



PMI RESEARCH & DEVELOPMENT

Study ZRHM-REXA-07-JP

Clinical Study Report Appendix 16.1.3

List of IRBs and/or IECs, IRB/IEC Approvals, Sample Consent Forms, and Written Subject Information

Study Title:	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting
Study Number:	ZRHM-REXA-07-JP
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	01 August 2013
Study Completed (last subject last visit):	03 July 2014
Principal Investigator and Affiliation:	Mamoru Oki, MD, PhD, Seishukai Clinic 3-18-5, Matsugaya, Taitou-ku Tokyo 111-0036, Japan Professor Masahiro Endo, MD, Tokyo Heart Center Osaki Hospital, 5-4-12, Kita-Shinagawa, Shinagawa-ku, Tokyo 141-0001, Japan
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Sponsor Signatories:	Christelle Haziza, PhD, Manager P1 Clinical Program, Clinical Scientist Nicola Lama, PhD, Biostatistician Andrea Donelli, Clinical Scientist Patrick Picavet, MD, Medical Safety Officer
Version:	1.0
Date:	24 February 2016

This study was conducted in accordance with Good Clinical Practice.

Confidentiality Statement

This document is confidential. Disclosure of any of its contents to third parties is not permitted except by the prior written consent of Philip Morris Products S.A.



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16.1.3 List of IRBs and/or IECs, IRB/IEC Approvals, Sample Consent Forms, and Written Subject Information

16.1.3.1 IEC/IRB Information

IEC/IRB	Investigator	Site Number
IRB of Yasuda Hospital 13-9 Narimasu 1 cho-me, Itabashi Ward Tokyo	Mamoru Oki, MD, PhD	SEI
Chairperson: Kazuhisa Yoshimoto	Professor Masahiro Endo	TOK



16.1.3.2 IEC/IRB Study Submission Letter (English)



Form 3

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study
	<input type="checkbox"/> Post-marketing Study
	<input type="checkbox"/> Medical Products
	<input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Other

Date: 5/July/2013

Clinical Study Request Form

Dear [Name of Head of Institution]

President of Clinic
Seishukai Clinic

Sponsor

(b) (4)
(b) (4)

We request the following clinical study.

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Clinical Study Name	<input checked="" type="checkbox"/> New Request <input type="checkbox"/> Continuing Request		
	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
	<input type="checkbox"/> The above-mentioned study name may be utilized in the summary of the IRB meeting record.		
	*In case of utilizing another study name, please enter it in the column below. Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting		
The Number of Subjects	80 subjects Example: The target number of prospective subjects shall be stated		
Period of Clinical Study	01 July 2013 to 28 February 2014		
Contact	Name: (b) (4) Affiliation: Clinical Pharmacology TEL: (b) (4) FAX: (b) (4) Email (b) (4)		

List of Attached Documents

Name of Documents	Documented Date	Version
<input checked="" type="checkbox"/> Protocol		
Clinical Study Protocol (ENG and JPN)	26/Jun/2013	1.0
<input checked="" type="checkbox"/> IB or Package Insert		
Investigator's Brochure (ENG and JPN)	11/Apr/2013	1.0
<input type="checkbox"/> Sample of CRF *Unnecessary, if its contents are sufficiently understood from Protocol.		
	—	
<input checked="" type="checkbox"/> Written Informed Consent Form (S)		
Informed Consent Form	5/Jul/2013	1.0
Informed Consent Form (Transcriptomics)	5/Jul/2013	1.0
Informed Consent Form (BoExp/risk markers)	5/Jul/2013	1.0
<input checked="" type="checkbox"/> CV of Principal Investigator		
	5/Jul/2013	
<input checked="" type="checkbox"/> Name List of Sub Investigators		
CV of Sub Investigator	5/Jul/2013	
<input checked="" type="checkbox"/> Documents concerning payments and compensation available to subjects (if any)		
	No date	
<input checked="" type="checkbox"/> Documents concerning the compensation available to the subjects in the event of study-related health injuries.		
Liability Insurance-Certificate of Insurance	06/May/2013	
<input checked="" type="checkbox"/> Documents concerning the procedures of subject recruitment (Advertisement, etc.)		

(Note)

(Head of Institution ≠ PI): Sponsor will create one copy of the original form of this document with the agreement of PI, and will submit it to the head of institution.

(Head of Institution = PI): Sponsor will create one copy of the original form of this document, and will submit it to the head of institution.



Form 3 Appendix

File Number

Cooperation for Clinical Study	5/Jul/2013	
<input type="checkbox"/> Documents related to the safety etc. of subjects		
	—	
■ Others		
Implementation system of clinical study at site	5/Jul/2013	
Patient Participation Card	5/Jul/2013	
Assessment of Cough	2012	
Fagerstrom-Nicotine-Dependence-Test	2012	
Modified Cigarette Evaluation Questionnaire (modified	Jul/2007	
Questionnaire of Smoking Urges brief	Feb/2012	
Minnesota Nicotine Withdrawal Scale	Jul/2012	
Socio-economic Status Questionnaire	—	
Human Smoking Topography Questionnaire	18/Apr/2013	2.0



Form 3

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Other

Date: 5/July/2013

Clinical Study Request Form

Dear [Name of Head of Institution]

President of Clinic

Osaki Hospital Tokyo heart center

Sponsor

(b) (4)

We request the following clinical study.

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Clinical Study Name	<input checked="" type="checkbox"/> New Request <input type="checkbox"/> Continuing Request A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting <input type="checkbox"/> The above-mentioned study name may be utilized in the summary of the IRB meeting record. *In case of utilizing another study name, please enter it in the column below. Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting		
The Number of Subjects	80 subjects Example: The target number of prospective subjects shall be stated		
Period of Clinical Study	01 July 2013 to 28 February 2014		
Contact	Name: (b) (4) Affiliation: Clinical Pharmacology TEL: (b) (4) FAX: (b) (4) mail: (b) (4)		

List of Attached Documents

Name of Documents	Documented Date	Version
■ Protocol		
Clinical Study Protocol (ENG and JPN)	26/Jun/2013	1.0
■ IB or Package Insert		
Investigator's Brochure (ENG and JPN)	11/Apr/2013	Version1.0 Edition1
<input type="checkbox"/> Sample of CRF *Unnecessary, if its contents are sufficiently understood from Protocol.	—	
■ Written Informed Consent Form (S)		
Informed Consent Form	5/Jul/2013	1.0
Informed Consent Form (Transcriptomics)	5/Jul/2013	1.0
Informed Consent Form (BoExp/risk markers)	5/Jul/2013	1.0
■ CV of Principal Investigator		
	7/Jun/2013	
■ Name List of Sub Investigators		
	5/Jul/2013	
■ Documents concerning payments and compensation available to subjects (if any)		
	5/Jul/2013	
■ Documents concerning the compensation available to the subjects in the event of study-related health injuries.		
Liability Insurance-Certificate of Insurance	6/May/2013	
■ Documents concerning the procedures of subject recruitment (Advertisement, etc.)		

(Note)

(Head of Institution ≠ PI): Sponsor will create one copy of the original form of this document with the agreement of PI, and will submit it to the head of institution.

(Head of Institution = PI): Sponsor will create one copy of the original form of this document, and will submit it to the head of institution.



