that nearly half of the subjects had increased their cigarette consumption over the last 3 years. Most subjects smoked most of a cigarette before extinguishing it and all of them always inhaled the smoke deeply into the lungs. Apart from some sporadic differences between groups, results from the Smoking History Questionnaire were generally homogeneous.

Table 17 - Summary of Demographics and Baseline Characteristics in THS 1.0 Study SPA05-01

Characteristics	SPA05-01					
	EHCSS-K3 (N=28)	**THS 1.0 (N=28)**	**Lark 1mg (N=28)**	**Marlboro 6mg (N=28)**	**Smoking Abstinence (N=16)**	**Overall (N=128)**
Age – yr	23.7±2.6	23.4±2.4	23.3±2.4	23.5±2.2	23.9±2.3	23.5±2.4
Male sex – no. (%)	21 (75.0%)	19 (67.9%)	19 (67.9%)	20 (71.4%)	10 (62.5%)	89 (69.5%)
Body-mass index - kg/m^2	20.7±2.0	20.9±1.6	20.5±2.3	20.8±2.3	21.8±2.5	20.8±2.1
Race – no. (%)						
Asian/Japanese	28 (100%)	28 (100%)	28 (100%)	28 (100%)	16 (100%)	128 (100%)
Daily consumption – no. (%):						
10 to 19 cpd	14 (50.0%)	14 (50.0%)	14 (50.0%)	14 (50.0%)	8 (50.0%)	64 (50.0%)
20 to 25 cpd	14 (50.0%)	9 (32.2%)	11 (39.3%)	11 (39.3%)	8 (50.0%)	53 (41.4%)
26 to 30 cpd	0 (00.0%)	5 (17.9%)	3 (10.7%)	3 (10.7%)	0 (00.0%)	11 (08.6%)
Smoking history – no. (%):						
up to 3 yr	8 (28.6%)	8 (28.6%)	14 (50.0%)	9 (32.1%)	4 (25.0%)	43 (33.6%)
4 to 9 yr	17 (60.7%)	15 (53.6%)	13 (46.4%)	17 (60.7%)	11 (68.8%)	73 (57.0%)
10 to 15 yr	3 (10.7%)	5 (17.9%)	1 (3.6%)	2 (7.1%)	1 (6.3%)	12 (9.4%)
Overall	28 (100%)	28 (100%)	28 (100%)	28 (100%)	16 (100%)	128 (100%)
FTND questionnaire score	3.9±1.2	3.6±1.8	4.1±2.1	4.1±1.8	3.9±1.7	3.9±1.7

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)

2.7.4.1.3.6 SPA 05-03

All 100 subjects randomized were of Japanese origin. Gender, age, BMI and baseline cigarette consumption for subjects are presented in Table 18. There were about twice as many male than female in each group. Mean age was 23.9 ± 2.8 years (range: 21-32 years) and very similar for women and men.

During the run-in period (data from the 7-day diary) the proportion of men smoking 20 CPD or more slightly exceeded the proportion smoking less than 20 CPD whereas the reverse was true for women.

Responses to the Fagerström questionnaire, assessing the subject's dependence to nicotine indicate that nicotine dependence was similar between women and men in all study groups, and more pronounced in heavy than light cigarette consumers except in the no smoking group. Nearly half of the subjects had a score of 3-4 (slightly dependent). Only 6 subjects (1 woman; 5 men) had high nicotine dependence scores (7-10) at the Fagerström questionnaire. The study groups were also comparable with regard to duration of smoking, while the majority of subjects (57, 57.0%) smoked for up to 9 years and only 8 subjects (8.0%) smoked for more than 9 years.

Table 18 - Summary of Demographics and Baseline Characteristics in THS 1.0 Studies: Studies SPA05-03

	SPA05-03				
Characteristics	**THS 1.0 M (N=28)**	**Lark M 1mg (N=28)**	**Marlboro M 4mg (N=28)**	**Smoking Abstinence (N=16)**	**Overall (N=100)**
Age – yr	23.6±2.1	24.1±3.3	23.9±2.9	24.0±3.1	23.9±2.8
Male sex – no. (%)	17 (60.7%)	18 (64.3%)	15 (53.6%)	11 (68.8%)	61 (61.0%)
Body-mass index - kg/m^2	20.2±2.2	20.2±2.0	21.2±2.5	20.8±2.3	20.6±2.3
Race – no. (%)					
Asian/Japanese	28 (100%)	28 (100%)	28 (100%)	16 (100%)	100 (100%)
Daily consumption – no. (%)					
10 to 19 cpd	14 (50.0%)	14 (50.0%)	14 (50.0%)	8 (50.0%)	50 (50.0%)
20 to 25 cpd	12 (42.9%)	12 (42.9%)	12 (42.9%)	6 (37.5%)	42 (42.0%)
26 to 30 cpd	2 (7.2%)	2 (7.2%)	2 (7.2%)	2 (12.5%)	8 (8.0%)
Smoking history – no. (%):					
up to 3 yr	9 (32.1%)	10 (35.7%)	9 (32.1%)	7 (43.8%)	35 (35.0%)
4 to 9 yr	17 (60.7%)	16 (57.1%)	18 (64.3%)	6 (37.5%)	57 (57.0%)
10 to 15 yr	2 (7.1%)	2 (7.1%)	1 (3.6%)	3 (18.8%)	8 (8.0%)
Overall	28 (100%)	28 (100%)	28 (100%)	16 (100%)	100 (100%)
FTND questionnaire score	3.8±1.6	3.9±1.9	3.9±1.4	4.0±1.7	3.9±1.6

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)
Note: THS 1.0 M identifies the menthol version of THS 1.0 (EHCSS-K6 M)

2.7.4.1.3.7 CS 06-02

From the 316 subjects randomized, 161 (51%) were male and 155 (49%) were female. All subjects were of Caucasian origin. The mean age was 43.6 years. The average age of the male and female subjects did not differ. The distribution of gender and average age were comparable in the three analysis datasets and in the two study arms. Table 19 provides an overview of the demographic characteristics of clinical study CS 06-02.

The BMI classification showed 47.2% of subjects to be normal weight with 36.7% overweight, 13.6% obese and 2.5% underweight (based on the safety population). A summary of BMI classification for subjects in the THS 1.0 and CC arms of the study (and overall) for are presented in Table 19.

The results for the Fagerström Test for Nicotine Dependence showed similar total scores for subjects subsequently randomized to the THS 1.0 and CC arms, with a mean score of 5.9. The score classifications showed a similar percentage of subjects for the THS 1.0 and CC arms to be “not or minimally dependent” and “highly dependent” for nicotine. For the intermediate classifications of nicotine dependence, there was a greater percentage of subjects being “slightly dependent” for the THS 1.0 compared to the CC arm (19% and 11%, respectively) whereas a lower percentage of subjects were ‘moderately dependent’ for the THS 1.0 compared to the CC arm (31% and 43%, respectively).

The Smoking History Questionnaire showed the majority of subjects in the safety population had smoked for more than 20 years (61% and 68%, for THS 1.0 and CC, respectively), compared to a duration of 11 to 20 years (38% and 32%, for THS 1.0 and CC, respectively). A small number of subjects (0.8%) in the THS 1.0 study arm only had smoked for less than this time (1 to 10 year duration).

Table 19 - Summary of Demographics and Baseline Characteristics in THS 1.0 Studies: Study CS06-02

Characteristics	CS06-02 EHCSS-K6 (N=237)	CS06-02 Conventional Cigarettes (N=79)	Overall (N=316)
Age – yr	43.5±8.0	43.9±8.2	43.6±8.1
Male sex – no. (%)	121 (51.1%)	40 (50.6%)	161 (51.0%)
Body-mass index - kg/m^2	25.6±4.6	24.4±3.3	25.3±4.3
Race – no (%)			
Caucasian/white	237 (100%)	79 (100%)	316 (100%)
Daily consumption – no. (%)			
< 10 cpd	0	1 (1.3)	1 (0.3)
10 to 19 cpd	87 (36.7)	20 (25.3)	107 (33.9)
20 to 30 cpd	138 (58.2)	53 (67.1)	191(60.4)
> 30 cpd	12 (5.1)	5 (6.3)	17 (5.4)
Smoking history – no. (%)			
up to 10 yr	2 (0.8%)	0 (0.0%)	2 (0.6%)
11 to 20 yr	90 (38.0%)	25 (31.6%)	115 (36.4%)
21+ yr	145 (61.2%)	54 (68.4%)	199 (63.0%)
Overall	237 (100%)	79 (100%)	316 (100%)
FTND questionnaire score	N=221, 5.9±2.0	N=74, 5.9±2.0	N=295, 5.9±2.0

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)

2.7.4.1.3.8 Studies ZRH-EX-01 and ZRHX-PK-02 (THS 2.1)

Subject demographic data are summarized in Table 20 along with baseline characteristics data for the safety age, weight, height, and BMI, race for the two clinical studies ZHRX-EX-01 and ZHRX-PK-02.

ZHRX-EX-01

All subjects were of Caucasian origin with an equal overall distribution between male (50.0%) and female (50.0%) subjects. No notable differences were observed between nicotine levels with regard to mean age or mean height. Demographic data are summarized by stratification parameters (gender and daily CC consumption) in Table 20. Gender and cigarette consumption data declared at screening were similar for the different study arms (20 subjects each).

No notable differences were observed between cigarette consumption with regard to mean weight, mean height or mean BMI, but the overall mean age for subjects who smoked 10-19 CPD was 35.9 years (SD=8.09 years) and for subjects who smoked >19 CPD the overall mean age was 40.8 years (SD=9.34 years).

No notable differences were observed between study arms with regard to BMI classification. The FTND overall classification is summarized by category (mild: 0-3; moderate: 4-6; severe: 7-10) for all subjects and by sub-group. Overall, seven subjects (25.0%) had an FTND overall classification of severe: of these, two (14.3%) were male and five (35.7%) were female, two subjects (16.7%) smoked CC with a nicotine yield of ≤0.6 mg and five (31.3%) smoked CC with a nicotine yield of >0.6 mg. Of the seven subjects (25.0%), five (20.0%) smoked 10-19 CPD and two (66.7%) smoked >19 CPD.

ZHRX-PK-02

Off the 78 subjects who were screened, 33 subjects tried the THS 2.1 product during the product trial, 45 subjects were screening failures. Of the 33 subjects who tried the THS 2.1 product, five were admitted to the clinic but were not randomized. Fourteen subjects were randomized to receive THS 2.1 followed by CC (Sequence 1) and 14 subjects were randomized to receive CC followed by THS 2.1 (Sequence 2). All 28 randomized subjects completed the study; no subjects were withdrawn from the study.

Study Demographic data (including gender, race, and age) and baseline characteristics (including cigarette consumption, weight, height, and BMI) were summarized by sequence, overall and by the three sub-groups (gender, nicotine levels, cigarette consumption), using descriptive statistics (Table 20). Summaries were provided for the FTND score of the number and percentage of subjects in each category (mild/moderate/severe) and the total scores were summarized by sequence, gender, smoking strata and cigarette consumption. Smoking history, including whether subjects had smoked for at least the last three consecutive years, the average number of CC smoked per day during the previous 4 weeks, and whether the

subject had smoked any mentholated CC during the previous 4 weeks was listed by sequence at Screening and Admission (Day -1).

Table 20 - Summary of Demographics and Baseline Characteristics in THS 2.1 Studies

	ZHRX-EX-01 Study			ZHRX-PK-02 Study		
Characteristics	**THS 2.1 (N=20)**	**CC (N=20)**	**Overall (N=40)**	**THS 2.1 - CC (N=14)**	**CC - THS 2.1 (N=14)**	**Overall (N=28)**
Age – yr	37.6±9.0	37.8±8.4	37.7±8.6	30.0±4.9	29.1±4.0	29.5±4.4
Male sex – no. (%)	10 (50.0%)	9 (45.0%)	19 (47.5%)	6 (42.9%)	8 (57.1%)	14 (50.0%)
Body-mass index - kg/m^2	24.1±2.4	23.4±2.6	23.8±2.5	23.2±2.2	24.3±2.7	23.8±2.5
Race – no. (%)						
Caucasian/white	20 (100%)	20 (100%)	40 (100%)	14 (100%)	14 (100%)	28 (100%)
Daily consumption – no. (%)						
10 to 19 cpd	10 (50.0%)	10 (50.0%)	20 (50.0%)	11 (78.6%)	14 (100.0%)	25 (89.3%)
20+ cpd	10 (50.0%)	10 (50.0%)	20 (50.0%)	3 (21.4%)	0 (0.0%)	3(10.7%)
Smoking history – no. (%)						
≥ 3 years	20 (100%)	20 (100%)	40 (100%)	14 (100%)	14 (100%)	28 (100%)
FTND questionnaire score	N=17 6.1±1.6	N=12 6.5±2.0	N=29 6.3±1.8	N=13 5.6±1.8	N=13 4.1±2.3	N=26 4.8±2.2
FTND questionnaire – no. (%)						
mild	1 (5.9%)	1 (8.3%)	2 (6.9%)	2 (15.4%)	5 (38.5%)	7 (26.9%)
moderate	8 (47.1%)	4 (33.3%)	12 (41.4%)	7 (53.9%)	5 (38.5%)	12 (46.2%)
severe	8 (47.1%)	7 (58.3%)	15 (51.7%)	4 (30.8%)	3 (23.1%)	7 (26.9%)
overall	17 (100%)	12 (100%)	29 (100%)	13 (100%)	13 (100%)	26 (100%)

Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)

Note: Two and five subjects enrolled but not randomized in study ZHRX-EX-01 and ZHRX-PK-02, respectively, are not included in this analysis.