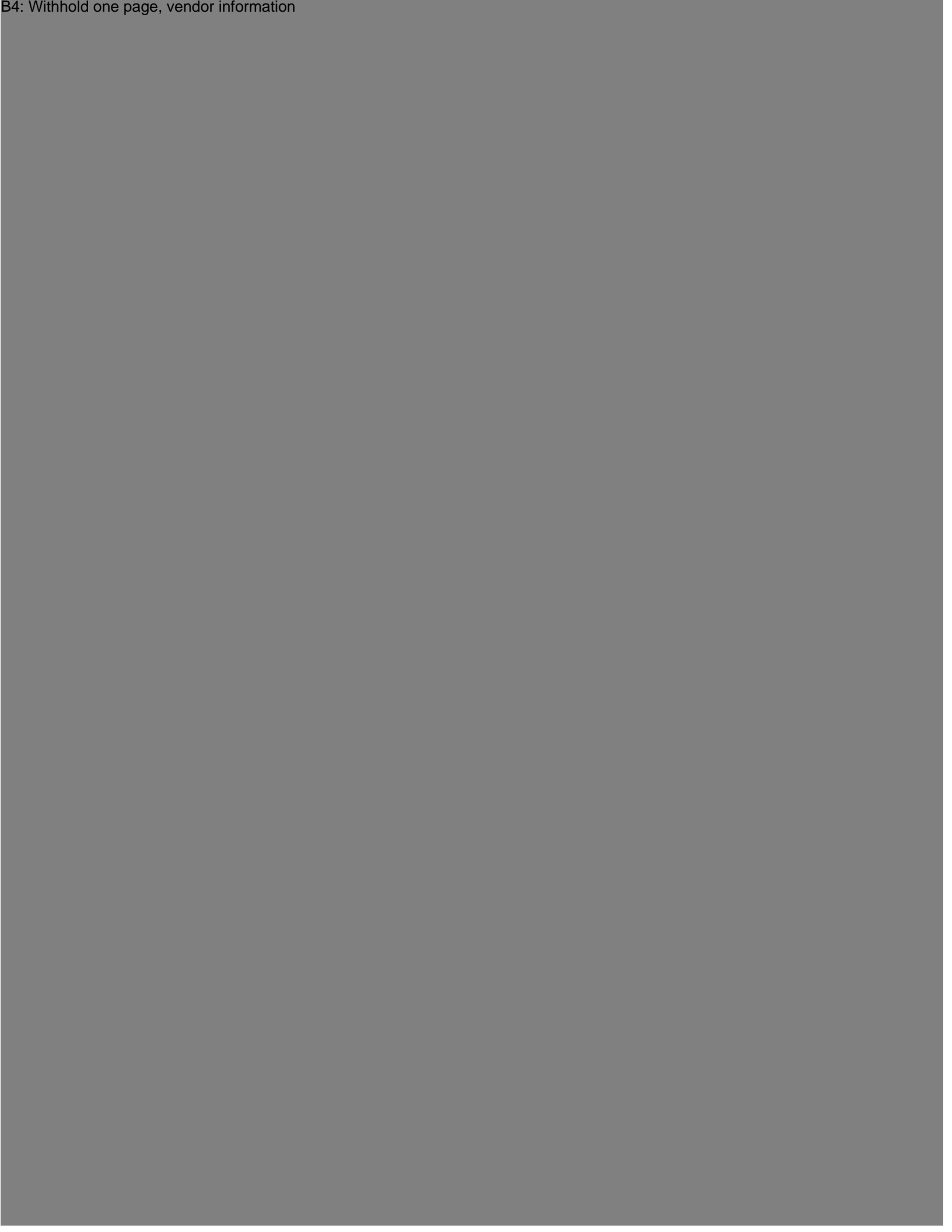
Form 3 Appendix

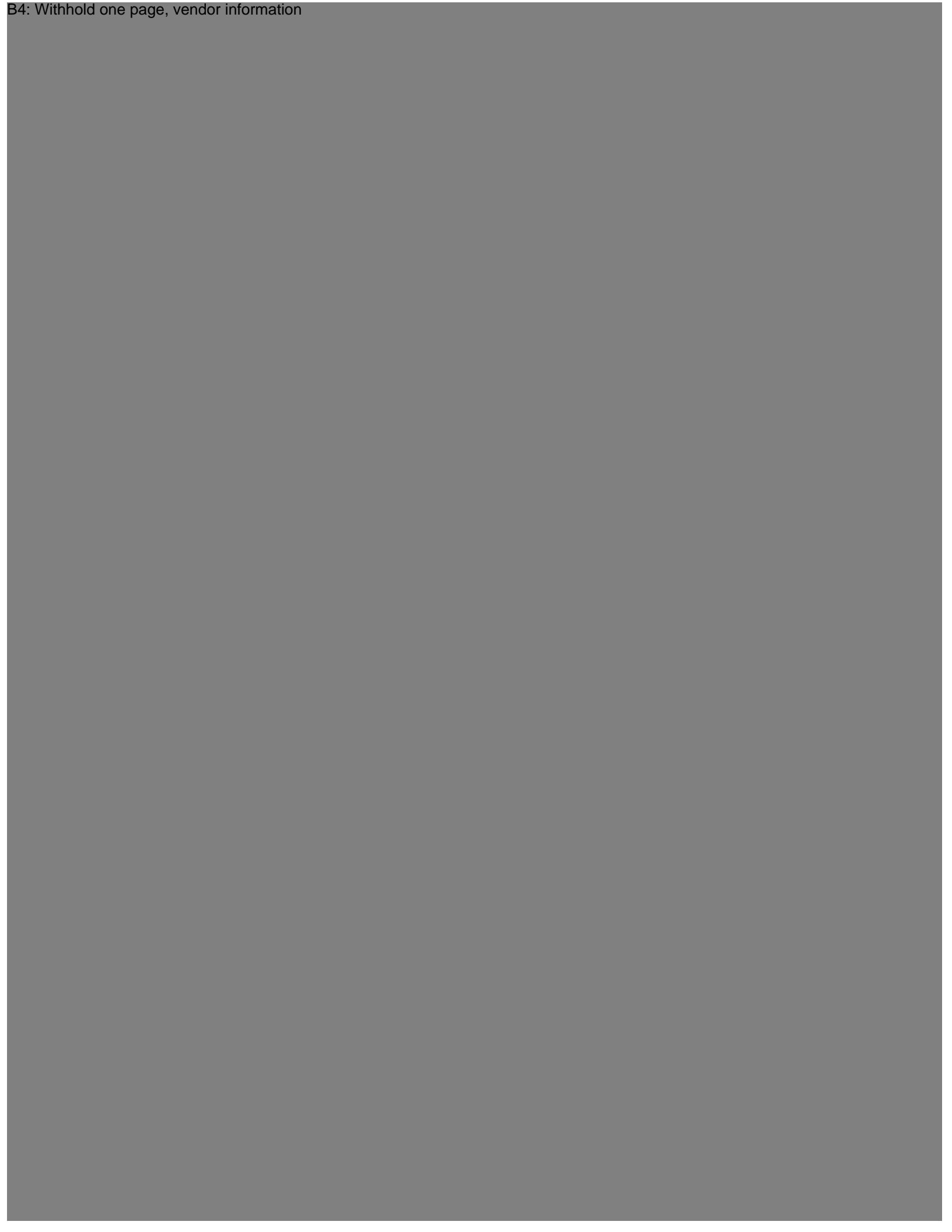
File Number

Cooperation for Clinical Study	5/Jul/2013	
<input type="checkbox"/> Documents related to the safety etc. of subjects		
	—	
■ Others		
Implementation system of clinical study at site	5/Jul/2013	
Patient Participation Card	5/Jul/2013	
Assessment of Cough	2012	
Fagerstrom-Nicotine-Dependence-Test	2012	
Modified Cigarette Evaluation Questionnaire (modified	Jul/2007	
Questionnaire of Smoking Urges brief	Feb/2012	
Minnesota Nicotine Withdrawal Scale	Jul/2012	
Socio-economic Status Questionnaire	—	
Human Smoking Topography Questionnaire	18/Apr/2013	2.0



16.1.3.3 IEC/IRB Study Submission Letter (Local Language)







16.1.3.4 IEC/IRB Study Approval Letter (English)



Form 5

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Others

Date: 17/Jul/2013

IRB Result Notification

Dear
President of hospital
Seishukai clinic

Institutional Review Board
IRB of Yasuda Hospital
13-9 Narimasu 1 cho-me, Itabashi Ward, Tokyo
Kazuhisa Yoshimoto

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Original Study Name	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers (1) switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or (2) observing smoking abstinence, compared to (3) continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Matters Deliberated (Materials Deliberated)	<input checked="" type="checkbox"/> Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 05/Jul/2013)) <input type="checkbox"/> Continuation/Discontinuation of the Clinical Study <input type="checkbox"/> Serious Adverse Event (SAE) (<input type="checkbox"/> Report on SAE (copy of Form 12 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Adverse Event (AE) (copy of Form 13 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on SAE and Defect (copy of Form 14 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on AE and Defect (copy of Form 15 dated dd/mmm/yyyy)) <input type="checkbox"/> Safety Information, etc. (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) <input type="checkbox"/> Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated dd/mmm/yyyy)) <input type="checkbox"/> Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated dd/mmm/yyyy)) <input type="checkbox"/> Continued Deliberation (Report on Performance of the Clinical Study (copy of Form 11 dated dd/mmm/yyyy)) <input type="checkbox"/> Others()		
Deliberation Type	<input checked="" type="checkbox"/> IRB Deliberation (Deliberation Date : 17/Jul/2013) <input type="checkbox"/> Rapid Deliberation (End Date of Deliberation : dd/mmm/yyyy)		
Deliberation Result	<input checked="" type="checkbox"/> Approval <input type="checkbox"/> Approval after corrections <input type="checkbox"/> Reject <input type="checkbox"/> Withdrawal of approved matters <input type="checkbox"/> Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)

Date: 19/Jul/2013

To: Principal Investigator (b) (4)

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Seishukai clinic, President

Note: (Head of Institution ≠ Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A." shall be stated in the column of the Principal Investigator.



File Number

IRB Attendees List

[illegible]

Note) Member's Classification: Described by numbers according to the below-mentioned classifications.

1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interests with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1-3.

Attendance: Described by signals according to the below-mentioned classifications.

O (Members who attended the meeting and have no involvement in the clinical study concerned)

- (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)

X (Members who did not attend the meeting.)

The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as "Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".



Form 5

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Others

Date: 17/Jul/2013

IRB Result Notification

Dear
President of hospital
Tokyo Heart Center, Osaka hospital

Institutional Review Board
IRB of Yasuda Hospital
13-9 Narimasu 1 cho-me, Itabashi Ward, Tokyo
Kazuhisa Yoshimoto

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Original Study Name	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers (1) switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or (2) observing smoking abstinence, compared to (3) continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Matters Deliberated (Materials Deliberated)	<input checked="" type="checkbox"/> Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 05/Jul/2013)) <input type="checkbox"/> Continuation/Discontinuation of the Clinical Study <input type="checkbox"/> Serious Adverse Event (SAE) (<input type="checkbox"/> Report on SAE (copy of Form 12 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Adverse Event (AE) (copy of Form 13 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on SAE and Defect (copy of Form 14 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on AE and Defect (copy of Form 15 dated dd/mmm/yyyy)) <input type="checkbox"/> Safety Information, etc. (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) <input type="checkbox"/> Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated dd/mmm/yyyy)) <input type="checkbox"/> Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated dd/mmm/yyyy)) <input type="checkbox"/> Continued Deliberation (Report on Performance of the Clinical Study (copy of Form 11 dated dd/mmm/yyyy)) <input type="checkbox"/> Others()		
Deliberation Type	<input checked="" type="checkbox"/> IRB Deliberation (Deliberation Date : 17/Jul/2013) <input type="checkbox"/> Rapid Deliberation (End Date of Deliberation : dd/mmm/yyyy)		
Deliberation Result	<input checked="" type="checkbox"/> Approval <input type="checkbox"/> Approval after corrections <input type="checkbox"/> Reject <input type="checkbox"/> Withdrawal of approved matters <input type="checkbox"/> Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)
To: Principal Investigator (b) (4)

Date: 18/Jul/2013

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Osaka hospital, Tokyo Heart Center, President

Note: (Head of Institution ≠ Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A." shall be stated in the column of the Principal Investigator.



File Number

Date: 17/Jul/2013

IRB Attendees List

[illegible]

Note) Member's Classification: Described by numbers according to the below-mentioned classifications.

1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interests with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1.-3.

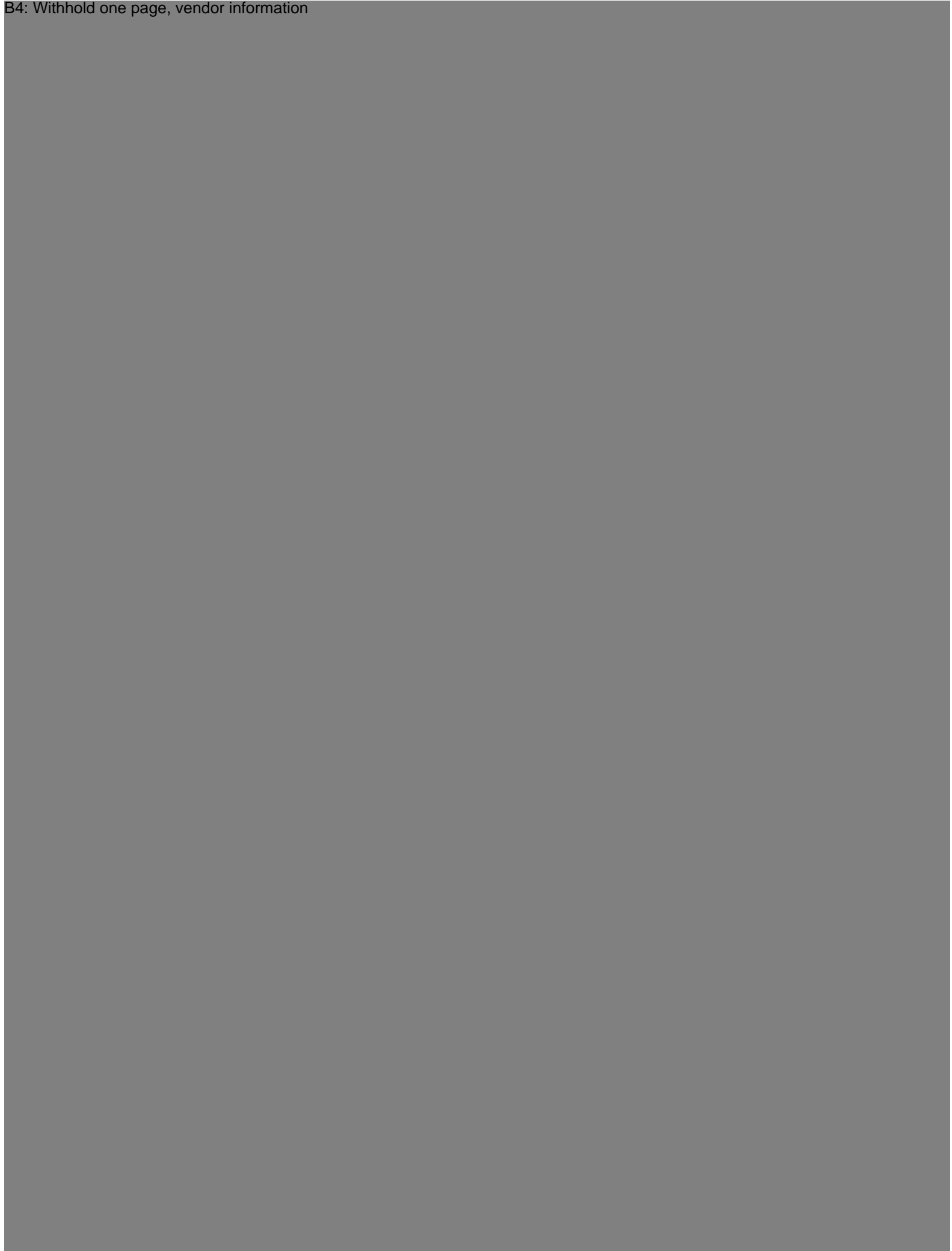
Attendance: Described by signals according to the below-mentioned classifications.