2.7.4.2 Adverse Events

2.7.4.2.1 Analysis of Adverse Events

2.7.4.2.1.1 Common Adverse Events

In the studies included in this clinical safety summary, the most commonly reported AEs, (incidence rate >10%), were nausea, dizziness, headache, and dyspepsia (reported in 6 out of 9 studies), followed by pharyngeal pain, dry mouth, diarrhea, vertigo, and facial pain (reported in 4 out of 9 studies).

The frequency and percentage of subjects with AEs and the incidence of AEs were calculated for each preferred term. Summaries are provided for each study arm within each study. The most common conditions reported by SOC were disorders of the nervous system, gastrointestinal disorders and respiratory, thoracic and mediastinal disorders.

Among the most commonly reported AEs, most were reported evenly between study arms in most of the studies.

The majority of AEs were either mild and moderate in severity, resolved promptly, and were most frequently considered to be unrelated to the investigational product or study procedures. Only five AEs were reported as severe.

In four out of nine studies, 13 subjects were withdrawn from the studies due to AEs. All of these AEs were resolved during the follow up period (see Section 2.7.4.3.4).

Seven SAEs were reported, representing less than 1% of subjects exposed to EHCSS Series JLI, THS 1.0, or THS 2.1.

A review of safety data reported in the studies to date revealed no meaningful safety concerns with the investigational products.

Safety data from individual and pooled studies are presented in Section 2.7.4.2.

2.7.4.2.1.2 Deaths

No deaths occurred in any of the studies.

2.7.4.2.1.3 Other Serious Adverse Events

EHCSS Series JLI

Four SAEs occurred in clinical study EHCJLI/02/02 and 2 subjects discontinued the study due to AEs (urticaria and appendicitis).The SAEs and AEs leading to discontinuation from the study all occurred in the EHCSS JLI group and were considered unrelated to the IP and study procedures.

One female subject experienced the SAE of appendicitis on Day 267, preceded by the AEs of abdominal pain, nausea, tremor and vomiting.

One female subject experienced the SAE of neck pain (verbatim term “cervical neck pain”) on Day 266.

One female subject experienced the SAE of appendicitis on Day 266.

One female subject experienced the SAE of severe headache on Day 328.

THS 1.0

Three SAEs were reported in l Study CS-0602. One SAE occurred prior to randomization and there was no THS use. A detailed description of those SAEs can be found in Section 2.7.4.2.2 of this document.

PMI000001: This SAE was an acute myocardial infarction (CS0602 subject #0609) during screening period, and the subject was not randomized into the study.

PMI000002: This SAE was a post-traumatic splenic injury (CS06-02 subject #0058) not related to the investigational or comparison product.

PMI000003: This SAE was an upper extremity deep vein thrombosis (DVT), which occurred one week post-study in a male subject (CS06-02 – subject #0336) in the THS 1.0 study arm.

Detailed narratives of all SAEs are provided in Section 2.7.4.2.2 and in the individual CSRs.

2.7.4.2.1.4 Other Significant Adverse Events

No other significant AEs occurred during the studies.

2.7.4.2.1.5 Analysis of Adverse Events by Study

1) Studies with EHCSS JLI

Clinical Study EHCJLI/01/02

No serious or severe AEs were reported and there were no withdrawals from the study due to an AE. Overall, a total of 121 AEs were reported by 46 of the 100 subjects (46%) during the study. Headache was the most common AE reported (17 of 100 subjects [17%]). Of the 33 headache events, 18 were mild in severity and 15 were moderate. The remaining AEs were reported by 9 or fewer subjects (≤9%) each. The Investigator considered all AEs to be unrelated to the investigational product or study procedures.

A brief summary of AEs for study EHCJLI/01/02 (US) on THS1.0 is presented in Table 21.

Table 21 - Summary of Adverse Events for the EHCJLI/01/02 Study

	Study Arms				Pooled Groups	
	JLI[1] (N=40)	CC ML[2] (N=20)	CC MU[3] (N=20)	SA (N=20)	Overall CC (N=40)	Overall (N=100)
Subjects with adverse events	27 (68%)	6 (30%)	9 (45%)	4 (20%)	15 (38%)	46 (46%)
Number of adverse events	71	18	24	8	42	121
Subjects with serious adverse events	---	---	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---	---	---
Adverse events related to IP						
Yes	---	---	--	---	---	---
No	27 (68%) [71]	6 (30%) [18]	9 (45%) [24]	4 (20%) [8]	15 (38%) [42]	46 (46%) [121]

Coded using MedDRA version 4.0

AE reporting period = 8 days

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied

Note (1) JLI = pooled summary of Accord JLI controlled smoking (limited maximum number of cigarettes/day) and Accord JLI uncontrolled smoking (smoking was capped at 60 cigarettes/day)

Note (2) ML = Marlboro Light controlled smoking (limited maximum number of cigarettes/day)

Note (3) MU = Merit Ultima controlled smoking (limited maximum number of cigarettes/day)

Clinical Study EHCJLI/02/02

Four serious and five severe AEs were reported during this study. Overall, a total of 268 AEs were reported by 65 (67%) of the 97 subjects. Headache was the most common AE during the study, reported by 27 (28%) of 97 subjects. The severe AEs were: hand fracture, jaw fracture, headache, toothache, and vomiting. All AEs of severe intensity occurred in the EHCSS ACCORD® JLI group and were considered unlikely or unrelated to the investigational product.

Overall the Investigator considered 34 of the 268 AEs to be possibly or probably related to the investigational product. All remaining AEs in this study were considered to be unlikely or unrelated to the investigational product.

Four SAEs (neck pain, headache, and two episodes of appendicitis) occurred in the EHCSS ACCORD® JLI group (all considered unrelated to study “Treatment”). Two subjects discontinued the study due to AEs (urticaria and appendicitis which were both considered unrelated to the investigational product. Serious AEs and AEs leading to study discontinuation are discussed further in the Analysis of Adverse Events section of this report.

A high-level summary of AEs for study EHCJLI/02/02 (US) is presented in Table 22.

Table 22 - Summary of Adverse Events EHCJLI/02/02

	Study Arms		Pooled Groups
	EHCSS JLI[(1)] (N=64)	**MUL[(2)] (N=33)**	**Overall (N=97)**
Subjects with adverse events	40 (63%)	25 (76%)	65 (67%)
Number of adverse events	161	107	268
Subjects with serious adverse events	4 (6%)	---	4 (4%)
Subjects discontinued due to adverse events	2 (3%)	---	2 (2%)
Adverse events related to IP			
Yes	10 (16%) [23]	6 (18%) [11]	16 (16%) [34]
No	30 (47%) [138]	19 (58%) [96]	49 (51%) [234]

Coded using MedDRA version 6.0

AE reporting period = 52 weeks

* Only AEs occurring during the in-house clinical conduct phase of the clinical trials were recorded in the CRF. Once subjects were discharged from the clinical, AEs were not captured.

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied

Note (1) EHCSS JLI = Electrically Heated Cigarette Smoking System (EHCSS) JLI using JLI cigarettes with unrestricted smoking

Note (2) MUL = Marlboro Ultra-Light with unrestricted smoking

2) Studies with THS 1.0

Clinical Study EHCK6/01/03

No serious or severe AEs were reported and there were no withdrawals from the study due to an AE. A total of 76 AEs were reported by 45 (38%) of the 120 subjects. Headache was the most common AE reported during this study. It was reported in 19 (16%) of 120 subjects. Of the 31 events, 4 were mild in severity and 27 were moderate. The remaining AEs were reported by 8 or fewer subjects (7%) each. The Investigator considered an AE of wheezing in the Marlboro LIGHTS group to be possibly related to study treatment and considered all remaining AEs to be unlikely or unrelated to study treatment.

A high level summary of AEs for study EHCK6/01/03 (US) is presented in Table 23.

Table 23 - Summary of Exposure Emergent Adverse Events in EHCK6/01/03 (US) by Specific Arm

	Study Arms				Pooled Groups	
	THS 1.0[(1)] (N=60)	CC ML[(2)] (N=20)	CC MUL[(3)] (N=20)	SA (N=20)	Overall CC (N=40)	Overall (N=120)
Subjects with adverse events	25 (42%)	8 (40%)	7 (35%)	5 (25%)	15 (38%)	45 (38%)
Number of adverse events	41	19	8	8	27	75
Subjects with serious adverse events	---	---	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---	---	---
Adverse events related to IP						
Yes	---	1 (5%) [1]	---	---	1 (3%) [1]	1 (1%) [1]
No	25 (42%) [41]	7 (35%) [18]	7 (35%) [8]	5 (25%) [8]	14 (35%) [26]	44 (37%) [75]

Coded using MedDRA version 6.0

AE reporting period = 8 days

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied

(1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

(2) ML = Marlboro Light controlled smoking (limited maximum number of cigarettes/day)

(3) MUL = Marlboro Ultra-Light controlled smoking (limited maximum number of cigarettes/day)

Clinical Study SPA 04-01

No serious or severe AEs were reported and there were no withdrawals from the study due to an AE. Overall, 55 of 160 subjects (34%) reported one or more AEs (92 AE episodes in total) after enrollment in the study. The numbers of subjects reporting AEs per study group were, 13 (40.6%), 4 (12.5%), 9 (28.1%), 16 (50.0%), and 11 (34.4%) for study groups THS 1.0, K3, M6, PM1, and NS in that order. The majority of the AEs reported were of mild severity, and all except two (PM1: 1subject with dyspepsia and vomiting) were judged to be not related to the investigational products by the investigator. The overall most common system organ classes (SOCs) reported were nervous system disorders (20 subjects, 12.5%), gastrointestinal disorders (19 subjects, 11.9%) and respiratory, thoracic, and mediastinal disorders (10 subjects, 6.3%). Clinically significant increases in transaminase levels, not related to study products or procedures were reported for 4 subjects (THS 1.0, K3, M6 and NS groups). Clinically significant abnormalities in vital signs or ECG assessments were not reported during the course of this study. Overall, there were no trends related to the study products observed in the AE reports, in clinical laboratory, vital signs, ECG, and physical examinations.

A brief summary of AEs, the incidence of AEs by specific arm, and SOC and the incidence of AEs in clinical study SPA 01-04 on THS1.0 by specific arm and related AEs reported for the safety population are presented in Table 24, Table 25 and Table 26, respectively.