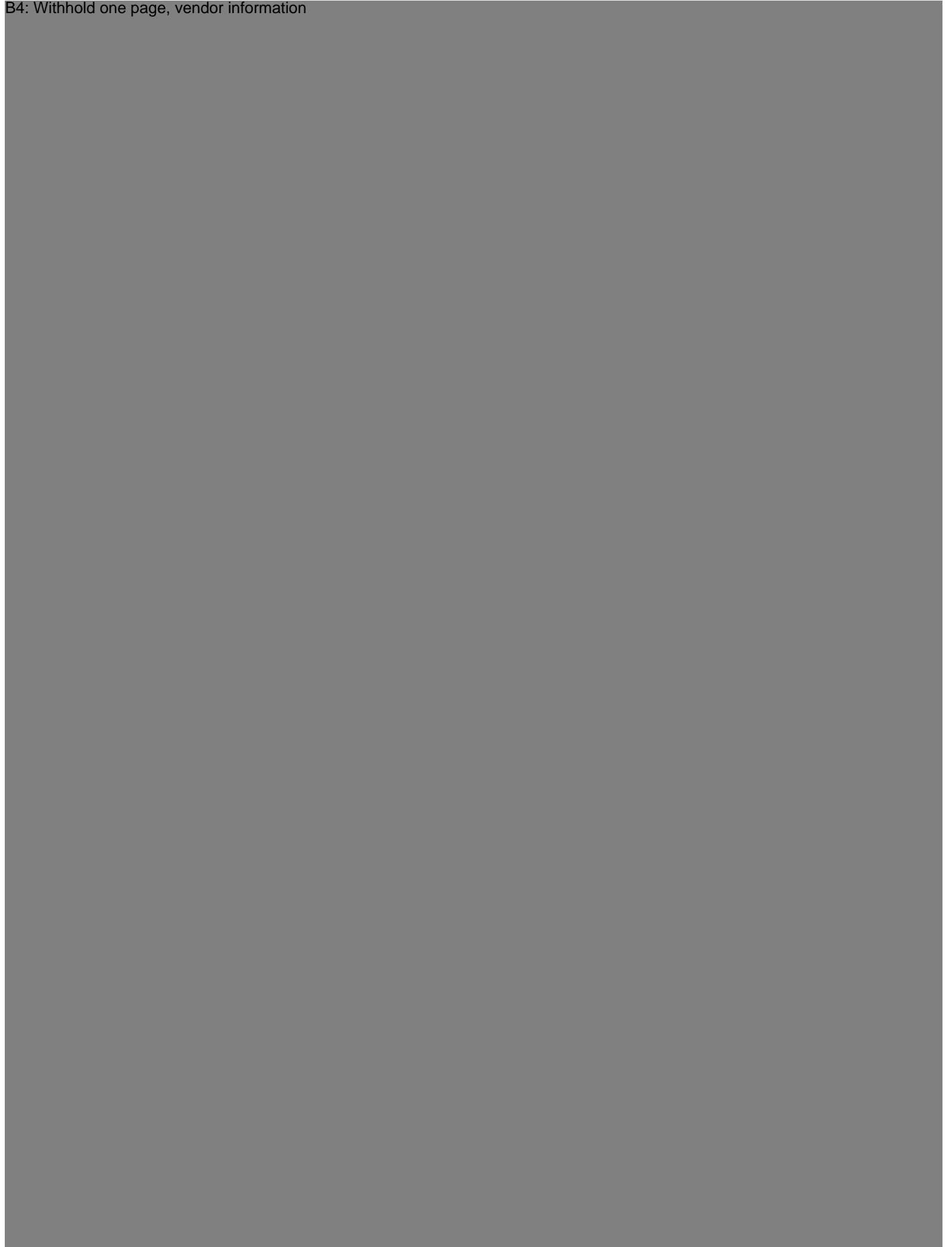
- O (Members who attended the meeting and have no involvement in the clinical study concerned)
- (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)
X (Members who did not attend the meeting.)

The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as "Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".



16.1.3.5 IEC/IRB Study Approval Letter (Local Language)









16.1.3.6 IEC/IRB Protocol Amendment Submission Letter (English)



Form 10

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Other

Date: 10/December/2013

Application for Clinical Study Change

Dear [Name of Head of Institution]

President of Clinic

Osaki Hospital Tokyo heart center

Sponsor

(b) (4)

Principal Investigator

(b) (4)

We will apply for change as following;

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP	
Clinical Study Name	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting			
Change documents, etc.	<input checked="" type="checkbox"/> Clinical Study Protocol <input checked="" type="checkbox"/> Informed Consent Form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Sub Investigators <input checked="" type="checkbox"/> other (Implementation system of clinical study at site. Documents concerning payments and compensation available to subjects. Document on the recruitment advertisement of the subject)			
C h a n g e d c o n t e n t s	Change matters	Before change	After changing	Reason for change
	Clinical Study Protocol (ENG and JPN)	Refer to Amendment N°1 (ENG and JPN)		Refer to Amendment N°1 (ENG and JPN)
	Informed Consent Form	Refer to The Comparative Table		· As reflected on protocol alternation due to discontinuation of study in Seishukai clinic · Clarification of the description
	Implementation system of clinical study at site	Refer to The Comparative Table		Refer to The Comparative Table
	Documents concerning payments and compensation available to subjects	Refer to The Comparative Table		Refer to The Comparative Table
	Document on the recruitment advertisement of the subject	—	New	Due to promotion of subject recruitment.
Attachment	· Clinical Study Protocol (ENG and JPN) (19 November 2013/Final 2.0) · Clinical Study Protocol ZRHM-REXA-07-JP Amendment N°1 (ENG and JPN) (19 November 2013) · Informed Consent Form (06/Dec/2013/ver.2.0) · Informed Consent Form (The Comparative Table) · Documents concerning payments and compensation available to subjects (Date:03/Dec/2013) · Documents concerning payments and compensation available to subjects(The Comparative Table) (Date:03/Dec/2013) · Implementation system of clinical study at site (As of 03 Dec 2013) · Implementation system of clinical study at site(The Comparative Table) (Date:03/Dec/2013) · Document on the recruitment advertisement of the subject (including a reference material) (04 December 2013)			
Contact	Name: (b) (4) TEL: (b) (4)	Affiliation: Clinical Pharmacology Email: (b) (4)		

Note) (Head of Institution ≠Principal Investigator): Sponsor shall make this document under the principal investigator's agreement to submit to the head of institution. If only Informed Consent Form is revised, principal investigator shall make this document to submit to the head of institution. In this case, the sponsor column shall be filled in with "N/A".

(Head of Institution = Principal Investigator): Sponsor shall make this document to submit to the head of institution. PI column shall be filled in with "N/A". If only Informed Consent Form is revised, principal Investigator (the head of institution) shall make this document. In this case, both PI and the head of institution column shall be filled in, and sponsor column shall be filled in with "N/A".



Form 10

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Other

Date: 07/May/2014

Application for Clinical Study Change

Dear [Name of Head of Institution]
President of Clinic
Osaki Hospital Tokyo heart center

Sponsor

(b) (4)

Principal Investigator

(b) (4)

We will apply for change as following;

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP	
Clinical Study Name	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting			
Change documents, etc.	<input checked="" type="checkbox"/> Clinical Study Protocol <input type="checkbox"/> Informed Consent Form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Sub Investigators <input checked="" type="checkbox"/> other (Documents concerning the compensation available to the subjects in the event of study-related health injuries)			
Changes to documents	Change matters	Before change	After changing	Reason for change
	Clinical Study Protocol (ENG and JPN)	Refer to Amendment N°2 (ENG and JPN)		Refer to Amendment N°2 (ENG and JPN)
	Liability Insurance-Certificate of Insurance	Period of insurance : 01/05/2013-30/04/2014 ⇒ 01/05/2014-30/04/2015		Due to update of insurance period
Attachment	· Clinical Study Protocol (ENG and JPN) (07 April 2014/Final 3.0) · Clinical Study Protocol ZRHM-REXA-07-JP Amendment N°2 (ENG and JPN) (07 April 2014) · Liability Insurance-Certificate of Insurance (17 April 2014)			
Contact	Name: (b) (4) Affiliation: Clinical Pharmacology TEL: (b) (4) FAX: (b) (4) Email: (b) (4)			

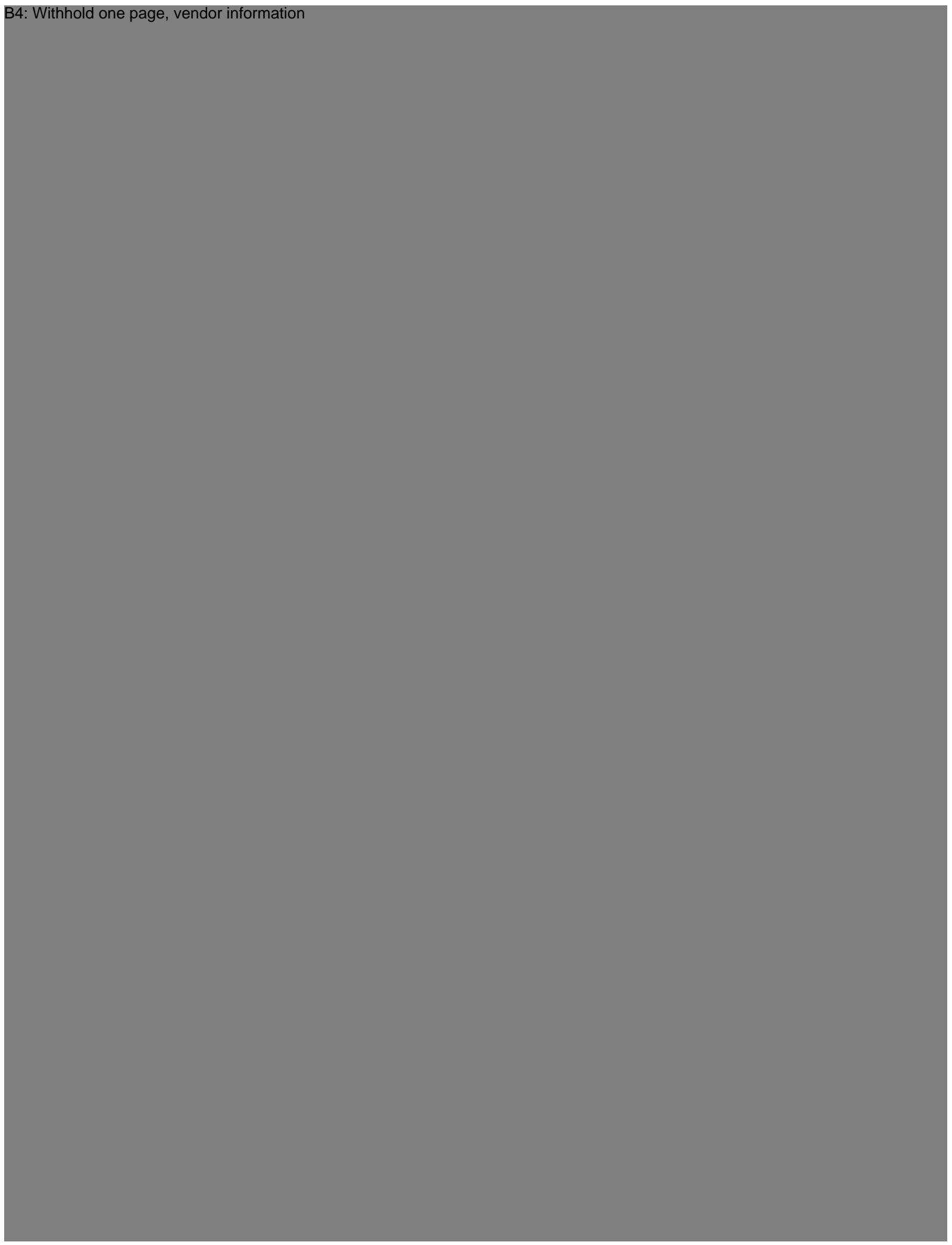
Note) (Head of Institution ≠Principal Investigator): Sponsor shall make this document under the principal investigator's agreement to submit to the head of institution. If only Informed Consent Form is revised, principal investigator shall make this document to submit to the head of institution. In this case, the sponsor column shall be filled in with "N/A".

(Head of Institution = Principal Investigator): Sponsor shall make this document to submit to the head of institution. PI column shall be filled in with "N/A". If only Informed Consent Form is revised, principal Investigator (the head of institution) shall make this document. In this case, both PI and the head of institution column shall be filled in, and sponsor column shall be filled in with "N/A".



16.1.3.7 IRC/IRB Protocol Amendment Submission Letter (Local Language)

(b)(4)





16.1.3.8 IEC/IRB Protocol Amendment Approval Letter (English)



Form 5

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study
	<input type="checkbox"/> Post-marketing Study
	<input type="checkbox"/> Medical Products
	<input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Others

Date: 12/18/2013

IRB Result Notification

Dear
President of hospital
Tokyo Heart Center, Osaki Hospital

Institutional Review Board
IRB of Yasuda Hospital
13-9 Narimasu 1 cho-me, Itabashi Ward, Tokyo
Kazuhisa Yoshimoto

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Original Study Name	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers (1) switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or (2) observing smoking abstinence, compared to (3) continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Matters Deliberated (Materials Deliberated)	<input type="checkbox"/> Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 07/05/2013)) <input checked="" type="checkbox"/> Continuation/Discontinuation of the Clinical Study <input type="checkbox"/> Serious Adverse Event (SAE) (<input type="checkbox"/> Report on SAE (copy of Form 12 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on Adverse Event (AE) (copy of Form 13 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on SAE and Defect (copy of Form 14 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on AE and Defect (copy of Form 15 dated mm/dd/yyyy)) <input type="checkbox"/> Safety Information, etc. (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) <input checked="" type="checkbox"/> Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated 12/10/2013)) <input type="checkbox"/> Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated mm/dd/yyyy)) <input type="checkbox"/> Continued Deliberation (Report on Performance of the Clinical Study (copy of Form 11 dated mm/dd/yyyy)) <input type="checkbox"/> Others ()		
Deliberation Type	<input checked="" type="checkbox"/> IRB Deliberation (Deliberation Date : 12/18/2013) <input type="checkbox"/> Rapid Deliberation (End Date of Deliberation : mm/dd/yyyy)		
Deliberation Result	<input checked="" type="checkbox"/> Approval <input type="checkbox"/> Approval after corrections <input type="checkbox"/> Reject <input type="checkbox"/> Withdrawal of approved matters <input type="checkbox"/> Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)

Date: 12/18/2013

To: Principal Investigator (b) (4)

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Tokyo Heart Center, Osaki Hospital, President

Note: (Head of Institution ≠ Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A." shall be stated in the column of the Principal Investigator.



File Number

Date: 12/18/2013

IRB Attendees List

[illegible]

Note) Member's Classification: Described by numbers according to the below-mentioned classifications.

1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interests with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1.-3.

Attendance: Described by signals according to the below-mentioned classifications.

- ☐ (Members who attended the meeting and have no involvement in the clinical study concerned)
- ☐ - (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)
- ☒ X (Members who did not attend the meeting.)

The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as "Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".



Form 5

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Others

Date: 21/May/2014

IRB Result Notification

Dear
President of hospital
Tokyo Heart Center, Osaki Hospital

Institutional Review Board
IRB of Yasuda Hospital
13-9 Narimasu 1 cho-me, Itabashi Ward, Tokyo
Kazuhisa Yoshimoto

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Original Study Name	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers (1) switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or (2) observing smoking abstinence, compared to (3) continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Matters Deliberated (Materials Deliberated)	<input type="checkbox"/> Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated dd/mmm/yyyy)) <input checked="" type="checkbox"/> Continuation/Discontinuation of the Clinical Study <input type="checkbox"/> Serious Adverse Event (SAE) (<input type="checkbox"/> Report on SAE (copy of Form 12 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Adverse Event (AE) (copy of Form 13 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on SAE and Defect (copy of Form 14 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on AE and Defect (copy of Form 15 dated dd/mmm/yyyy)) <input type="checkbox"/> Safety Information, etc. (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) <input checked="" type="checkbox"/> Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated 07/May/2014)) <input type="checkbox"/> Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated dd/mmm/yyyy)) <input type="checkbox"/> Continued Deliberation (Report on Performance of the Clinical Study (copy of Form 11 dated dd/mmm/yyyy)) <input type="checkbox"/> Others()		
Deliberation Type	<input checked="" type="checkbox"/> IRB Deliberation (Deliberation Date : 21/May/2014) <input type="checkbox"/> Rapid Deliberation (End Date of Deliberation : dd/mmm/yyyy)		
Deliberation Result	<input checked="" type="checkbox"/> Approval <input type="checkbox"/> Approval after corrections <input type="checkbox"/> Reject <input type="checkbox"/> Withdrawal of approved matters <input type="checkbox"/> Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)
To: Principal Investigator (b) (4)

Date: 22/May/2014

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Tokyo Heart Center, Osaki Hospital, President

Note: (Head of Institution ≠ Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A." shall be stated in the column of the Principal Investigator.



File Number

IRB Attendees List

[illegible]

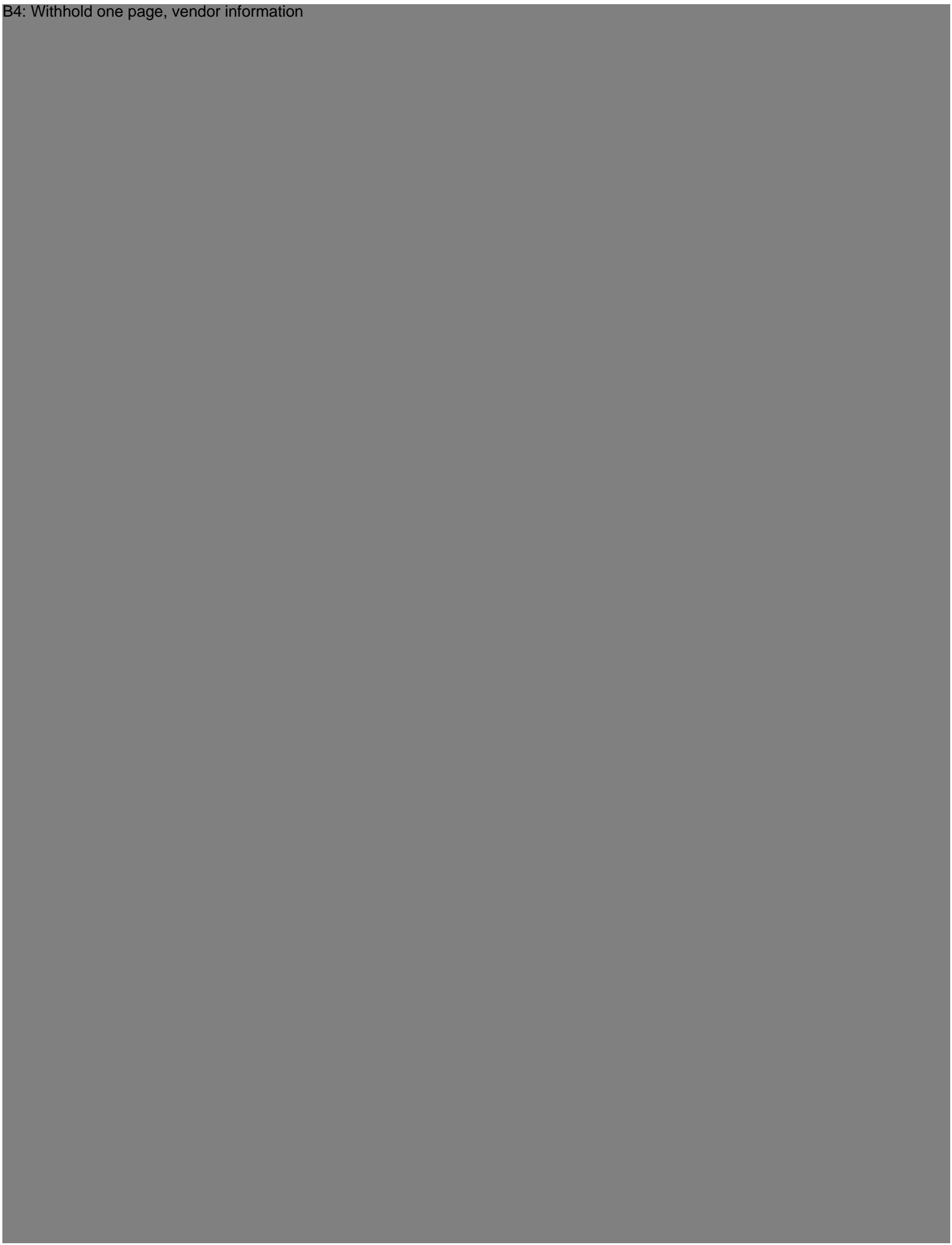
1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interests with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1.-3.

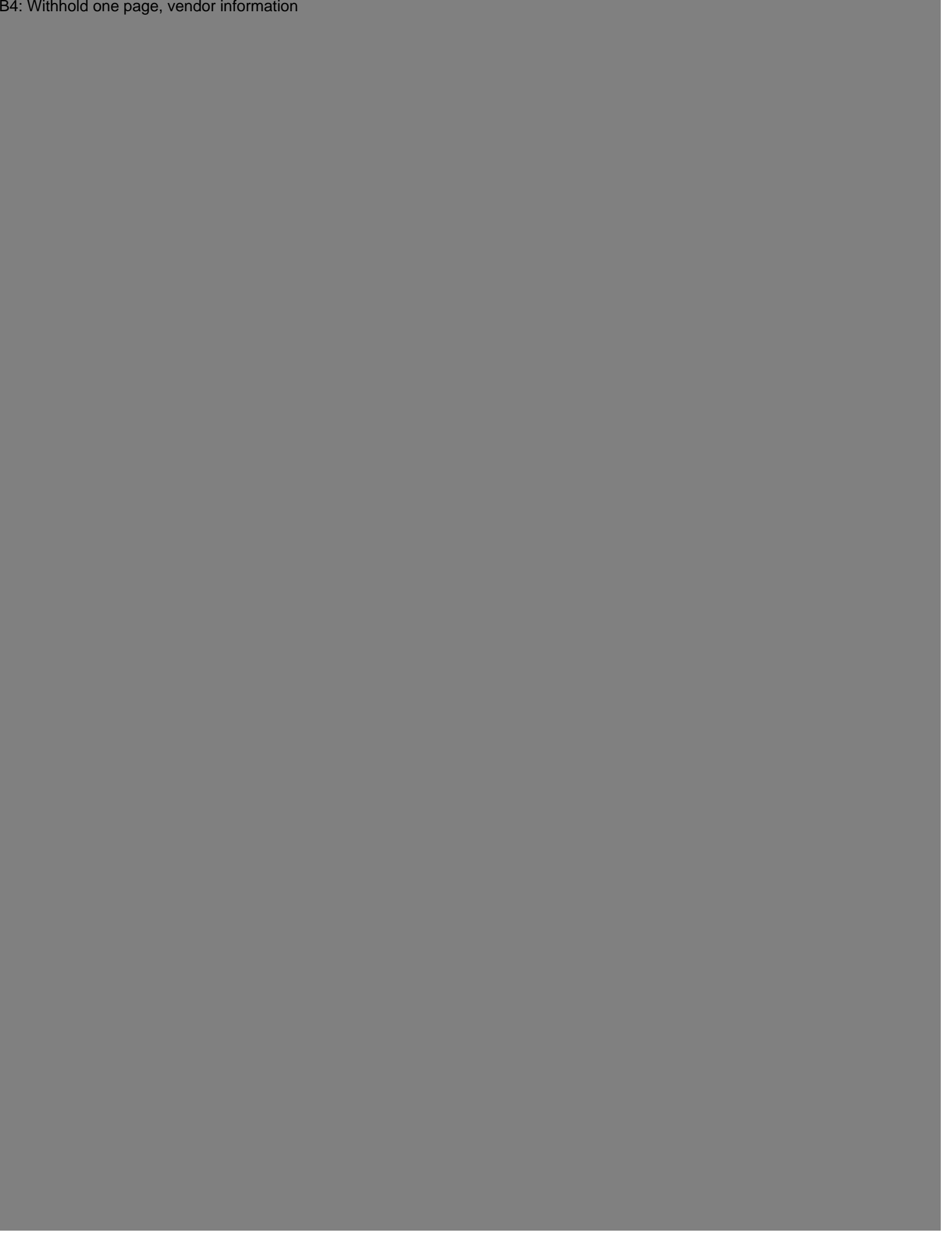
O (Members who attended the meeting and have no involvement in the clinical study concerned)
- (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)
X (Members who did not attend the meeting.)