Table 24 - Summary of Exposure Emergent Adverse Events in SPA04-01 (UK) by Specific Arm

	Study Arms					Pooled Groups	
	K3[1] (N=32)	THS 1.0[2] (N=32)	CC PM1[3] (N=32)	CC M6[4] (N=32)	SA[5] (N=32)	Overall CC (N=64)	Overall (N=160)
Subjects with adverse events	4 (13%)	13 (41%)	17 (53%)	10 (31%)	11 (34%)	27 (42%)	55 (34%)
Number of adverse events	6	19	33	18	16	51	92
Subjects with serious adverse events	---	---	---	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---	---	---	---
Severity (all adverse events)*							
Mild	4 (13%) [6]	12 (38%) [18]	14 (44%) [30]	8 (25%) [16]	8 (25%) [11]	22 (34%) [46]	46 (29%) [81]
Moderate	---	1 (3%) [1]	3 (9%) [3]	2 (6%) [2]	3 (9%) [5]	5 (8%) [5]	9 (6%) [11]
Severe	---	---	---	---	---	---	---
Total	4 (13%) [6]	13 (41%) [19]	17 (53%) [33]	10 (31%) [18]	11 (34%) [16]	27 (42%) [51]	55 (34%) [92]
Adverse events related to IP *							
Yes	---	---	1 (3%) [2]	---	---	1 (2%) [2]	1 (1%) [2]
No	4 (13%) [6]	13 (41%) [19]	16 (50%) [31]	10 (31%) [18]	11 (34%) [16]	26 (41%) [49]	54 (34%) [90]
Severity (Related AEs)*							
Mild	---	---	1 (3%) [2]	---	---	1 (2%) [2]	1 (1%) [2]
Moderate	---	---	---	---	---	---	---
Severe	---	---	---	---	---	---	---
Total	---	---	1 (3%) [2]	---	---	1 (2%) [2]	1 (1%) [2]

	Study Arms					Pooled Groups	
	K3[(1)] (N=32)	THS 1.0[(2)] (N=32)	CC PM1[(3)] (N=32)	CC M6[(4)] (N=32)	SA[(5)] (N=32)	Overall CC (N=64)	Overall (N=160)

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied

* Frequency of subjects by relationship and/or severity

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC PM1 = Phillip Morris One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Table 25 - Incidence of AEs in SPA04-01 (UK) by Specific Arm - All Causalities

	Study Arms					Pooled Groups	
Characteristic	K3[1] (N=32)	THS 1.0[2] (N=32)	CC PM1[3] (N=32)	CC M6[4] (N=32)	SA[5] (N=32)	Overall CC (N=64)	Overall (N=160)
Total no. Subjects with AE	4 (13%, 4-29) [6]	13 (41%, 24-59) [19]	17 (53%, 29-65) [33]	10 (31%, 16-50) [18]	11 (34%, 19-53) [16]	27 (42%, 30-55) [51]	55 (34%, 27-42) [92]
Gastrointestinal disorders	1 (3%, 0-16) [2]	3 (9%, 2-25) [4]	6 (19%, 7-36) [11]	8 (25%, 11-43) [9]	4 (13%, 4-29) [8]	14 (22%, 13-34) [20]	22 (14%, 9-20) [34]
Dyspepsia	---	1 (3%, 0-16) [1]	2 (6%, 1-21) [2]	---	3 (9%, 2-25) [5]	2 (3%, 0-11) [2]	6 (4%, 1-8) [8]
Abdominal discomfort	---	1 (3%, 0-16) [1]	---	2 (6%, 1-21) [3]	1 (3%, 0-16) [1]	2 (3%, 0-11) [3]	4 (3%, 1-6) [5]
Abdominal pain upper	---	1 (3%, 0-16) [1]	1 (3%, 0-16) [1]	2 (6%, 1-21) [2]	---	3 (5%, 1-13) [3]	4 (3%, 1-6) [4]
Constipation	---	---	2 (6%, 1-21) [2]	2 (6%, 1-21) [2]	---	4 (6%, 2-15) [4]	4 (3%, 1-6) [4]
Vomiting	---	---	1 (3%, 0-16) [1]	2 (6%, 1-21) [2]	1 (3%, 0-16) [1]	3 (5%, 1-13) [3]	4 (3%, 1-6) [4]
Toothache	---	---	1 (3%, 0-16) [2]	---	1 (3%, 0-16) [1]	1 (2%, 0-8) [2]	2 (1%, 0-4) [3]
Diarrhoea	---	---	1 (3%, 0-16) [2]	---	---	1 (2%, 0-8) [2]	1 (1%, 0-3) [2]
Gingival bleeding	1 (3%, 0-16) [2]	---	---	---	---	---	1 (1%, 0-3) [2]
Nausea	---	1 (3%, 0-16) [1]	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	2 (1%, 0-4) [2]
Nervous system disorders	1 (3%, 0-16) [1]	7 (22%, 9-40) [9]	7 (22%, 9-40) [7]	1 (3%, 0-16) [1]	4 (13%, 4-29) [4]	8 (13%, 6-23) [8]	20 (13%, 8-19) [22]
Headache	1 (3%, 0-16) [1]	6 (19%, 7-36) [8]	5 (16%, 5-33) [5]	1 (3%, 0-16) [1]	3 (9%, 2-25) [3]	6 (9%, 4-19) [6]	16 (10%, 6-16) [18]
Dizziness	---	1 (3%, 0-16) [1]	2 (6%, 1-21) [2]	---	1 (3%, 0-16) [1]	2 (3%, 0-11) [2]	4 (3%, 1-6) [4]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC PM1 = Phillip Morris One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Table 25- Incidence of AEs in SPA04-01 (UK) by Specific Arm - All Causalities (cont.)

	Study Arms					Pooled Groups	
Characteristic	K3[1] (N=32)	THS 1.0[2] (N=32)	CC PM1[3] (N=32)	CC M6[4] (N=32)	SA[5] (N=32)	Overall CC (N=64)	Overall (N=160)
Respiratory, thoracic and mediastinal disorders	1 (3%, 0-16) [1]	---	8 (25%, 11-43) [8]	2 (6%, 1-21) [3]	---	10 (16%, 8-27) [11]	11 (7%, 3-12) [12]
Oropharyngeal pain	---	---	7 (22%, 9-40) [7]	2 (6%, 1-21) [2]	---	9 (14%, 7-25) [9]	9 (6%, 3-10) [9]
Cough	---	---	---	1 (3%, 0-16) [1]	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Epistaxis	1 (3%, 0-16) [1]	---	---	---	---	---	1 (1%, 0-3) [1]
Nasal obstruction	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Skin and subcutaneous tissue disorders	1 (3%, 0-16) [1]	1 (3%, 0-16) [1]	2 (6%, 1-21) [2]	2 (6%, 1-21) [3]	1 (3%, 0-16) [1]	4 (6%, 2-15) [5]	7 (4%, 2-9) [8]
Dry skin	---	---	1 (3%, 0-16) [1]	2 (6%, 1-21) [2]	---	3 (5%, 1-13) [3]	3 (2%, 0-5) [3]
Rash	---	---	---	1 (3%, 0-16) [1]	1 (3%, 0-16) [1]	1 (2%, 0-8) [1]	2 (1%, 0-4) [2]
Dermatitis acneiform	---	1 (3%, 0-16) [1]	---	---	---	---	1 (1%, 0-3) [1]
Erythema	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Rash maculo-papular	1 (3%, 0-16) [1]	---	---	---	---	---	1 (1%, 0-3) [1]
General disorders and administration site conditions	---	1 (3%, 0-16) [1]	2 (6%, 1-21) [2]	1 (3%, 0-16) [1]	1 (3%, 0-16) [1]	3 (5%, 1-13) [3]	5 (3%, 1-7) [5]
Feeling hot	---	---	2 (6%, 1-21) [2]	---	---	2 (3%, 0-11) [2]	2 (1%, 0-4) [2]
Asthenia	---	---	---	1 (3%, 0-16) [1]	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Local swelling	---	1 (3%, 0-16) [1]	---	---	---	---	1 (1%, 0-3) [1]
Vessel puncture site reaction	---	---	---	---	1 (3%, 0-16) [1]	---	1 (1%, 0-3) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC PM1 = Phillip Morris One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Table 25 - Incidence of AEs in SPA04-01 (UK) by Specific Arm - All Causalities (cont.)

	Study Arms					Pooled Groups	
Characteristic	K3[1] (N=32)	THS 1.0[2] (N=32)	CC PM1[3] (N=32)	CC M6[4] (N=32)	SA[5] (N=32)	Overall CC (N=64)	Overall (N=160)
Investigations	1 (3%, 0-16) [1]	1 (3%, 0-16) [2]	---	---	1 (3%, 0-16) [2]	---	3 (2%, 0-5) [5]
Alanine aminotransferase increased	1 (3%, 0-16) [1]	1 (3%, 0-16) [1]	---	---	1 (3%, 0-16) [1]	---	3 (2%, 0-5) [3]
Aspartate aminotransferase increased	---	1 (3%, 0-16) [1]	---	---	1 (3%, 0-16) [1]	---	2 (1%, 0-4) [2]
Infections and infestations	---	2 (6%, 1-21) [2]	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	3 (2%, 0-5) [3]
Oral herpes	---	1 (3%, 0-16) [1]	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	2 (1%, 0-4) [2]
Candidiasis	---	1 (3%, 0-16) [1]	---	---	---	---	1 (1%, 0-3) [1]
Injury, poisoning and procedural complications	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Thermal burn	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Reproductive system and breast disorders	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Dysmenorrhoea	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Vascular disorders	---	---	---	1 (3%, 0-16) [1]	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Flushing	---	---	---	1 (3%, 0-16) [1]	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC PM1 = Phillip Morris One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Table 26- Incidence of AEs in SPA04-01 (UK) by Specific Arm Related AEs

	Study Arms					Pooled Groups	
Characteristic	K3[1] (N=32)	THS 1.0[2] (N=32)	CC PM1[3] (N=32)	CC M6[4] (N=32)	SA[5] (N=32)	Overall CC (N=64)	Overall (N=160)
Total no. Subjects with AE	0 (0%) [0]	0 (0%) [0]	1 (3%, 0-16) [2]	0 (0%) [0]	0 (0%) [0]	1 (2%, 0-8) [2]	1 (1%, 0-3) [2]
Gastrointestinal disorders	---	---	1 (3%, 0-16) [2]	---	---	1 (2%, 0-8) [2]	1 (1%, 0-3) [2]
Dyspepsia	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]
Nausea	---	---	1 (3%, 0-16) [1]	---	---	1 (2%, 0-8) [1]	1 (1%, 0-3) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC PM1 = Phillip Morris One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Clinical Study SPA 05-01

Overall there were 12 AEs reported in 9 (7%) out of 128 subjects included in the safety population after randomization. None of the AEs reported were severe or serious or led to the subjects' withdrawal from the study. None of these AEs was considered related to the product tested by the Investigator. All AEs observed in the study resolved rapidly except two of them:

A brief summary of AEs, the incidence of AEs by specific arm, and SOC and the incidence of AEs in clinical study SPA 05-01 on THS1.0 by specific arm and related AEs reported for the safety population are presented in Table 27, Table 28, and Table 29, respectively.

Table 27 - Summary of Exposure Emergent Adverse Events in SPA05-01 (JPN) by Specific Arm

	Study Arms					Pooled Groups	
	K3[1] (N=28)	THS 1.0[2] (N=28)	CC L1[3] (N=28)	CC M6[4] (N=28)	SA[5] (N=16)	Overall CC (N=56)	Overall (N=128)
Subjects with adverse events	2 (7%)	1 (4%)	3 (11%)	2 (7%)	1 (6%)	5 (9%)	9 (7%)
Number of adverse events	2	2	4	2	2	6	12
Subjects with serious adverse events	---	---	---	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---	---	---	---
Severity (all adverse events)*							
Mild	2 (7%) [2]	1 (4%) [2]	3 (11%) [4]	---	1 (6%) [2]	3 (5%) [4]	7 (5%) [10]
Moderate	---	---	---	2 (7%) [2]	---	2 (4%) [2]	2 (2%) [2]
Severe	---	---	---	---	---	---	---
Total	2 (7%) [2]	1 (4%) [2]	3 (11%) [4]	2 (7%) [2]	1 (6%) [2]	5 (9%) [6]	9 (7%) [12]
Adverse events related to IP*							
Yes	---	---	---	---	---	---	---
No	2 (7%) [2]	1 (4%) [2]	3 (11%) [4]	2 (7%) [2]	1 (6%) [2]	5 (9%) [6]	9 (7%) [12]
Severity (Related AEs)*							
Mild	---	---	---	---	---	---	---
Moderate	---	---	---	---	---	---	---
Severe	---	---	---	---	---	---	---
Total	---	---	---	---	---	---	---

	Study Arms					Pooled Groups	
	K3[(1)] (N=28)	THS 1.0[(2)] (N=28)	CC L1[(3)] (N=28)	CC M6[(4)] (N=28)	SA[(5)] (N=16)	Overall CC (N=56)	Overall (N=128)

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied

* Frequency of subjects by greatest relationship and/or severity

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC L1 = Lark One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Table 28 - Incidence of AEs in SPA05-01 (JPN) by Specific Arm All Causalities