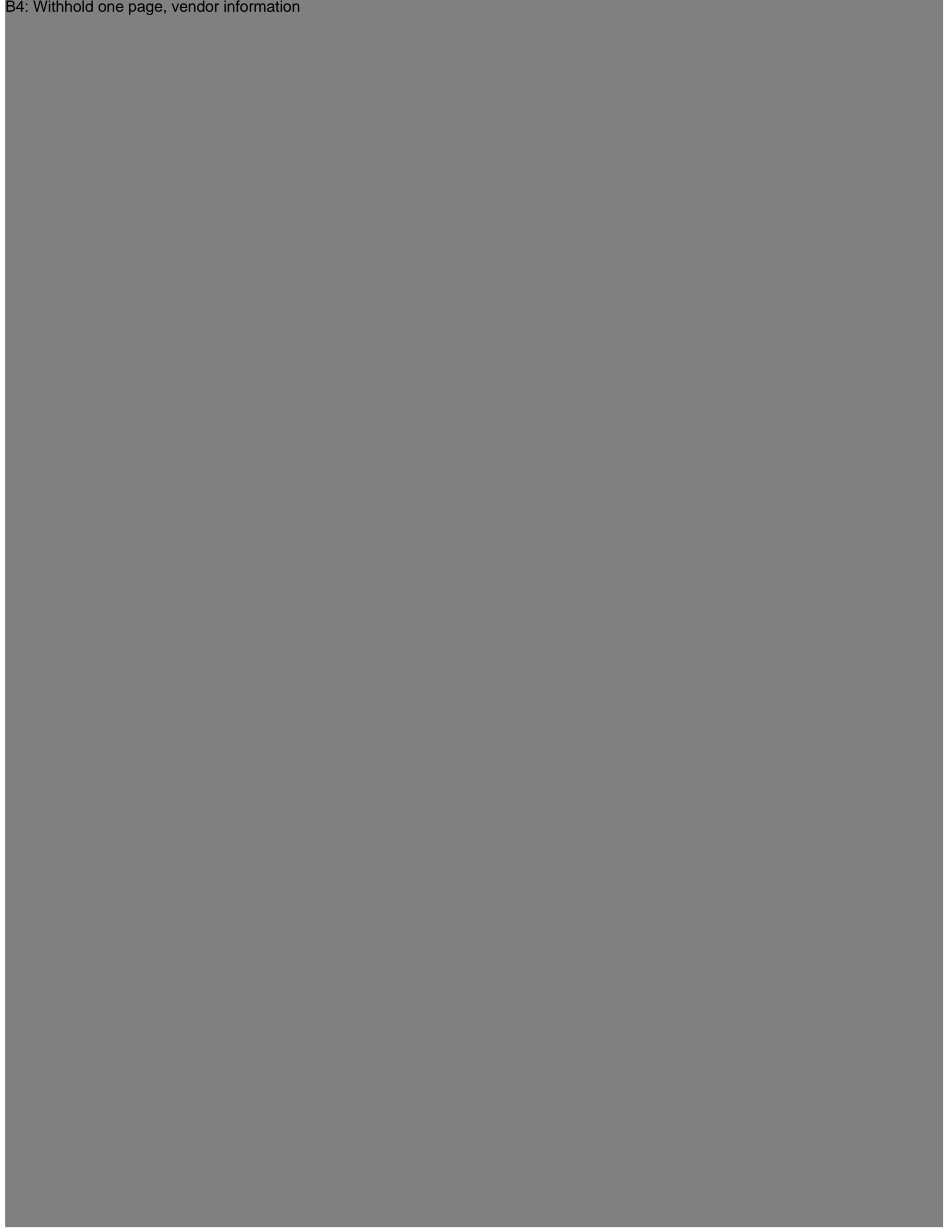
The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as "Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".



16.1.3.9 IEC/IRB Protocol Amendment Approval Letter (Local Language)









16.1.3.10 IEC/IRB Subject Information and Informed Consent Form Version 001
Submission Letter (English)



Form 3

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study
	<input type="checkbox"/> Post-marketing Study
	<input type="checkbox"/> Medical Products
	<input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Other

Date: 5/July/2013

Clinical Study Request Form

Dear [Name of Head of Institution]

President of Clinic
Seishukai Clinic

Sponsor

(b) (4)

We request the following clinical study.

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Clinical Study Name	<input checked="" type="checkbox"/> New Request <input type="checkbox"/> Continuing Request		
	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
	<input type="checkbox"/> The above-mentioned study name may be utilized in the summary of the IRB meeting record.		
	*In case of utilizing another study name, please enter it in the column below. Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting		
The Number of Subjects	80 subjects Example: The target number of prospective subjects shall be stated		
Period of Clinical Study	01 July 2013 to 28 February 2014		
Contact	Name: (b) (4) Affiliation: Clinical Pharmacology TEL: (b) (4) FAX: (b) (4) Email: (b) (4)		

List of Attached Documents

Name of Documents	Documented Date	Version
<input checked="" type="checkbox"/> Protocol		
Clinical Study Protocol (ENG and JPN)	26/Jun/2013	1.0
<input checked="" type="checkbox"/> IB or Package Insert		
Investigator's Brochure (ENG and JPN)	11/Apr/2013	1.0
<input type="checkbox"/> Sample of CRF *Unnecessary, if its contents are sufficiently understood from Protocol.		
	—	
<input checked="" type="checkbox"/> Written Informed Consent Form (S)		
Informed Consent Form	5/Jul/2013	1.0
Informed Consent Form (Transcriptomics)	5/Jul/2013	1.0
Informed Consent Form (BoExp/risk markers)	5/Jul/2013	1.0
<input checked="" type="checkbox"/> CV of Principal Investigator		
	5/Jul/2013	
<input checked="" type="checkbox"/> Name List of Sub Investigators		
CV of Sub Investigator	5/Jul/2013	
<input checked="" type="checkbox"/> Documents concerning payments and compensation available to subjects (if any)		
	No date	
<input checked="" type="checkbox"/> Documents concerning the compensation available to the subjects in the event of study-related health injuries.		
Liability Insurance-Certificate of Insurance	06/May/2013	
<input checked="" type="checkbox"/> Documents concerning the procedures of subject recruitment (Advertisement, etc.)		

(Note)

(Head of Institution ≠ PI): Sponsor will create one copy of the original form of this document with the agreement of PI, and will submit it to the head of institution.

(Head of Institution = PI): Sponsor will create one copy of the original form of this document, and will submit it to the head of institution.



Form 3 Appendix

File Number

Cooperation for Clinical Study	5/Jul/2013	
<input type="checkbox"/> Documents related to the safety etc. of subjects		
	—	
■ Others		
Implementation system of clinical study at site	5/Jul/2013	
Patient Participation Card	5/Jul/2013	
Assessment of Cough	2012	
Fagerstrom-Nicotine-Dependence-Test	2012	
Modified Cigarette Evaluation Questionnaire (modified	Jul/2007	
Questionnaire of Smoking Urges brief	Feb/2012	
Minnesota Nicotine Withdrawal Scale	Jul/2012	
Socio-economic Status Questionnaire	—	
Human Smoking Topography Questionnaire	18/Apr/2013	2.0



Form 3

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Other

Date: 5/July/2013

Clinical Study Request Form

Dear [Name of Head of Institution]

President of Clinic

Osaki Hospital Tokyo heart center

Sponsor

(b) (4)

We request the following clinical study.

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Clinical Study Name	<input checked="" type="checkbox"/> New Request <input type="checkbox"/> Continuing Request A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting <input type="checkbox"/> The above-mentioned study name may be utilized in the summary of the IRB meeting record. *In case of utilizing another study name, please enter it in the column below. Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting		
The Number of Subjects	80 subjects Example: The target number of prospective subjects shall be stated		
Period of Clinical Study	01 July 2013 to 28 February 2014		
Contact	Name: (b) (4) Affiliation: Clinical Pharmacology TEL (b) (4) FAX: (b) (4) mail: (b) (4)		

List of Attached Documents

Name of Documents	Documented Date	Version
■ Protocol		
Clinical Study Protocol (ENG and JPN)	26/Jun/2013	1.0
■ IB or Package Insert		
Investigator's Brochure (ENG and JPN)	11/Apr/2013	Version1.0 Edition1
<input type="checkbox"/> Sample of CRF *Unnecessary, if its contents are sufficiently understood from Protocol.	—	
■ Written Informed Consent Form (S)		
Informed Consent Form	5/Jul/2013	1.0
Informed Consent Form (Transcriptomics)	5/Jul/2013	1.0
Informed Consent Form (BoExp/risk markers)	5/Jul/2013	1.0
■ CV of Principal Investigator		
	7/Jun/2013	
■ Name List of Sub Investigators		
	5/Jul/2013	
■ Documents concerning payments and compensation available to subjects (if any)		
	5/Jul/2013	
■ Documents concerning the compensation available to the subjects in the event of study-related health injuries.		
Liability Insurance-Certificate of Insurance	6/May/2013	
■ Documents concerning the procedures of subject recruitment (Advertisement, etc.)		

(Note)

(Head of Institution ≠ PI): Sponsor will create one copy of the original form of this document with the agreement of PI, and will submit it to the head of institution.

(Head of Institution = PI): Sponsor will create one copy of the original form of this document, and will submit it to the head of institution.



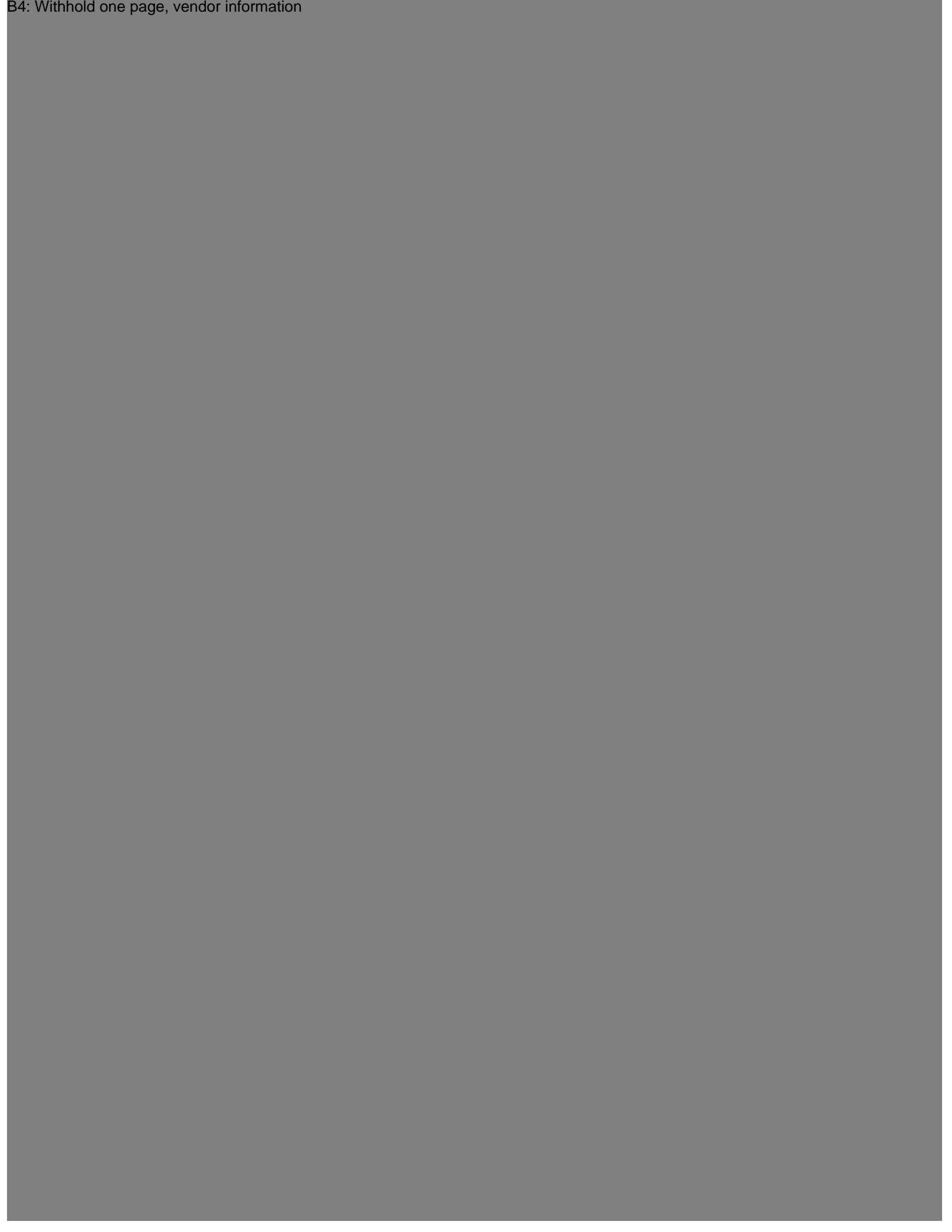
Form 3 Appendix

File Number

Cooperation for Clinical Study	5/Jul/2013	
<input type="checkbox"/> Documents related to the safety etc. of subjects		
	—	
■ Others		
Implementation system of clinical study at site	5/Jul/2013	
Patient Participation Card	5/Jul/2013	
Assessment of Cough	2012	
Fagerstrom-Nicotine-Dependence-Test	2012	
Modified Cigarette Evaluation Questionnaire (modified	Jul/2007	
Questionnaire of Smoking Urges brief	Feb/2012	
Minnesota Nicotine Withdrawal Scale	Jul/2012	
Socio-economic Status Questionnaire	—	
Human Smoking Topography Questionnaire	18/Apr/2013	2.0

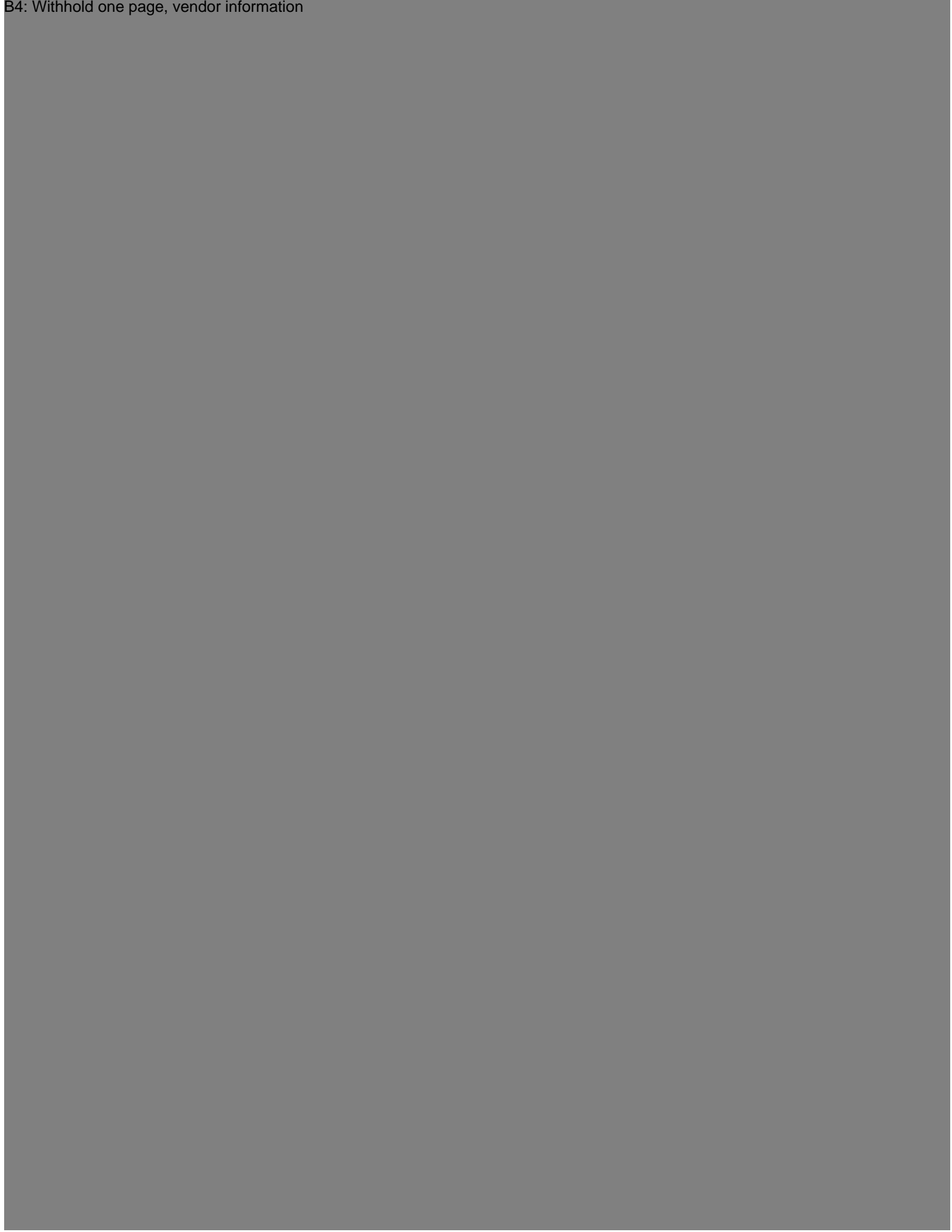


16.1.3.11 IEC/IRB Subject Information and Informed Consent Form Version 001
Submission Letter (Local Language)











16.1.3.12 IEC/IRB Subject Information and Informed Consent Form Version 001 Approval Letter (English)



Form 5

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Others

Date: 17/Jul/2013

IRB Result Notification

Dear
President of hospital
Seishukai clinic

Institutional Review Board
IRB of Yasuda Hospital
13-9 Narimasu 1 cho-me, Itabashi Ward, Tokyo
Kazuhisa Yoshimoto

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Original Study Name	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers (1) switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or (2) observing smoking abstinence, compared to (3) continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Matters Deliberated (Materials Deliberated)	<input checked="" type="checkbox"/> Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 05/Jul/2013)) <input type="checkbox"/> Continuation/Discontinuation of the Clinical Study <input type="checkbox"/> Serious Adverse Event (SAE) (<input type="checkbox"/> Report on SAE (copy of Form 12 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Adverse Event (AE) (copy of Form 13 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on SAE and Defect (copy of Form 14 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on AE and Defect (copy of Form 15 dated dd/mmm/yyyy)) <input type="checkbox"/> Safety Information, etc. (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) <input type="checkbox"/> Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated dd/mmm/yyyy)) <input type="checkbox"/> Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated dd/mmm/yyyy)) <input type="checkbox"/> Continued Deliberation (Report on Performance of the Clinical Study (copy of Form 11 dated dd/mmm/yyyy)) <input type="checkbox"/> Others()		
Deliberation Type	<input checked="" type="checkbox"/> IRB Deliberation (Deliberation Date : 17/Jul/2013) <input type="checkbox"/> Rapid Deliberation (End Date of Deliberation : dd/mmm/yyyy)		
Deliberation Result	<input checked="" type="checkbox"/> Approval <input type="checkbox"/> Approval after corrections <input type="checkbox"/> Reject <input type="checkbox"/> Withdrawal of approved matters <input type="checkbox"/> Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)

Date: 19/Jul/2013

To: Principal Investigator (b) (4)

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Seishukai clinic, President

Note: (Head of Institution ≠ Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A." shall be stated in the column of the Principal Investigator.



Form 5

File Number

Date: 17/Jul/2013

IRB Attendees List

Name	Occupation, License(s) & Affiliation	Classification of members	Attendance	Remarks
Kazuhisa Yoshimoto	Surgeon, Yasuda Hospital	4	O	Chairperson
Akemi Mitsui	Pharmacist, Yasuda Hospital	4	O	Vice Chairperson
Sayuri Yasuda	Physician, Yasuda Hospital	4	O	
Motoyasu Chibai	Surgeon, Yasuda Hospital	4	O	
Naka Mizutani	Surgeon, Yasuda Hospital	4	X	
Kouichi Shibano	Orthopedist, Yasuda Hospital	4	O	
Shinichi Nakamura	Manager of Account department, Yasuda Hospital	1	O	
Mariko Eguchi	Clerk, Nihonbashi Kokoro no clinic	1	X	
Yoshifumi Nogami	Clerk, NPO Japan transplantation support association	2, 3	X	
Kenshi Hikiami	Team leader, liaison division, sales department, SANRITSU Corp.	2, 3	X	
Akira Ozawa	President, Ogawa fire equipment Service	2, 3	O	

Note) Member's Classification: Described by numbers according to the below-mentioned classifications.

1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interests with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1.-3.

Attendance: Described by signals according to the below-mentioned classifications.

- O (Members who attended the meeting and have no involvement in the clinical study concerned)
- (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)
- X (Members who did not attend the meeting.)

The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as "Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".



Form 5

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Others

Date: 17/Jul/2013

IRB Result Notification

Dear
President of hospital
Tokyo Heart Center, Osaka hospital

Institutional Review Board
IRB of Yasuda Hospital
13-9 Narimasu 1 cho-me, Itabashi Ward, Tokyo
Kazuhisa Yoshimoto

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Original Study Name	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers (1) switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or (2) observing smoking abstinence, compared to (3) continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Matters Deliberated (Materials Deliberated)	<input checked="" type="checkbox"/> Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 05/Jul/2013)) <input type="checkbox"/> Continuation/Discontinuation of the Clinical Study <input type="checkbox"/> Serious Adverse Event (SAE) (<input type="checkbox"/> Report on SAE (copy of Form 12 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Adverse Event (AE) (copy of Form 13 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on SAE and Defect (copy of Form 14 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on AE and Defect (copy of Form 15 dated dd/mmm/yyyy)) <input type="checkbox"/> Safety Information, etc. (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated dd/mmm/yyyy)) <input type="checkbox"/> Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated dd/mmm/yyyy)) <input type="checkbox"/> Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated dd/mmm/yyyy)) <input type="checkbox"/> Continued Deliberation (Report on Performance of the Clinical Study (copy of Form 11 dated dd/mmm/yyyy)) <input type="checkbox"/> Others()		
Deliberation Type	<input checked="" type="checkbox"/> IRB Deliberation (Deliberation Date : 17/Jul/2013) <input type="checkbox"/> Rapid Deliberation (End Date of Deliberation : dd/mmm/yyyy)		
Deliberation Result	<input checked="" type="checkbox"/> Approval <input type="checkbox"/> Approval after corrections <input type="checkbox"/> Reject <input type="checkbox"/> Withdrawal of approved matters <input type="checkbox"/> Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)
To: Principal Investigator (b) (4)

Date: 18/Jul/2013

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Osaka hospital, Tokyo Heart Center, President

Note: (Head of Institution ≠ Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A." shall be stated in the column of the Principal Investigator.