	Study Arms					Pooled Group	
Characteristic	K3[1] (N=28)	THS 1.0[2] (N=28)	CC L1[3] (N=28)	CC M6[4] (N=28)	SA[5] (N=16)	Overall CC (N=56)	Overall (N=128)
Total no. Subjects with AE	2 (7%, 1-24) [2]	1 (4%, 0-18) [2]	3 (11%, 2-28) [4]	2 (7%, 1-24) [2]	1 (6%, 0-30) [2]	5 (9%, 3-20) [6]	9 (7%, 3-13) [12]
Investigations	2 (7%, 1-24) [2]	1 (4%, 0-18) [2]	3 (11%, 2-28) [4]	---	1 (6%, 0-30) [2]	3 (5%, 1-15) [4]	7 (5%, 2-11) [10]
Alanine aminotransferase increased	---	1 (4%, 0-18) [1]	2 (7%, 1-24) [2]	---	---	2 (4%, 0-12) [2]	3 (2%, 0-7) [3]
Aspartate aminotransferase increased	1 (4%, 0-18) [1]	1 (4%, 0-18) [1]	---	---	---	---	2 (2%, 0-6) [2]
Blood bilirubin increased	---	---	1 (4%, 0-18) [1]	---	1 (6%, 0-30) [1]	1 (2%, 0-10) [1]	2 (2%, 0-6) [2]
White blood cell count increased	---	---	1 (4%, 0-18) [1]	---	1 (6%, 0-30) [1]	1 (2%, 0-10) [1]	2 (2%, 0-6) [2]
White blood cells urine positive	1 (4%, 0-18) [1]	---	---	---	---	---	1 (1%, 0-4) [1]
Reproductive system and breast disorders	---	---	---	2 (7%, 1-24) [2]	---	2 (4%, 0-12) [2]	2 (2%, 0-6) [2]
Dysmenorrhoea	---	---	---	2 (7%, 1-24) [2]	---	2 (4%, 0-12) [2]	2 (2%, 0-6) [2]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC L1 = Lark One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Table 29 - Incidence of AEs in SPA05-01 (JPN) by Specific Arm Related AEs

	Study Arms					Pooled Group	
Characteristic	K3[1] (N=28)	THS 1.0[2] (N=28)	CC L1[3] (N=28)	CC M6[4] (N=28)	SA[5] (N=16)	Overall CC (N=56)	Overall (N=128)
Total no. Subjects with AE	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) EHCSS K3 = Electrically Heated Cigarette Smoking System (EHCSS) using K3 cigarettes with controlled smoking (limited maximum number of cigarettes/day)

Note (2) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (3) CC L1 = Lark One controlled smoking (limited maximum number of cigarettes/day)

Note (4) CC M6 = Marlboro 6mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (5) SA = Smoking Abstinence

Clinical Study SPA 05-03

Of the 100 subjects included in the safety population, three subjects (3%) reported an AE. In total, 3 AEs were reported. None of the AEs reported was severe or serious or was considered related to the investigational product by the Investigator or related to study procedure. None led to subjects' withdrawal from the study. All AEs observed in the study resolved rapidly within 1 to 3 days. Initiation of a specific therapy was required for two cases: post-traumatic headache and painful menses.

A brief summary of AEs, the incidence of AEs by specific arm, and SOC and the incidence of AEs in clinical study SPA 05-03 on THS1.0 by specific arm and related AEs reported for the safety population are presented in Table 30, Table 31, and Table 32, respectively.

Table 30 - Summary of Exposure Emergent Adverse Events in SPA05-03 (JPN) by Specific Arm

	Study Arms				Pooled Groups	
	THS 1.0[(1)] (N=28)	CC LM1[(2)] (N=28)	CC MM4[(3)] (N=28)	SA[(4)] (N=16)	Overall CC (N=56)	Overall (N=100)
Subjects with adverse events	0 (0%)	2 (7%)	1 (4%)	0 (0%)	3 (5%)	3 (3%)
Number of adverse events	0	2	1	0	3	3
Subjects with serious adverse events	---	---	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---	---	---
Severity (all adverse events)*						
Mild	---	1 (4%) [1]	---	---	1 (2%) [1]	1 (1%) [1]
Moderate	---	1 (4%) [1]	1 (4%) [1]	---	2 (4%) [2]	2 (2%) [2]
Severe	---	---	---	---	---	---
Total	---	2 (7%) [2]	1 (4%) [1]	---	3 (5%) [3]	3 (3%) [3]
Adverse events related to IP *						
Yes	---	---	---	---	---	---
No	---	2 (7%) [2]	1 (4%) [1]	---	3 (5%) [3]	3 (3%) [3]
Severity (Related AEs)*						
Mild	---	---	---	---	---	---
Moderate	---	---	---	---	---	---
Severe	---	---	---	---	---	---
Total	---	---	---	---	---	---

	Study Arms				Pooled Groups	
	THS 1.0[(1)] (N=28)	CC LM1[(2)] (N=28)	CC MM4[(3)] (N=28)	SA[(4)] (N=16)	Overall CC (N=56)	Overall (N=100)

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied
* Frequency of subjects by greatest relationship and/or severity
Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day
Note (2) CC LM1 = Lark Menthol 1mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)
Note (3) CC MM4 = Marlboro Menthol 4mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)
Note (4) SA = Smoking Abstinence

Table 31 - Incidence of AEs in SPA05-03 (JPN) by Specific Arm - All Causalities

	Study Arms				Pooled Group	
Characteristic	THS 1.0[(1)] (N=28)	CC LM1[(2)] (N=28)	CC MM4[(3)] (N=28)	SA[(4)] (N=16)	Overall CC (N=56)	Overall (N=100)
Total no. Subjects with AE	0 (0%) [0]	2 (7%, 1-24) [2]	1 (4%, 0-18) [1]	0 (0%) [0]	3 (5%, 1-15) [3]	3 (3%, 1-9) [3]
Investigations	---	1 (4%, 0-18) [1]	---	---	1 (2%, 0-10) [1]	1 (1%, 0-5) [1]
Protein urine present	---	1 (4%, 0-18) [1]	---	---	1 (2%, 0-10) [1]	1 (1%, 0-5) [1]
Nervous system disorders	---	---	1 (4%, 0-18) [1]	---	1 (2%, 0-10) [1]	1 (1%, 0-5) [1]
Post-traumatic headache	---	---	1 (4%, 0-18) [1]	---	1 (2%, 0-10) [1]	1 (1%, 0-5) [1]
Reproductive system and breast disorders	---	1 (4%, 0-18) [1]	---	---	1 (2%, 0-10) [1]	1 (1%, 0-5) [1]
Dysmenorrhoea	---	1 (4%, 0-18) [1]	---	---	1 (2%, 0-10) [1]	1 (1%, 0-5) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day
Note (2) CC LM1 = Lark Menthol 1mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)
Note (3) CC MM4 = Marlboro Menthol 4mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)
Note (4) SA = Smoking Abstinence

Table 32 - Incidence of AEs in SPA05-03 (JPN) by Specific Arm Related AEs

	Study Arms				Pooled Group	
Characteristic	THS 1.0[(1)] (N=28)	CC LM1[(2)] (N=28)	CC MM4[(3)] (N=28)	SA[(4)] (N=16)	Overall CC (N=56)	Overall (N=100)
Total no. Subjects with AE	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC LM1 = Lark Menthol 1mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (3) CC MM4 = Marlboro Menthol 4mg ISO Tar controlled smoking (limited maximum number of cigarettes/day)

Note (4) SA = Smoking Abstinence

Clinical Study CS 06-02

Overall, 299 AEs were recorded in this study. A similar percentage of subjects reported AEs in the THS 1.0 and CC study arms at 53% and 58%, respectively. The majority of AEs were mild or moderate in intensity. A total of seven AEs reported were severe. These included increased triglyceride levels on two occasions in one subject and single episodes of toothache, ischialgia, post-traumatic spleen injury, and arterial hypertension in the THS 1.0 study arm and a single episode of menstruation pain in the CC study arm. None of these severe AEs were considered related to the investigational product.

Of the total number of AEs, those that occurred in greater than 5% of subjects in the K6 or CC study arms were nasopharyngitis, headache, increased CRP, increased blood fibrinogen, decreased neutrophil count, rhinitis, and increased COHb levels. None of these AEs was severe or serious, or considered related to the study procedures.

Overall, the SOC of "investigations" was the most frequently reported category, with a total of 60 subjects (25%) in the K6 study arm and 22 subjects (28%) in the CC study arm reporting AEs. The most frequent of these were increased CRP, increased fibrinogen, and decreased neutrophil count, all of which were mild in severity with the exception of one finding of increased CRP which was moderate in severity

A total of eight out of 225 AEs (4% of AEs) were considered related to the THS 1.0. None out of 74 AEs were considered related to CC.

One subject from the safety population was withdrawn due to AEs.

A brief summary of AEs, the incidence of AEs by specific arm, and SOC and the incidence of AEs in CS06-02 (EU) on THS1.0 by specific arm and related AEs reported for the safety population is presented in Table 33, Table 34, and Table 35, respectively.

Table 33 - Summary of Exposure Emergent Adverse Events in CS06-02 (EU) by Specific Arm

	Study Arms		Pooled Group
	THS 1.0[(1)] (N=237)	CC[(2)] (N=79)	Overall (N=316)
Subjects with adverse events	125 (53%)	46 (58%)	171 (54%)
Number of adverse events	225	74	299
Subjects with serious adverse events[3]	2 (1%) [2]	---	2 (1%) [2]
Subjects discontinued due to adverse events	---	1 (1%) [2]	1 (0%) [2]
Severity (all adverse events)*			
Mild	81 (34%) [169]	29 (37%) [55]	110 (35%) [224]
Moderate	40 (17%) [50]	16 (20%) [18]	56 (18%) [68]
Severe	4 (2%) [6]	1 (1%) [1]	5 (2%) [7]
Total	125 (53%) [225]	46 (58%) [74]	171 (54%) [299]
Adverse events related to IP*			
Yes	8 (3%) [8]	---	8 (3%) [8]
No	117 (49%) [217]	46 (58%) [74]	163 (52%) [291]
Severity (Related AEs)*			
Mild	5 (2%) [5]	---	5 (2%) [5]
Moderate	3 (1%) [3]	---	3 (1%) [3]
Severe	---	---	---
Total	8 (3%) [8]	---	8 (3%) [8]

	Study Arms		Pooled Group
	THS 1.0(1) (N=237)	CC(2) (N=79)	Overall (N=316)

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied
Data includes all Adverse Events reported by subjects in the safety population, including those reported prior to Product usage
* Frequency of subjects by greatest relationship and/or severity

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC = Own preferred brand of conventional cigarettes

Note (3) SAE (PMI000001) was an acute myocardial infarction (CS0602 subject #0609) during the screening period and the subject was not randomized into the study and therefore not included in the ssafety population. Therefore the count of SAEs in CS 06-02 is hear reported as two SAEs

Table 34 - Incidence of AEs in CS06-02 (EU) by Specific Arm All Causalities

Characteristic	Study Arms		Pooled Group
	THS 1.0[(1)] (N=237)	CC[(2)] (N=79)	Overall (N=316)
Total no. Subjects with AE	125 (53%, 41-54) [225]	46 (58%, 31-53) [74]	171 (54%, 40-52) [299]
Investigations	60 (25%, 20-31) [98]	22 (28%, 18-39) [33]	82 (26%, 21-31) [131]
C-reactive protein increased	22 (9%, 6-14) [23]	9 (11%, 5-21) [11]	31 (10%, 7-14) [34]
Blood fibrinogen increased	21 (9%, 6-13) [24]	7 (9%, 4-17) [7]	28 (9%, 6-13) [31]
Blood triglycerides increased	9 (4%, 2-7) [15]	---	9 (3%, 1-5) [15]
Neutrophil count decreased	5 (2%, 1-5) [6]	4 (5%, 1-12) [5]	9 (3%, 1-5) [11]
Carboxyhaemoglobin increased	2 (1%, 0-3) [2]	5 (6%, 2-14) [6]	7 (2%, 1-5) [8]
Blood bilirubin increased	5 (2%, 1-5) [5]	1 (1%, 0-7) [1]	6 (2%, 1-4) [6]
Neutrophil count increased	4 (2%, 0-4) [4]	1 (1%, 0-7) [1]	5 (2%, 1-4) [5]
Blood cholesterol increased	3 (1%, 0-4) [4]	---	3 (1%, 0-3) [4]
Interleukin level increased	4 (2%, 0-4) [4]	---	4 (1%, 0-3) [4]
White blood cell count increased	3 (1%, 0-4) [3]	---	3 (1%, 0-3) [3]
Alanine aminotransferase increased	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Aspartate aminotransferase increased	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Haemoglobin decreased	---	2 (3%, 0-9) [2]	2 (1%, 0-2) [2]
Blood homocysteine increased	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Lymphocyte count decreased	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Platelet count decreased	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Red blood cells urine positive	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data includes all Adverse Events reported by subjects in the safety population, including those reported prior to Product usage

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC = Own preferred brand of conventional cigarettes

Table 34 - Incidence of AEs in CS06-02 (EU) by Specific Arm All Causalities (Con't)

Characteristic	Study Arms		Pooled Group
	THS 1.0[(1)] (N=237)	CC[(2)] (N=79)	Overall (N=316)
Infections and infestations	36 (15%, 11-20) [41]	14 (18%, 10-28) [15]	50 (16%, 12-20) [56]
Nasopharyngitis	26 (11%, 7-16) [28]	8 (10%, 4-19) [9]	34 (11%, 8-15) [37]
Rhinitis	9 (4%, 2-7) [10]	4 (5%, 1-12) [4]	13 (4%, 2-7) [14]
Asymptomatic bacteriuria	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Influenza	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]
Laryngitis	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]
Urinary tract infection	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Nervous system disorders	25 (11%, 7-15) [27]	9 (11%, 5-21) [9]	34 (11%, 8-15) [36]
Headache	23 (10%, 6-14) [24]	9 (11%, 5-21) [9]	32 (10%, 7-14) [33]
Hypoaesthesia	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Migraine	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Sciatica	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Gastrointestinal disorders	13 (5%, 3-9) [14]	2 (3%, 0-9) [2]	15 (5%, 3-8) [16]
Toothache	4 (2%, 0-4) [5]	---	4 (1%, 0-3) [5]
Dry mouth	4 (2%, 0-4) [4]	---	4 (1%, 0-3) [4]
Abdominal pain	1 (0%, 0-2) [1]	1 (1%, 0-7) [1]	2 (1%, 0-2) [2]
Diarrhoea	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Dyspepsia	1 (0%, 0-2) [1]	1 (1%, 0-7) [1]	2 (1%, 0-2) [2]
Gastritis	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]

Characteristic	Study Arms		Pooled Group
	THS 1.0(1) (N=237)	CC(2) (N=79)	Overall (N=316)

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data includes all Adverse Events reported by subjects in the safety population, including those reported prior to Product usage

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC = Own preferred brand of conventional cigarettes

Table 34 - Incidence of AEs in CS06-02 (EU) by Specific Arm All Causalities (Con't)

Characteristic	Study Arms		Pooled Group
	THS 1.0[(1)] (N=237)	CC[(2)] (N=79)	Overall (N=316)
Musculoskeletal and connective tissue disorders	7 (3%, 1-6) [8]	5 (6%, 2-14) [5]	12 (4%, 2-7) [13]
Back pain	3 (1%, 0-4) [3]	2 (3%, 0-9) [2]	5 (2%, 1-4) [5]
Arthralgia	2 (1%, 0-3) [2]	1 (1%, 0-7) [1]	3 (1%, 0-3) [3]
Musculoskeletal pain	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Muscle contracture	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]
Musculoskeletal stiffness	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Pain in extremity	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]
Renal and urinary disorders	6 (3%, 1-5) [8]	3 (4%, 1-11) [3]	9 (3%, 1-5) [11]
Haematuria	5 (2%, 1-5) [5]	3 (4%, 1-11) [3]	8 (3%, 1-5) [8]
Leukocyturia	3 (1%, 0-4) [3]	---	3 (1%, 0-3) [3]
Reproductive system and breast disorders	6 (3%, 1-5) [6]	3 (4%, 1-11) [3]	9 (3%, 1-5) [9]
Dysmenorrhea	6 (3%, 1-5) [6]	3 (4%, 1-11) [3]	9 (3%, 1-5) [9]
Respiratory, thoracic and mediastinal disorders	7 (3%, 1-6) [8]	1 (1%, 0-7) [1]	8 (3%, 1-5) [9]
Cough	4 (2%, 0-4) [4]	1 (1%, 0-7) [1]	5 (2%, 1-4) [5]
Dry throat	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Dysphonia	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Oropharyngeal pain	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data includes all Adverse Events reported by subjects in the safety population, including those reported prior to Product usage

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC = Own preferred brand of conventional cigarettes

Table 34 - Incidence of AEs in CS06-02 (EU) by Specific Arm All Causalities (Con't)

Characteristic	Study Arms		Pooled Group
	THS 1.0[(1)] (N=237)	CC[(2)] (N=79)	Overall (N=316)
General disorders and administration site conditions	4 (2%, 0-4) [4]	---	4 (1%, 0-3) [4]
Facial pain	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Induration	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Spinal pain	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Vessel puncture site haematoma	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Blood and lymphatic system disorders	2 (1%, 0-3) [3]	---	2 (1%, 0-2) [3]
Neutropenia	1 (0%, 0-2) [2]	---	1 (0%, 0-2) [2]
Leukocytosis	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Injury, poisoning and procedural complications	2 (1%, 0-3) [3]	---	2 (1%, 0-2) [3]
Contusion	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Splenic injury	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Wound	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Metabolism and nutrition disorders	1 (0%, 0-2) [1]	1 (1%, 0-7) [1]	2 (1%, 0-2) [2]
Hyperglycaemia	1 (0%, 0-2) [1]	1 (1%, 0-7) [1]	2 (1%, 0-2) [2]
Vascular disorders	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Deep vein thrombosis	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Hypertension	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]

Characteristic	Study Arms		Pooled Group
	THS 1.0(1) (N=237)	CC(2) (N=79)	Overall (N=316)

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data includes all Adverse Events reported by subjects in the safety population, including those reported prior to Product usage

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC = Own preferred brand of conventional cigarettes

Table 34 - Incidence of AEs in CS06-02 (EU) by Specific Arm All Causalities (Con't)

Characteristic	Study Arms		Pooled Group
	THS 1.0[(1)] (N=237)	CC[(2)] (N=79)	Overall (N=316)
Ear and labyrinth disorders	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Vertigo	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Eye disorders	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Conjunctivitis	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Skin and subcutaneous tissue disorders	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]
Rash	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]
Surgical and medical procedures	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]
Dental care	---	1 (1%, 0-7) [1]	1 (0%, 0-2) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data includes all Adverse Events reported by subjects in the safety population, including those reported prior to Product usage

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC = Own preferred brand of conventional cigarettes

Table 35 - Incidence of AEs in CS06-02 (EU) by Specific Arm Related AEs

Characteristic	Study Arms		Pooled Group
	THS 1.0[(1)] (N=237)	CC[(2)] (N=79)	Overall (N=316)
Total no. Subjects with AE	8 (3%, 1-7) [8]	0 (0%) [0]	8 (3%, 1-5) [8]
Gastrointestinal disorders	4 (2%, 0-4) [4]	---	4 (1%, 0-3) [4]
Dry mouth	3 (1%, 0-4) [3]	---	3 (1%, 0-3) [3]
Diarrhoea	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Respiratory, thoracic and mediastinal disorders	3 (1%, 0-4) [3]	---	3 (1%, 0-3) [3]
Dry throat	2 (1%, 0-3) [2]	---	2 (1%, 0-2) [2]
Cough	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Vascular disorders	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]
Deep vein thrombosis	1 (0%, 0-2) [1]	---	1 (0%, 0-2) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data includes all Adverse Events reported by subjects in the safety population, including those reported prior to Product usage

Note (1) THS 1.0 = Electrically Heated Cigarette Smoking System (EHCSS) using K6 cigarettes with controlled smoking (limited maximum number of cigarettes/day

Note (2) CC = Own preferred brand of conventional cigarettes

3) Studies with THS 2.1

ZRHX-PK-02 (UK)

This was a single center open label cross over design study. No serious or severe AEs were reported and there were no withdrawals from the study due to an AE took place. Overall, there were 39 AEs reported in 17 of the 28 subjects randomized. More AEs were reported during the first study period (30 AEs in 16 subjects), than the second study period (nine AEs in five subjects). Eleven 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.

A total of six presyncope events were experienced by five subjects (one subject after THS 2.1 exposure and four subjects after CC use). The investigator suggested allowing a light breakfast before product use in future studies to prevent such events. This practice of a light breakfast prior to product use is now included in the proposed PK/PD study (ZRHR_PK_06-US).

The assessment of cough showed that the number of subjects who experienced a regular need to cough was low (≤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.

A brief summary of AEs, the incidence of AEs by specific arm, and SOC and the incidence of AEs in ZRHX-PK-02 (EU) on THS1.0 by specific arm and related AEs reported for the safety population is presented in Table 36, Table 37, and Table 38, respectively.

Study ZRHX-EX-01 (Poland)

No serious or severe AEs were reported and there were no withdrawals from the study because of an AE. Overall, there were 18 AEs reported after randomization in 14 subjects. 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.

The assessment of cough showed that the overall number of subjects who experienced a regular need to cough was l0 out of 20 subjects enrolled in THS 2.1 arm. 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.

A brief summary of AEs, the incidence of AEs by specific arm, and SOC and the incidence of AEs in ZRHX-EX-01 (EU) on THS1.0 by specific arm and related AEs reported for the safety population is presented in Table 36, Table 37, and Table 38, respectively.

Table 36 - Summary of Exposure Emergent Adverse Events in Individual Studies on THS 2.1

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
	THS 2.1[(1)] (N=28[(3)])	CC[(2)] (N=28)	Overall (N=28)	THS 2.1[(1)] (N=20)	CC[(2)] (N=20)	Overall (N=40)
Subjects with adverse events	11 (39%)	10 (36%)	17 (61%)	4 (20%)	10 (50%)	14 (35%)
Number of adverse events	23	16	39	5	13	18
Subjects with serious adverse events	---	---	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---	---	---
Severity (all adverse events)*						
Mild	8 (29%) [20]	7 (25%) [13]	11 (39%) [33]	3 (15%) [4]	5 (25%) [8]	8 (20%) [12]
Moderate	3 (11%) [3]	3 (11%) [3]	6 (21%) [6]	1 (5%) [1]	5 (25%) [5]	6 (15%) [6]
Severe	---	---	---	---	---	---
Total	11 (39%) [23]	10 (36%) [16]	17 (61%) [39]	4 (20%) [5]	10 (50%) [13]	14 (35%) [18]
Adverse events related to IP *						
Yes	5 (18%) [11]	5 (18%) [7]	9 (32%) [18]	---	4 (20%) [4]	4 (10%) [4]
No	6 (21%) [12]	5 (18%) [9]	8 (29%) [21]	4 (20%) [5]	6 (30%) [9]	10 (25%) [14]
Severity (Related AEs)*						
Mild	4 (14%) [10]	4 (14%) [6]	7 (25%) [16]	---	3 (15%) [3]	3 (8%) [3]
Moderate	1 (4%) [1]	1 (4%) [1]	2 (7%) [2]	---	1 (5%) [1]	1 (3%) [1]
Severe	---	---	---	---	---	---
Total	5 (18%) [11]	5 (18%) [7]	9 (32%) [18]	---	4 (20%) [4]	4 (10%) [4]

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
	THS 2.1[1] (N=28[3])	CC[2] (N=28)	Overall (N=28)	THS 2.1[1] (N=20)	CC[2] (N=20)	Overall (N=40)

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied. *
Frequency of subjects by greatest relationship and/or severity

Note (1) THS 2.1 = Tobacco Heating System 2.1 single and ad-libitum use

Note (2) CC = Own preferred brand of conventional cigarettes

Note (3) 28 subjects were randomized into the study and are presented in this safety summary. Five additional subjects were exposed to the THS2.1 at Admission during a product trial of up to 3 THS Tobacco Sticks, however, were not randomized in the study. The five subjects were are not included in the safety summary presented here .Two of those five subjects experienced in total three adverse events, all mild in nature.