File Number

IRB Attendees List

[illegible]

Note) Member's Classification: Described by numbers according to the below-mentioned classifications.

1. Non-Expert Members
2. Members who have no interests with the institution (except for the members designated in 1. above)
3. Members who have no interests with the incorporator of IRB (except for the members designated in 1. above)
4. Members other than 1.-3.

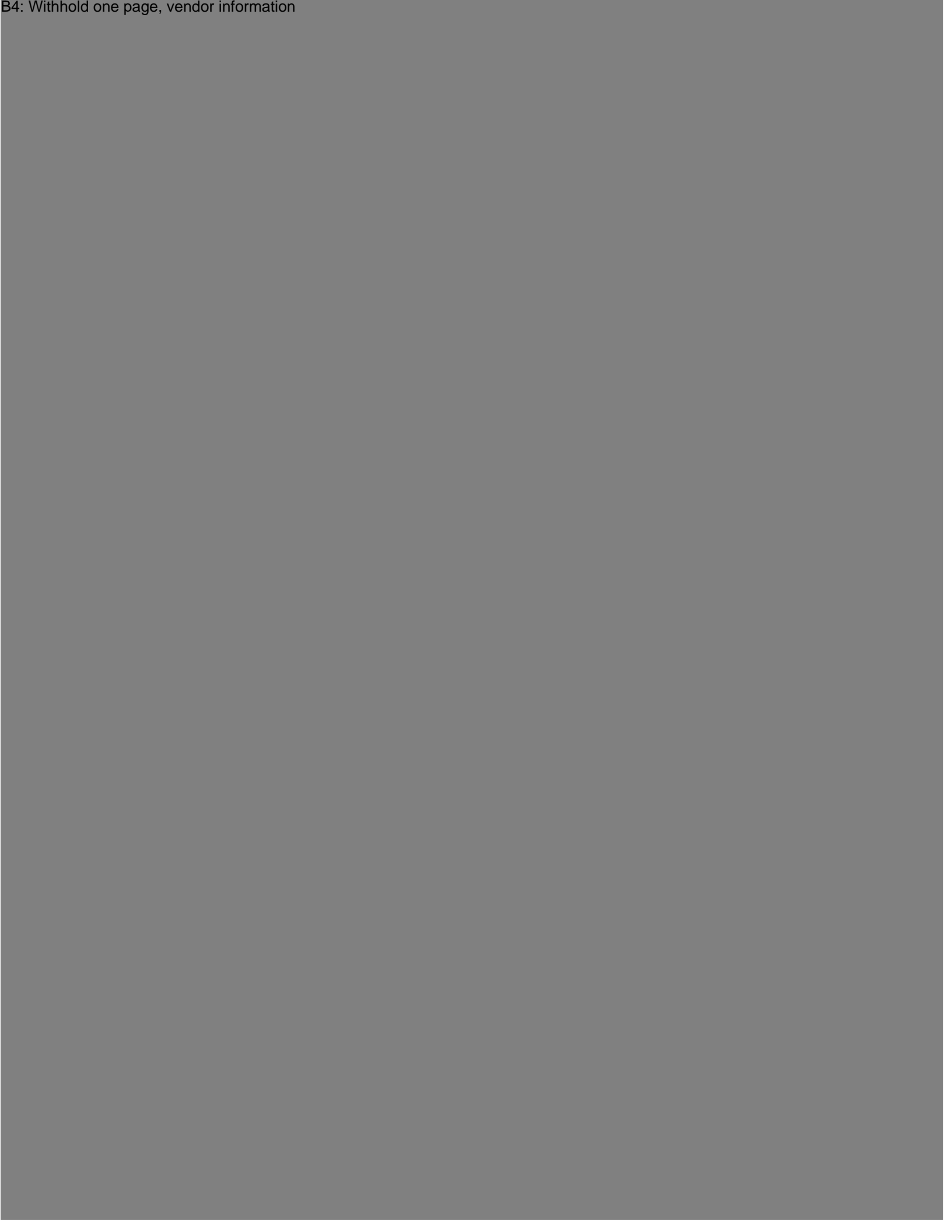
Attendance: Described by signals according to the below-mentioned classifications.

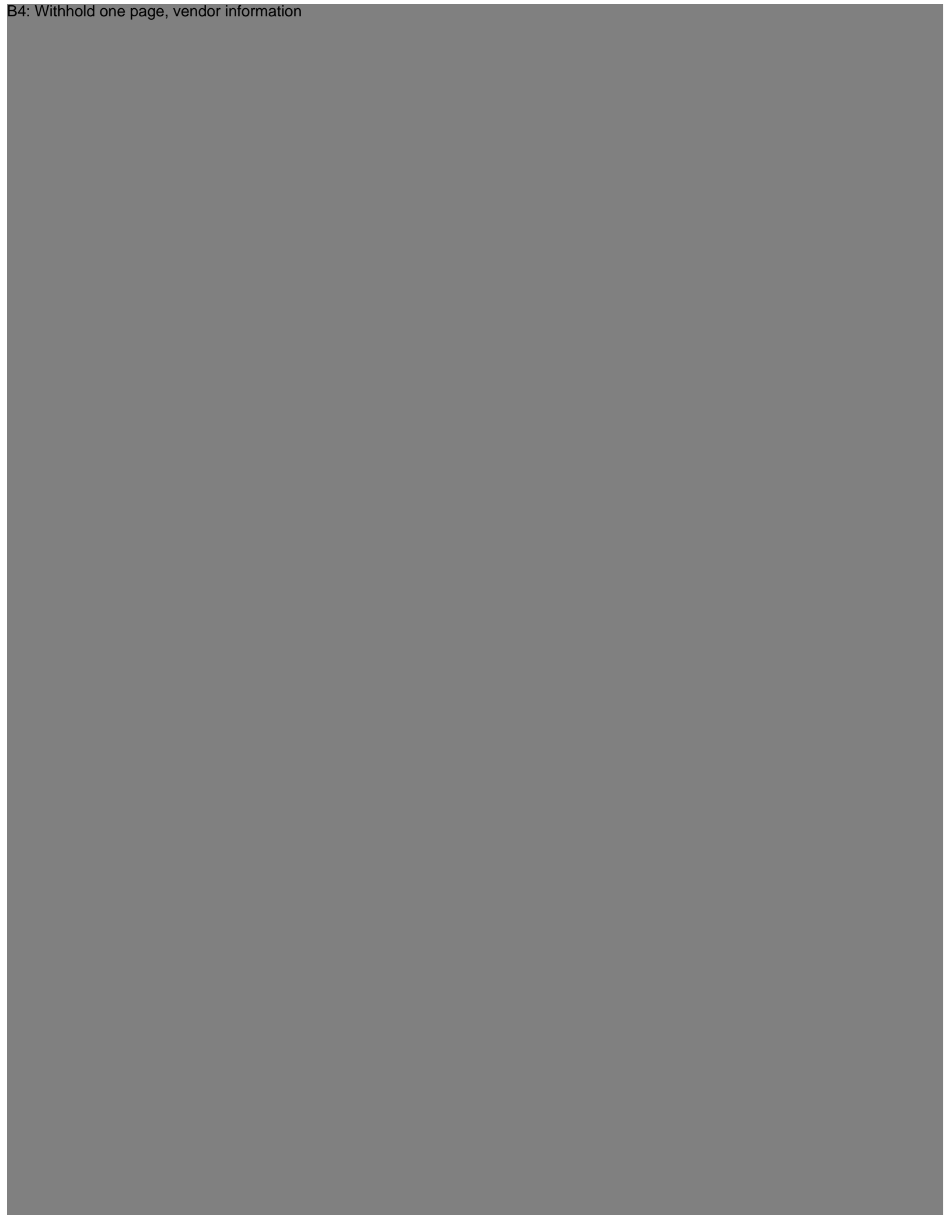
- O (Members who attended the meeting and have no involvement in the clinical study concerned)
- (Members who attended the meeting but who did not attend the deliberation and the vote due to the involvement in the clinical study concerned.)
X (Members who did not attend the meeting.)

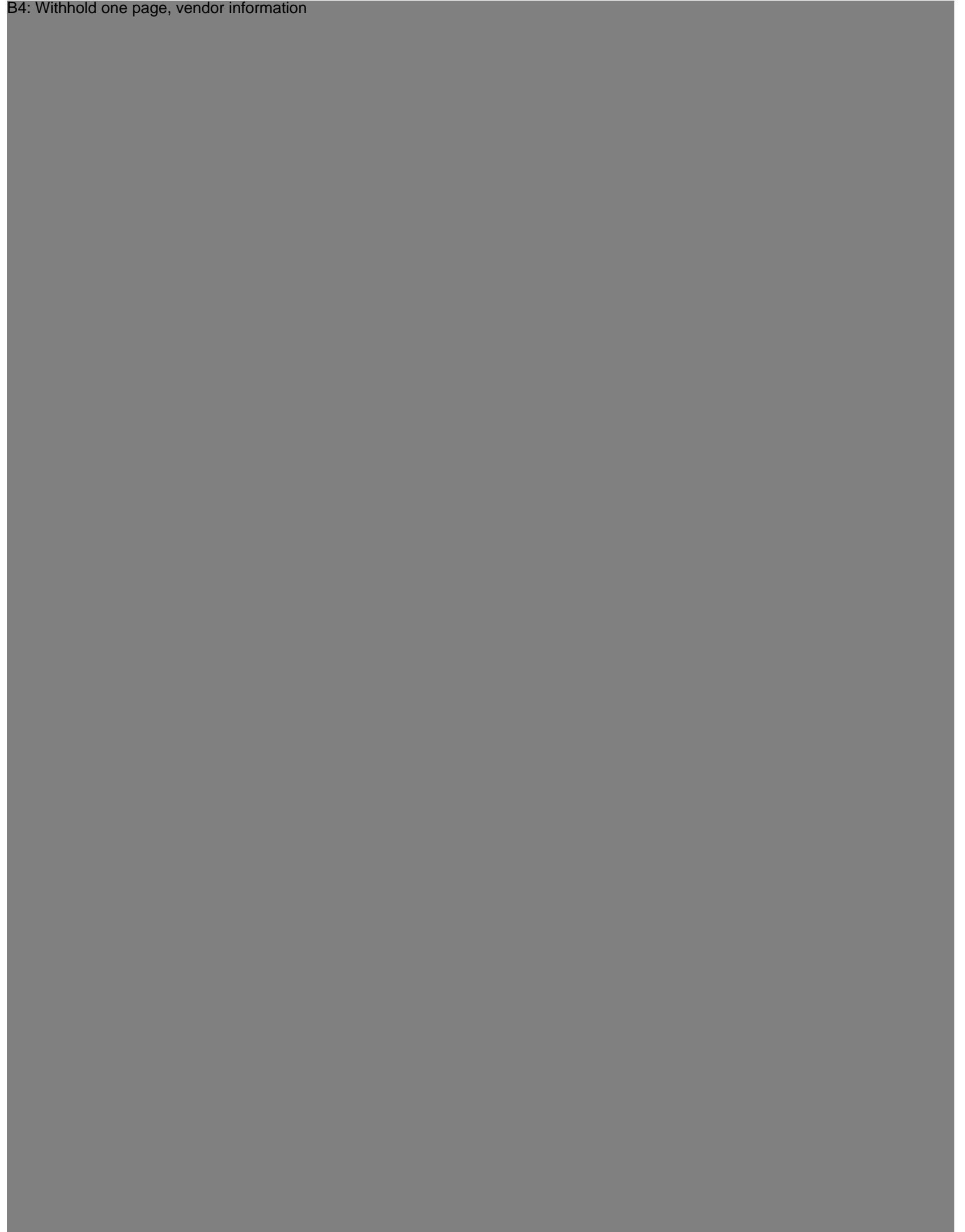
The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as "Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".