Table 37 - Incidence of AEs in Individual Studies on THS 2.1 - All Causalities

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
Characteristic	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=28)	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=40)
Total no. Subjects with AE	11 (39%, 22-59) [23]	10 (36%, 19-56) [16]	17 (61%, 22-59) [39]	4 (20%, 6-44) [5]	10 (50%, 27-73) [13]	14 (35%, 21-52) [18]
Gastrointestinal disorders	5 (18%, 6-37) [6]	6 (21%, 8-41) [7]	10 (36%, 19-56) [13]	1 (5%, 0-25) [1]	2 (10%, 1-32) [2]	3 (8%, 2-20) [3]
Nausea	4 (14%, 4-33) [4]	5 (18%, 6-37) [5]	8 (29%, 13-49) [9]	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Constipation	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	1 (5%, 0-25) [1]	1 (5%, 0-25) [1]	2 (5%, 1-17) [2]
Abdominal pain	---	2 (7%, 1-24) [2]	2 (7%, 1-24) [2]	---	---	---
Vomiting	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Respiratory, thoracic and mediastinal disorders	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	2 (10%, 1-32) [2]	2 (10%, 1-32) [2]	4 (10%, 3-24) [4]
Oropharyngeal pain	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	1 (5%, 0-25) [1]	1 (5%, 0-25) [1]	2 (5%, 1-17) [2]
Hiccups	---	---	---	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Pharyngeal erythema	---	---	---	1 (5%, 0-25) [1]	---	1 (3%, 0-13) [1]
General disorders and administration site conditions	2 (7%, 1-24) [2]	---	2 (7%, 1-24) [2]	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Chest discomfort	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Chest pain	---	---	---	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Fatigue	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---

Characteristic	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=28)	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=40)

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) THS 2.1 = Tobacco Heating System 2.1 single and ad-libitum use
Note (2) CC = Own preferred brand of conventional cigarettes

Table 37 - Incidence of AEs in Individual Studies on THS 2.1 - All Causalities (Con't)

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
Characteristic	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=28)	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=40)
Musculoskeletal and connective tissue disorders	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Back pain	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Ear and labyrinth disorders	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Ear pain	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Hepatobiliary disorders	---	---	---	1 (5%, 0-25) [1]	1 (5%, 0-25) [1]	2 (5%, 1-17) [2]
Hyperbilirubinaemia	---	---	---	1 (5%, 0-25) [1]	1 (5%, 0-25) [1]	2 (5%, 1-17) [2]
Infections and infestations	---	---	---	1 (5%, 0-25) [1]	1 (5%, 0-25) [1]	2 (5%, 1-17) [2]
Nasopharyngitis	---	---	---	1 (5%, 0-25) [1]	1 (5%, 0-25) [1]	2 (5%, 1-17) [2]
Investigations	---	---	---	---	4 (20%, 6-44) [4]	4 (10%, 3-24) [4]
Blood triglycerides increased	---	---	---	---	2 (10%, 1-32) [2]	2 (5%, 1-17) [2]
Carboxyhaemoglobin increased	---	---	---	---	2 (10%, 1-32) [2]	2 (5%, 1-17) [2]
Nervous system disorders	6 (21%, 8-41) [8]	7 (25%, 11-45) [9]	10 (36%, 19-56) [17]	---	---	---
Disturbance in attention	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Dizziness	3 (11%, 2-28) [3]	2 (7%, 1-24) [2]	5 (18%, 6-37) [5]	---	---	---
Headache	3 (11%, 2-28) [3]	2 (7%, 1-24) [2]	3 (11%, 2-28) [5]	---	---	---
Presyncope	1 (4%, 0-18) [1]	4 (14%, 4-33) [5]	4 (14%, 4-33) [6]	---	---	---

Characteristic	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=28)	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=40)

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) THS 2.1 = Tobacco Heating System 2.1 single and ad-libitum use

Note (2) CC = Own preferred brand of conventional cigarettes

Table 37 - Incidence of AEs in Individual Studies on THS 2.1 - All Causalities (Con't)

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
Characteristic	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=28)	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=40)
Psychiatric disorders	---	---	---	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Insomnia	---	---	---	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Skin and subcutaneous tissue disorders	3 (11%, 2-28) [4]	---	3 (11%, 2-28) [4]	---	---	---
Cold sweat	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Dermatitis contact	1 (4%, 0-18) [2]	---	1 (4%, 0-18) [2]	---	---	---
Hyperhidrosis	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) THS 2.1 = Tobacco Heating System 2.1 single and ad-libitum use

Note (2) CC = Own preferred brand of conventional cigarettes

Table 38 - Incidence of AEs in Individual Studies on THS 2.1 - Related AEs

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
Characteristic	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=28)	THS 2.1[1] (N=28)	CC[2] (N=28)	Overall (N=40)
Total no. Subjects with AE	5 (18%, 6-37) [11]	5 (18%, 6-37) [7]	9 (32%, 16-52) [18]	0 (0%) [0]	4 (20%, 6-44) [4]	4 (10%, 3-24) [4]
Gastrointestinal disorders	3 (11%, 2-28) [3]	3 (11%, 2-28) [3]	6 (21%, 8-41) [6]	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Constipation	---	---	---	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Nausea	3 (11%, 2-28) [3]	3 (11%, 2-28) [3]	6 (21%, 8-41) [6]	---	---	---
Respiratory, thoracic and mediastinal disorders	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Hiccups	---	---	---	---	1 (5%, 0-25) [1]	1 (3%, 0-13) [1]
Oropharyngeal pain	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
General disorders and administration site conditions	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Chest discomfort	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Investigations	---	---	---	---	2 (10%, 1-32) [2]	2 (5%, 1-17) [2]
Carboxyhaemoglobin increased	---	---	---	---	2 (10%, 1-32) [2]	2 (5%, 1-17) [2]
Nervous system disorders	3 (11%, 2-28) [4]	3 (11%, 2-28) [4]	5 (18%, 6-37) [8]	---	---	---
Disturbance in attention	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Dizziness	2 (7%, 1-24) [2]	1 (4%, 0-18) [1]	3 (11%, 2-28) [3]	---	---	---
Presyncope	1 (4%, 0-18) [1]	3 (11%, 2-28) [3]	3 (11%, 2-28) [4]	---	---	---

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
Characteristic	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=28)	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=40)

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) THS 2.1 = Tobacco Heating System 2.1 single and ad-libitum use

Note (2) CC = Own preferred brand of conventional cigarettes

Table 38 - Incidence of AEs in Individual Studies on THS 2.1 - Related AEs (cont.)

	Study ZRHX-PK-02 (UK)			Study ZRHX-EX-01 (PL)		
Characteristic	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=28)	THS 2.1[(1)] (N=28)	CC[(2)] (N=28)	Overall (N=40)
Skin and subcutaneous tissue disorders	2 (7%, 1-24) [2]	---	2 (7%, 1-24) [2]	---	---	---
Cold sweat	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---
Hyperhidrosis	1 (4%, 0-18) [1]	---	1 (4%, 0-18) [1]	---	---	---

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events

Note (1) THS 2.1 = Tobacco Heating System 2.1 single and ad-libitum use

Note (2) CC = Own preferred brand of conventional cigarettes

2.7.4.2.2 Narratives

2.7.4.2.2.1 EHCSS JLI:

Four SAEs (neck pain, headache, and two episodes of appendicitis) occurred in the EHCSS JLI group.

One female subject, experienced the SAE of appendicitis on Day 267, preceded by the AEs of abdominal pain, nausea, tremor, and vomiting. The subject was administered Tylenol®, Tylenol® Extra Strength, and a heat pack for abdominal pain therapy. The subject was also administered compazine, crackers, ice chips, and an ice bag for nausea and vomiting therapy. When the subject reported that she was unable to stop vomiting on Day 267, the Investigator was notified and the subject was transported to the hospital where an appendectomy was performed on Day 268 (source documents on file at MDSPS; letter to IRB and Medwatch forms located in Appendix 16.3.1). The subject was withdrawn from the study on Day 272. The Investigator considered the SAE to be unrelated to the study "Treatment" and the SAE resolved without sequelae.

One female subject experienced the SAE of neck pain (verbatim term "cervical neck pain") on Day 266. At Admission, the subject reported that she had been involved in a motor vehicle accident on 11 September 2002 and was diagnosed with acute cervical sprain (source data on file at MDSPS); this was documented as an AE unrelated to the study product. During the study the subject obtained follow-up with her physician regarding the neck pain, and on Day 353 the subject reported she was hospitalized for surgery to correct a disc problem (source documents on file at MDSPS; letter to IRB and Medwatch forms located in Appendix 16.3.1). During the study, the subject was administered ibuprofen, Skelaxin®, Ultram®, tramadol, and Vicodin® for the AEs related to neck sprain/pain. The Investigator considered the SAE to be unrelated to the study "Treatment" and the SAE remained unchanged at the end of the study.

One subject, female, experienced the SAE of appendicitis on Day 266. At this time, the subject underwent an appendectomy and was hospitalized until Day 269. This SAE occurred outside of study confinement and was therefore not included in the study AE dataset (please see IRB letters and the Notes to File located in Appendix 16.1.3 and Medwatch forms located in Appendix 16.3.1). The Investigator considered the SAE to be unrelated to study "Treatment" and withdrew the subject from the study on Day 291 due to the hospitalization. Subject 95 fully recovered from the appendectomy.

One subject, female, experienced the SAE of severe headache on Day 328. At this 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, and the subject was released from the hospital after being prescribed Percocet® (source documents on file at MDSPS; letter to IRB and Medwatch forms located in Appendix 16.3.1). During the study, the subject was also administered ibuprofen and Motrin® for headache therapy. The

Investigator considered the SAE to be unrelated to the study "Treatment" and the SAE resolved without sequelae.

2.7.4.2.2.2 THS 1.0

Subject 0609, Safety case N°: PMI000001; Event Preferred Term: Acute myocardial infarction; Seriousness criterion: hospitalization; Outcome: Resolved with sequelae:

A 59 year-old male subject who had undergone all screening procedures but had not been exposed to the investigational product (EHCSS-K6) felt a strong pain on the left side of his chest at noon on 17 Feb 2008 and was admitted to the hospital on the same day. During hospitalization, echocardiography revealed regional wall motion abnormalities in septum and apex (segments of the lateral, inferior and anterior left ventricular walls). His ejection fraction (EF) was 40% and troponin level was 191.83 ng/dl (normal range not provided). He was diagnosed with "anterior acute myocardial infarction." The investigator assessed the event as severe in intensity. A coronarography (X-ray of the coronary arteries) was performed with primary angioplasty of the left coronary artery (LAD: left anterior descending) and stenting. Contrapulsation was performed and the subject was treated with Reo-pro® (abciximab) due to increased arterial blood pressure in the first 24 hours after the infarction. The course of the disease was complicated by pneumonia and left ventricular insufficiency. Cardiac insufficiency was treated with Furosemid® (furosemide) and Spironol® (spironolactone) and pneumonia was treated with antibiotic therapy (Augmentin® [amoxicillin/clavulanic acid] and ciprofloxacin). After treatment, regression of signs of heart failure and pneumonia were observed. A chest X-ray on an unspecified date revealed residual post-inflammatory changes. The following medications were prescribed: Aspirin® (acetylsalicylic acid), Areplex® (clopidogrel), Atoris® (atorvastatin), Spironol® (spironolactone), Vivace® (Ramipril), Furosemid® (furosemide), and Vivacor® (Carvedilol). The subject recovered with sequelae and was discharged in "good cardiological and general health status" on 06 Mar 2008. The regional wall motion abnormalities in the septum and apex with 40% EF, recorded in the echocardiography at the discharge from hospital was considered as a sequelae of the myocardial infarction. The subject signed the ICF on 13 Feb 2008. During screening, EGG examination, chest X-ray and physical examination including vital signs (blood pressure 130/90 mmHg, pulse 66 bpm) were normal. Results of laboratory tests revealed increased levels of total cholesterol. The subject was disqualified on 14 Feb 2008 due to high cholesterol levels and was not randomized; therefore, he was not exposed to the investigational product (EHCSS-K6).

Subject 0058; Safety case N°: PMI000002; Event Preferred Term: Splenic injury; Seriousness criterion: hospitalization; Outcome: Resolved

A 51 year-old female subject used the investigational product EHCSS-K6 from 14 Nov 2007 to Jan 2008 (precise date of last use not known as subject did not attend the post-study visit). On 09 Feb 2008, the subject was admitted to hospital with "post-traumatic spleen injury"

after being attacked in the street on 05-Feb-2008. The investigator assessed the event as severe in intensity. A spleenectomy was performed on 09 Feb 2008. The subject recovered and was discharged on 18 Feb 2008. The subject did not show up for a planned visit on 10 Dec 2007, therefore she was withdrawn from the study on 12 Dec 2007. A follow-up visit was performed on 23 Jan 2008. The investigator assessed the causal relationship between the event and the investigational product as not related because of "other non-drug cause (post traumatic injury)."

Subject 0336; Safety case N°: PMI000003; Event Preferred Term: Deep vein thrombosis; Seriousness criterion: hospitalization; Outcome: Resolved with sequelae

A 48 year-old male subject with no history of vascular disease used EHCSS-K6 from 01 Mar 2008 to 04 Apr 2008. The subject had been smoking an average of 25 CPD for more than 20 years. During the study, the subject smoked 25-30 K6 CPD per day on average with decreasing tendency. After the study, the subject resumed smoking the same quantity and brand of cigarettes as before the study. On 12 Apr 2008, he began to complain of left upper extremity pain involving the axillary area, entire left arm and hand. The subject had reportedly travelled by bus for 1 week after Visit 8 in an abnormal position with his arm outstretched and with a heavy bag under his armpit, resulting in pain at night. The pain was accompanied by general edema of the entire left extremity. He was hospitalized on 17 Apr 2008 and diagnosed with "upper extremity deep vein (brachial, axillary) thrombosis" which came partially to the radial vein. The investigator assessed the event as moderate in intensity. The subject was treated with low molecular weight heparin from 17 to 23 Apr 2008 and Sintrom® (acenocumarol) since 17 Apr 2008. After achieving a therapeutic International Normalized Ratio (INR) range, the subject was discharged on 23 Apr 2008 without disease complications, in "good cardiological and general health status." He was further advised not to take pain killers or anti-inflammatory drugs and to eliminate risk factors of deep vein thrombosis (DVT). The subject did not experience any diseases, symptoms or complications after his discharge from the hospital. He remained in "good physical and medical condition", not requiring nursing care. The subject was considered as recovered with sequelae on 23 April 2008. The investigator considered the sequelae to be "chronic DVT," treated with acenocumarol. The subject's INR was monitored every 2 weeks. From 25 Apr 2008 to 14 Jul 2008, his INR was between 2.05 and 3.0 (normal range: 2.0-3.0). He continued treatment with acenocumarol, 3-4 mg daily, adjusted according to the INR. The dosing protocol rapidly achieved a stable INR (2.05-3.0) range after the thrombosis. With respect to biological risk factors, the subject had increased fibrinogen levels across the study, with a trend toward a higher increase at the end of the study. No abnormalities were found with respect to homocysteine levels and platelet function (ADP-induced platelet aggregation). On average, the subject smoked ca. 25% less K6 cigarettes than other K6 smokers did. In contrast to the general observation in the K6 arm, his exposure to nicotine and CO remained high. Based on these results and despite the subject's self-reported full compliance to K6, it cannot be excluded that he smoked other tobacco products in addition to K6 cigarettes. The investigator assessed the causal relationship between the event and the investigational

product as related because “cigarette smoking is one of the risk factors for deep vein thrombosis.” However, the investigator suggested that the immobilization of the subject’s arm when he travelled by bus or muscle injury from carrying a heavy bag under his armpit provides a possible explanation for the AE.

2.7.4.2.3 Integrated safety analysis of Adverse Events

Adverse events reported in six clinical studies of up to four weeks duration were pooled per study arm for further evaluation.

Table 39 summarizes the number of subjects included in pooled analysis of the six clinical studies by study arm (THS 1.0, THS 2.1, CC, SA).

Table 39 - Number of subjects in study safety population and included in pooled analysis of safety at Week-1

	ZHRX-PK-02 (UK) [1]	ZHRX-EX-01 (PL)	SPA04-01 (UK)	SPA05-01 (JP)	SPA05-03 (JP)	CS06-02 (PL) [2]	Total[5]
Number of subjects in the study safety population							
THS 1.0	0	0	32	28	28	237	325
THS 2.1	28[3]	20[4]	0	0	0	0	48
CC	28	20	64	56	56	79	303
SA	0	0	32	16	16	0	64
Number of subjects included in the pooled analysis of safety at Week-1							
THS 1.0	0	0	32	28	28	237[2]	325
THS 2.1	0	20	0	0	0	0	20
CC	0	20	64	56	56	79[2]	275
SA	0	0	32	16	16	0	64

Note: CC: conventional cigarette. THS: Tobacco heating System. SA: smoking abstinence

(1) Note: excluded from pooled analysis because it includes only 1 day of ad libitum exposure and is a cross-over study design

(2) Note: Only data at 1-week will be used

(3) Note: 28 subjects randomized and 5 additional subjects (not) exposed to THS 2.1 during product trial (product trial of up to 3 THS Tobacco Sticks)

(4) Note: 20 subjects randomized to CC were exposed to THS 2.1 during product trial (product trial of up to 3 THS Tobacco Sticks)

(5) Note: 60 subjects exposed to THS 1.0 in study EHCK6/01/03 are reported based on the clinical study report in this safety overview and are not included in the pooled analysis.

Demographic data reported in five clinical studies (SPA04-01, SPA05-01, SPA05-3, and CS06-02 and ZRHX_EX_01) of up to four weeks duration were pooled per study arm for further evaluation.

Table 40 presents the detailed demographic data of subjects included in pooled analysis of the five clinical studies by study arm (THS 1.0, CC and SA).

Table 40 - Summary of Demographic Characteristics in Pooled Analysis (THS, CC, and SA)

Characteristics	CC (N=275)	THS 1.0 (N=325)	THS 2.1 (N=20)	SA (N=64)	Overall (N=684)
Age – yr	31.8±10.6	38.6±10.9	37.6±9.0	25.7±5.0	34.6±11.2
Male sex – no. (%)	153 (55.6)	173 (53.2)	10 (50)	37 (57.8)	373 (54.5)
Body-mass Index - kg/m2	22.6±3.2	24.5±4.5	24.1±2.3	22.5±3.0	23.6±4.0
Race – no. (%)					
Asian/Japanese	112 (40.7)	56 (17.2)	0	32 (50)	200 (29.2)
Caucasian/white	163 (59.3)	269 (82.8)	20 (100)	32 (50)	484 (70.8)
Daily consumption – no. (%)					
< 20 cpd	119 (43.3)	131 (4.3)	10 (50)	32 (50)	292 (42.7)
20 + cpd	156 (56.7)	194 (59.7)	10 (50)	32 (50)	392 (57.3)
Smoking history – no. (%)[a]					
SPA Studies CS Study					
0-9 yr 0-10 yr	129 (50.6)	66 (20.3)		44 (68.8)	239 (37.1%)
10-19 yr 11-20 yr	57 (22.4)	108 (33.2)		16 (25.0)	181 (28.1%)
20+ yr 21+ yr	69 (27.1)	151 (46.5)		4 (6.3)	224 (34.8%)
FTND questionnaire score	4.9±2.1 (N=262)	5.4±2.1 (N=309)	6.1±1.6 (N=17)	4.5±1.9 (N=64)	5.2±2.1 (N=652)

Note: cpd=cigarette per day; yr: year ; SA: Smoking Abstinence
Note: Continuous data presented as mean±SD, frequencies as numbers (percentages)
Note: Actual sample size (N) is provided within the cells in case of missing values
Note: Studies pooled are: SPA04-01, SPA05-01, SPA05-03, CS0602, and ZRHX-EX-01
Note: The data of two subjects, enrolled in ZRHX-EX-01 study but not randomized, are not included in this summary
Note: The data for Smoking History does not include data from studies ZRHX_EX_01

Exposure data reported in four clinical studies of up to one week duration were pooled per study arm for further evaluation.

Table 41 presents the detailed mean daily exposure and mean cumulative daily exposure data of subjects included in pooled analysis of the four clinical studies by study arm (THS 2.1, THS 1.0 and CC).

Table 41 - Summary of Exposure in Pooled Analysis (THS, CC, and SA)

Exposure Period	Mean Daily Exposure				Mean Cumulative Daily Exposure		
	CC Mean±SD (no.)	THS 1.0 Mean±SD (no.)	THS 2.1 Mean±SD (no.)	SA Mean±SD (no.)	CC Mean±SD (no.)	THS 1.0 Mean±SD (no.)	THS 2.1 Mean±SD (no.)
Baseline (CC only)	17.5±4.2 (196)	17.5±4.3 (88)	18.9±4.5 (20)	17.4±4.0 (64)	17.5±4.2 (196)	17.5±4.3 (88)	18.9±4.5 (20)
At 1-Day	17.0±4.1 (196)	16.3±4.7 (88)	21.4±7.4 (20)	0	17.0±4.1 (196)	16.3±4.7 (88)	21.4±7.4 (20)
At 5-Day	17.2±4.3 (193)	17.2±4.8 (86)	27.2±9.1 (20)	0	85.5±20.5 (193)	84.0±23.6 (86)	124.0±37.0 (20)
At 6-Day	16.9±4.2 (173)	17.1±4.9 (86)	------	0	101.5±24.9 (173)	101.1±28.4 (86)	------
At 8-Day	17.1±4.4 (117)	17.4±4.8 (58)	------	0	134.4±33.0 (117)	134.4±37.7 (58)	------

Note: CC: conventional cigarette. THS 1.0: Tobacco heating System 1.0 (previously named K6);
Note: Studies pooled are: SPA04-01, SPA05-01, SPA05-03, and ZRHX-EX-01. CS0602 data sets were not available for pooling
Note: A restricted smoking regime was adopted in the SPA04-01, SPA05-01, SPA05-03 studies; smoking was at libitum in ZRH-EX-01

	CC Mean±SD (no.)	THS 1.0 Mean±SD (no.)	THS 2.1 Mean±SD (no.)	CC Mean±SD (no.)	THS 1.0 Mean±SD (no.)	THS 2.1 Mean±SD (no.)
Baseline (CC only)	17.5±4.2 (196)	17.5±4.3 (88)	18.9±4.5 (20)	17.5±4.2 (196)	17.5±4.3 (88)	18.9±4.5 (20)
At 1-Day	17.0±4.1 (196)	16.3±4.7 (88)	21.4±7.4 (20)	17.0±4.1 (196)	16.3±4.7 (88)	21.4±7.4 (20)
At 5-Day	17.2±4.3 (193)	17.2±4.8 (86)	27.2±9.1 (20)	85.5±20.5 (193)	84.0±23.6 (86)	124.0±37.0 (20)
At 6-Day	16.9±4.2 (173)	17.1±4.9 (86)	------	101.5±24.9 (173)	101.1±28.4 (86)	------
At 8-Day	17.1±4.4 (117)	17.4±4.8 (58)	------	134.4±33.0 (117)	134.4±37.7 (58)	------

Note: CC: conventional cigarette. THS 1.0: Tobacco heating System 1.0 (previously named K6);
Note: Studies pooled are: SPA04-01, SPA05-01, SPA05-03, and ZRHX-EX-01. CS0602 data sets were not available for pooling
Note: A restricted smoking regime was adopted in the SPA04-01, SPA05-01, SPA05-03 studies; smoking was ad libitum in ZRH-EX-01

A brief summary of AEs and the incidence of AEs by specific arm and SOC and the incidence of AEs pooled across clinical studies on THS2.1 and THS1.0 by specific arm for the safety population are presented in Table 42 and

Table 43.

Table 42 - Summary of Exposure Emergent Adverse Events in Pooled Analysis (THS, CC, and SA)

	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)
Subjects with adverse events	4 (20%)	24 (7%)	51 (19%)	12 (19%)	91 (13%)
Number of adverse events	5	31	79	18	133
Subjects with serious adverse events	---	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---	---
Severity (all adverse events)*					
Mild	3 (15%) [4]	20 (6%) [27]	33 (12%) [61]	9 (14%) [13]	65 (10%) [105]
Moderate	1 (5%) [1]	4 (1%) [4]	17 (6%) [17]	3 (5%) [5]	25 (4%) [27]
Severe	---	---	1 (0%) [1]	---	1 (0%) [1]
Total	4 (20%) [5]	24 (7%) [31]	51 (19%) [79]	12 (19%) [18]	91 (13%) [133]
Adverse events related to IP *					
Yes	---	4 (1%) [4]	5 (2%) [6]	---	9 (1%) [10]
No	4 (20%) [5]	20 (6%) [27]	46 (17%) [73]	12 (19%) [18]	82 (12%) [123]
Severity (Related AEs)*					
Mild	---	3 (1%) [3]	4 (1%) [5]	---	7 (1%) [8]

	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)
Moderate	---	1 (0%) [1]	1 (0%) [1]	---	2 (0%) [2]
Severe	---	---	---	---	---
Total	---	4 (1%) [4]	5 (2%) [6]	---	9 (1%) [10]

( ) = Percentage of subjects with adverse events [ ] = Number of adverse events N = Number of subjects studied
* Frequency of subjects by greatest relationship and/or severity
Data included: SPA04-01, SPA05-01, SPA05-03, CS06-02, ZRHX_EX_01(Data collected from safety population, events occurring between 1 and 7 days inclusive from product exposure)

Table 43 - Incidence of AEs in Pooled Analysis (THS, CC, and SA) - All Causalities

Characteristic	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)
Total no. Subjects with AE	4 (20%, 6-44) [5]	24 (7%, 5-11) [31]	51 (19%, 14-24) [79]	12 (19%, 10-30) [18]	91 (13%, 11-16) [133]
Gastrointestinal disorders	1 (5%, 0-25) [1]	6 (2%, 1-4) [7]	16 (6%, 3-9) [22]	4 (6%, 2-15) [8]	27 (4%, 3-6) [38]
Dyspepsia	---	1 (0%, 0-2) [1]	2 (1%, 0-3) [2]	3 (5%, 1-13) [5]	6 (1%, 0-2) [8]
Abdominal discomfort	---	1 (0%, 0-2) [1]	2 (1%, 0-3) [3]	1 (2%, 0-8) [1]	4 (1%, 0-1) [5]
Abdominal pain upper	---	1 (0%, 0-2) [1]	3 (1%, 0-3) [3]	---	4 (1%, 0-1) [4]
Constipation	1 (5%, 0-25) [1]	---	5 (2%, 1-4) [5]	---	6 (1%, 0-2) [6]
Vomiting	---	---	3 (1%, 0-3) [3]	1 (2%, 0-8) [1]	4 (1%, 0-1) [4]
Diarrhoea	---	1 (0%, 0-2) [1]	1 (0%, 0-2) [2]	---	2 (0%, 0-1) [3]
Toothache	---	---	1 (0%, 0-2) [2]	1 (2%, 0-8) [1]	2 (0%, 0-1) [3]
Dry mouth	---	2 (1%, 0-2) [2]	---	---	2 (0%, 0-1) [2]
Nausea	---	1 (0%, 0-2) [1]	2 (1%, 0-3) [2]	---	3 (0%, 0-1) [3]
Nervous system disorders	---	9 (3%, 1-5) [11]	11 (4%, 2-7) [11]	4 (6%, 2-15) [4]	24 (4%, 2-5) [26]
Headache	---	8 (2%, 1-5) [10]	8 (3%, 1-6) [8]	3 (5%, 1-13) [3]	19 (3%, 2-4) [21]
Dizziness	---	1 (0%, 0-2) [1]	2 (1%, 0-3) [2]	1 (2%, 0-8) [1]	4 (1%, 0-1) [4]
Post-traumatic headache	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data included: SPA04-01, SPA05-01, SPA05-03, CS06-02, ZRHX_EX_01 (Data collected from safety population, events occurring between 1 and 7 days inclusive from product exposure)

Table 43 - Incidence of AEs in Pooled Analysis (THS, CC, and SA) - All Causalities (cont.)

Characteristic	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)
Investigations	---	2 (1%, 0-2) [4]	9 (3%, 2-6) [10]	2 (3%, 0-11) [4]	13 (2%, 1-3) [18]
Alanine aminotransferase increased	---	2 (1%, 0-2) [2]	2 (1%, 0-3) [2]	1 (2%, 0-8) [1]	5 (1%, 0-2) [5]
Aspartate aminotransferase increased	---	2 (1%, 0-2) [2]	---	1 (2%, 0-8) [1]	3 (0%, 0-1) [3]
Blood triglycerides increased	---	---	2 (1%, 0-3) [2]	---	2 (0%, 0-1) [2]
Blood bilirubin increased	---	---	1 (0%, 0-2) [1]	1 (2%, 0-8) [1]	2 (0%, 0-1) [2]
White blood cell count increased	---	---	1 (0%, 0-2) [1]	1 (2%, 0-8) [1]	2 (0%, 0-1) [2]
Carboxyhaemoglobin increased	---	---	3 (1%, 0-3) [2]	---	3 (0%, 0-1) [3]
Protein urine present	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Respiratory, thoracic and mediastinal disorders	2 (10%, 1-32) [2]	1 (0%, 0-2) [1]	12 (4%, 2-8) [13]	---	15 (2%, 1-4) [16]
Oropharyngeal pain	1 (5%, 0-25) [1]	---	10 (4%, 2-7) [10]	---	11 (2%, 1-3) [11]
Cough	---	1 (0%, 0-2) [1]	1 (0%, 0-2) [1]	---	2 (0%, 0-1) [2]
Hiccups	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Nasal obstruction	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Pharyngeal erythema	1 (5%, 0-25) [1]	---	---	---	1 (0%, 0-1) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data included: SPA04-01, SPA05-01, SPA05-03, CS06-02, ZRHX_EX_01 (Data collected from safety population, events occurring between 1 and 7 days inclusive from product exposure)

Table 43 - Incidence of AEs in Pooled Analysis (THS, CC, and SA) - All Causalities (cont.)

Characteristic	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)
Skin and subcutaneous tissue disorders	---	1 (0%, 0-2) [1]	4 (1%, 0-4) [5]	1 (2%, 0-8) [1]	6 (1%, 0-2) [7]
Dry skin	---	---	3 (1%, 0-3) [3]	---	3 (0%, 0-1) [3]
Rash	---	---	1 (0%, 0-2) [1]	1 (2%, 0-8) [1]	2 (0%, 0-1) [2]
Dermatitis acneiform	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]
Erythema	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
General disorders and administration site conditions	---	2 (1%, 0-2) [2]	4 (1%, 0-4) [4]	1 (2%, 0-8) [1]	7 (1%, 0-2) [7]
Feeling hot	---	---	2 (1%, 0-3) [2]	---	2 (0%, 0-1) [2]
Asthenia	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Chest pain	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Facial pain	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]
Local swelling	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]
Vessel puncture site reaction	---	---	---	1 (2%, 0-8) [1]	1 (0%, 0-1) [1]
Infections and infestations	1 (5%, 0-25) [1]	4 (1%, 0-3) [4]	3 (1%, 0-3) [3]	---	8 (1%, 1-2) [8]
Nasopharyngitis	1 (5%, 0-25) [1]	2 (1%, 0-2) [2]	2 (1%, 0-2) [2]	---	5 (1%, 0-2) [5]
Oral herpes	---	1 (0%, 0-2) [1]	1 (0%, 0-2) [1]	---	2 (0%, 0-1) [2]
Candidiasis	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]

Characteristic	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data included: SPA04-01, SPA05-01, SPA05-03, CS06-02, ZRHX_EX_01 (Data collected from safety population, events occurring between 1 and 7 days inclusive from product exposure)

Table 43 - Incidence of AEs in Pooled Analysis (THS, CC, and SA) - All Causalities (cont.)

Characteristic	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)
Reproductive system and breast disorders	---	---	5 (2%, 1-4) [5]	---	5 (1%, 0-2) [5]
Dysmenorrhoea	---	---	5 (2%, 1-4) [5]	---	5 (1%, 0-2) [5]
Hepatobiliary disorders	1 (5%, 0-25) [1]	---	1 (0%, 0-2) [1]	---	2 (0%, 0-1) [2]
Hyperbilirubinaemia	1 (5%, 0-25) [1]	---	1 (0%, 0-2) [1]	---	2 (0%, 0-1) [2]
Ear and labyrinth disorders	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]
Vertigo	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]
Injury, poisoning and procedural complications	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Thermal burn	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Musculoskeletal and connective tissue disorders	---	---	2 (1%, 0-2) [2]	---	2 (0%, 0-1) [2]
Back pain	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Pain in extremity	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Psychiatric disorders	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Insomnia	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Vascular disorders	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Flushing	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data included: SPA04-01, SPA05-01, SPA05-03, CS06-02, ZRHX_EX_01 (Data collected from safety population, events occurring between 1 and 7 days inclusive from product exposure)

A brief summary of the incidence of related AEs by specific arm and SOC pooled across clinical studies on THS2.1 and THS1.0 is presented in Table 44.

Table 44 - Incidence of AEs in Pooled Analysis (THS, CC, and SA) - Related AEs

Characteristic	THS 2.1 (N=20)	THS 1.0 (N=325)	CC (N=275)	SA (N=64)	Overall (N=684)
Total no. Subjects with AE	0 (0%) [0]	4 (1%, 0-3) [4]	5 (2%, 0-4) [6]	0 (0%) [0]	5 (1%, 0-2) [6]
Gastrointestinal disorders	---	3 (1%, 0-3) [3]	2 (1%, 0-3) [3]	---	4 (1%, 0-1) [5]
Dry mouth	---	2 (1%, 0-2) [2]	---	---	2 (0%, 0-1) [2]
Constipation	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Diarrhoea	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]
Dyspepsia	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Nausea	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]
Investigations	---	---	2 (1%, 0-3) [2]	---	2 (0%, 0-1) [2]
Carboxyhaemoglobin increased	---	---	2 (1%, 0-3) [2]	---	2 (0%, 0-1) [2]
Respiratory, thoracic and mediastinal disorders	---	1 (0%, 0-2) [1]	1 (0%, 0-2) [1]	---	2 (0%, 0-1) [2]
Cough	---	1 (0%, 0-2) [1]	---	---	1 (0%, 0-1) [1]
Hiccups	---	---	1 (0%, 0-2) [1]	---	1 (0%, 0-1) [1]

N = Number of subjects studied ( ) = Percentage, 95% CI of subjects with adverse events [ ] = Number of adverse events
Data included: SPA04-01, SPA05-01, SPA05-03, CS06-02, and ZRHX_EX_01 (Data collected from safety population, events occurring between 1 and 7 days inclusive from product exposure)

2.7.4.3.4 Withdrawals

2.7.4.3.4.1 Study EHCJLI/01/02

Three subjects discontinued the study. Two withdrew from the study for personal reasons. One subject from the EHCSS ACCORD® JLI group withdrew from the study due to an AE.

2.7.4.3.4.2 Study EHCJLI/02/02

Two subjects discontinued the study due to AEs (urticaria and appendicitis). Adverse events leading to discontinuation from the study all occurred in the EHCSS JLI group and were considered unrelated to the study "Treatment." Subject 52 (39-year-old Caucasian female) experienced the SAE of appendicitis on Day 267, preceded by the AEs of abdominal pain, nausea, tremor and vomiting. The subject was administered Tylenol®, Tylenol® Extra Strength, and a heat pack for abdominal pain therapy. The subject was also administered compazine, crackers, ice chips, and an ice bag for nausea and vomiting therapy. When the subject reported that she was unable to stop vomiting on Day 267, the Investigator was notified and the subject was transported to the hospital where an appendectomy was performed on Day 268 (source documents on file at MDSPS; letter to IRB and Medwatch forms located in Appendix 16.3.1). The subject was dropped from the study on Day 272. The Investigator considered the SAE to be unrelated to the study "Treatment" and the SAE resolved without sequelae. The following two subjects in the EHCSS JLI group discontinued the study due to AEs.

Subject 17 (49-year-old Caucasian female) reported the AE of urticaria (verbatim term "hives over body") on Day 13, which was preceded by the AE of hives on the neck. The subject reported that she noticed hives on her neck initially and the number of hives began to increase (source data on file at MDSPS). The Investigator discontinued the study "Treatment" and prescribed the subject oral Benadryl® for urticaria therapy. The subject was dropped from the study on Day 31. The Investigator considered the AEs of urticaria to be unrelated to the study. "Treatment" and the AEs resolved within 20 days from onset. The subject had no history of urticarial reactions. Subject 52 was dropped from the study due to the SAE of appendicitis as discussed previously.

2.7.4.3.4.3 Study CS 06-02

A total of seven subjects were withdrawn (three subjects in the THS 1.0 arm and four subjects in the CC arm). The reasons for withdrawal included withdrawal of consent, AEs, violation of selection criteria and other protocol violations. One subject withdrew from the study due to an adverse event. Subject 0459 (a male) was withdrawn during the CC study arm due to a moderately severe adverse event of influenza, which occurred on Day 13 and resolved after 8 days.

2.7.4.3.4.4 Study ZRHX_EX_01

One subject (Subject 9064, a back-up subject) was withdrawn due to an AE (apnea) during the baseline period, prior to randomization, and was thus considered an early terminator. No withdrawals due to AEs occurred during the main study.

2.7.4.3 Device Misuse

There were no AEs associated with device use. No misuse of the device or deterioration in its effectiveness was reported in any clinical study.

2.7.4.4 Post marketing Data

Not available.

2.7.4.5 Summary of Clinical Safety

In the studies included in this clinical safety summary, the most commonly reported AEs were headache, oropharyngeal pain, dyspepsia, constipation, nasopharyngitis, and dysmenorrhea. The majority of AEs was mild and moderate in severity, resolved promptly, and was most frequently considered to be unrelated to the investigational product, the conventional cigarette or study procedures.

A total of 13 subjects withdrew due to AEs. All of these AEs were resolved during the follow up period. Seven SAEs were reported, only one of which (DVT) was considered related to investigational product.

The types and incidences of AEs reported with THS were similar to those reported when smoking conventional cigarettes. The comparative assessment did not show an increased risk of AEs with the use of the THS.