16.1.3.13 IEC/IRB Subject Information and Informed Consent Form Version 001 Approval Letter (Local Language)









16.1.3.14 IEC/IRB Subject Information and Informed Consent Form Version 002
Submission Letter



Form 10

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study <input type="checkbox"/> Post-marketing Study <input type="checkbox"/> Medical Products <input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Other

Date: 10/December/2013

Application for Clinical Study Change

Dear [Name of Head of Institution]

President of Clinic

Osaki Hospital Tokyo heart center

Sponsor

(b) (4)

Principal Investigator

We will apply for change as following;

Chemical Name or Identification Number of IP	THS2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Clinical Study Name	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Change documents, etc.	<input checked="" type="checkbox"/> Clinical Study Protocol <input checked="" type="checkbox"/> Informed Consent Form <input type="checkbox"/> Investigator's Brochure <input type="checkbox"/> Sub Investigators <input checked="" type="checkbox"/> other (Implementation system of clinical study at site. Documents concerning payments and compensation available to subjects. Document on the recruitment advertisement of the subject)		
Changes	Change matters	Before change	After changing
	Clinical Study Protocol (ENG and JPN)	Refer to Amendment N°1 (ENG and JPN)	
	Informed Consent Form	Refer to The Comparative Table	
	Implementation system of clinical study at site	Refer to The Comparative Table	
	Documents concerning payments and compensation available to subjects	Refer to The Comparative Table	
	Document on the recruitment advertisement of the subject	—	New
Reason for change	Refer to Amendment N°1 (ENG and JPN) · As reflected on protocol alternation due to discontinuation of study in Seishukai clinic · Clarification of the description Refer to The Comparative Table Refer to The Comparative Table Due to promotion of subject recruitment.		
Attachment	· Clinical Study Protocol (ENG and JPN) (19 November 2013/Final 2.0) · Clinical Study Protocol ZRHM-REXA-07-JP Amendment N°1 (ENG and JPN) (19 November 2013) · Informed Consent Form (06/Dec/2013/ver.2.0) · Informed Consent Form (The Comparative Table) · Documents concerning payments and compensation available to subjects (Date:03/Dec/2013) · Documents concerning payments and compensation available to subjects(The Comparative Table) (Date:03/Dec/2013) · Implementation system of clinical study at site (As of 03 Dec 2013) · Implementation system of clinical study at site(The Comparative Table) (Date:03/Dec/2013) · Document on the recruitment advertisement of the subject (including a reference material) (04 December 2013)		
Contact	Name: (b) (4) TEL: (b) (4)	Affiliation: Clinical Pharmacology Email: (b) (4)	

Note) (Head of Institution ≠Principal Investigator): Sponsor shall make this document under the principal investigator's agreement to submit to the head of institution. If only Informed Consent Form is revised, principal investigator shall make this document to submit to the head of institution. In this case, the sponsor column shall be filled in with "N/A".

(Head of Institution = Principal Investigator): Sponsor shall make this document to submit to the head of institution. PI column shall be filled in with "N/A". If only Informed Consent Form is revised, principal Investigator (the head of institution) shall make this document. In this case, both PI and the head of institution column shall be filled in, and sponsor column shall be filled in with "N/A".



16.1.3.15 IEC/IRB Subject Information and Informed Consent Form Version 002
Submission Letter (Local Language)





16.1.3.16 IEC/IRB Subject Information and Informed Consent Form Version 002 Approval Letter



Form 5

File Number	
Classifications	<input checked="" type="checkbox"/> Clinical Study
	<input type="checkbox"/> Post-marketing Study
	<input type="checkbox"/> Medical Products
	<input type="checkbox"/> Medical Devices <input checked="" type="checkbox"/> Others

Date: 12/18/2013

IRB Result Notification

Dear
President of hospital
Tokyo Heart Center, Osaki Hospital

Institutional Review Board
IRB of Yasuda Hospital
13-9 Narimasu 1 cho-me, Itabashi Ward, Tokyo
Kazuhisa Yoshimoto

We are notifying you the IRB deliberation results as follows.

Chemical Name or Identification Number of IP	THS 2.2 Menthol	Protocol Number	ZRHM-REXA-07-JP
Original Study Name	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers (1) switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or (2) observing smoking abstinence, compared to (3) continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting		
Matters Deliberated (Materials Deliberated)	<input type="checkbox"/> Pass/Fail of the Clinical Study Implementation (Clinical Study Request Form (copy of Form3 dated 07/05/2013)) <input checked="" type="checkbox"/> Continuation/Discontinuation of the Clinical Study <input type="checkbox"/> Serious Adverse Event (SAE) (<input type="checkbox"/> Report on SAE (copy of Form 12 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on Adverse Event (AE) (copy of Form 13 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on SAE and Defect (copy of Form 14 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on AE and Defect (copy of Form 15 dated mm/dd/yyyy)) <input type="checkbox"/> Safety Information, etc. (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) (<input type="checkbox"/> Report on Safety Information, etc. (copy of Form 16 dated mm/dd/yyyy)) <input checked="" type="checkbox"/> Changes on the clinical Study (Application for Changes on the Clinical Study (copy of Form 10 dated 12/10/2013)) <input type="checkbox"/> Protocol Deviation to Avoid Emergency Dangers (Report on Protocol Deviation to Avoid Emergency Dangers (copy of Form 8 dated mm/dd/yyyy)) <input type="checkbox"/> Continued Deliberation (Report on Performance of the Clinical Study (copy of Form 11 dated mm/dd/yyyy)) <input type="checkbox"/> Others ()		
Deliberation Type	<input checked="" type="checkbox"/> IRB Deliberation (Deliberation Date : 12/18/2013) <input type="checkbox"/> Rapid Deliberation (End Date of Deliberation : mm/dd/yyyy)		
Deliberation Result	<input checked="" type="checkbox"/> Approval <input type="checkbox"/> Approval after corrections <input type="checkbox"/> Reject <input type="checkbox"/> Withdrawal of approved matters <input type="checkbox"/> Pending		
Reasons, etc. for the result other than "Approval"			
Notes			

To: Sponsor (b) (4)

Date: 12/18/2013

To: Principal Investigator (b) (4)

As per your request, we are notifying you the results of the deliberated matters concerning the clinical study mentioned above.

Name of Head of Institution
Tokyo Heart Center, Osaki Hospital, President

Note: (Head of Institution ≠ Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of two (2) copies of the form, and shall submit one copy to the sponsor and one copy to the Principal Investigator respectively. If they are different, reference form 1 shall be used.

(Head of Institution = Principal Investigator)

The IRB shall make one original copy of this form to submit to the head of institution. If the IRB's decision and the instructions of the head of the institution are the same, the head of the institution shall describe the remarks of "Notice Date" and "Head of Institution" at the bottom of one (1) copy of the form, and shall submit the sponsor. If they are different, reference form 1 shall be used. "N.A." shall be stated in the column of the Principal Investigator.



File Number

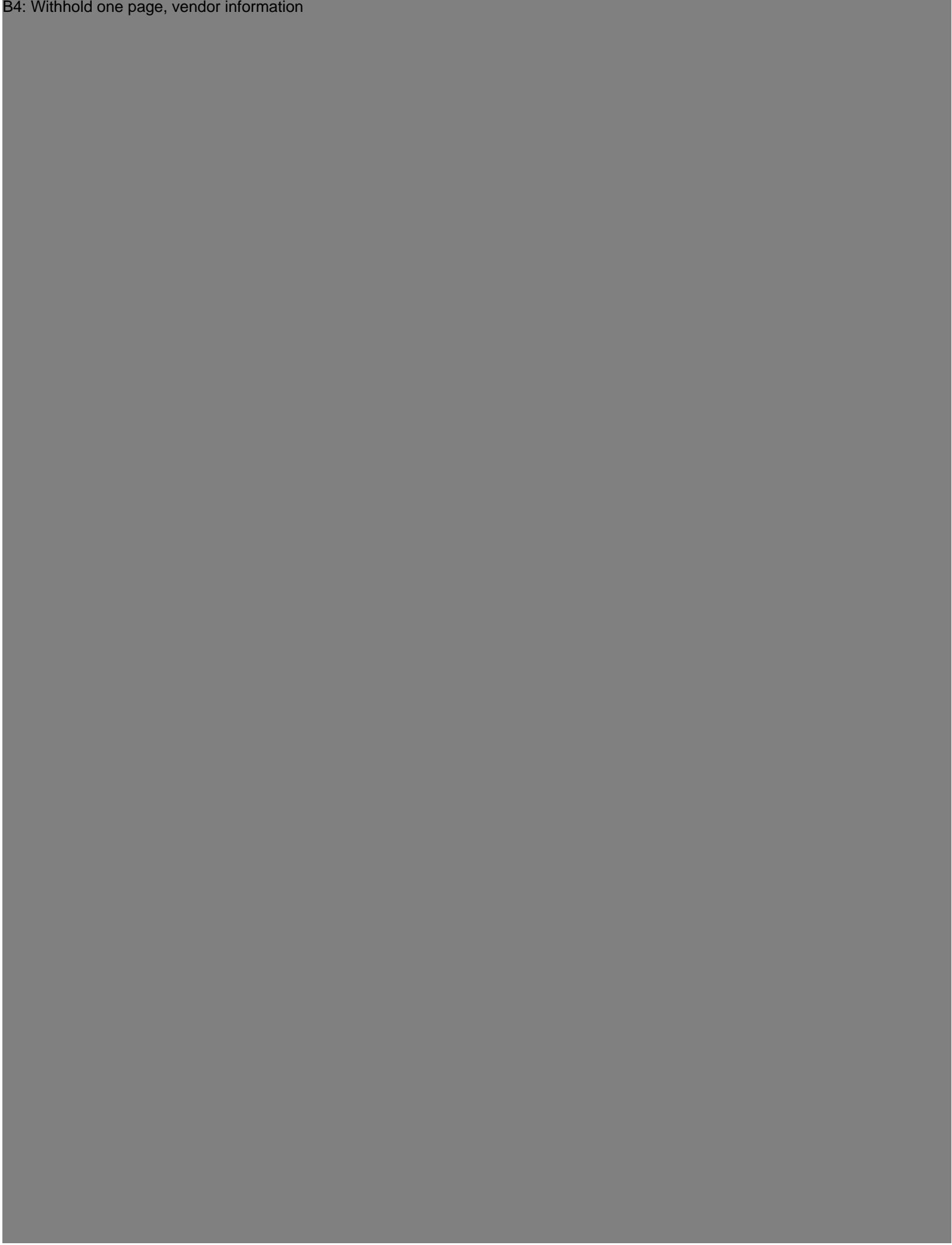
IRB Attendees List

[illegible]

The IRB ensures and guarantees that the board is organized and operated in accordance with the Standard Operating Procedures of this IRB, as well as "Good Clinical Practice for Drugs (MHW Ordinance No. 28, 1997)", "Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)", "Good Post-marketing Study Practice for Drugs (MHLW Ordinance No. 171, 2004)", "Good Post-marketing Study Practice for Medical Devices (MHLW Ordinance No. 38, 2005)".



16.1.3.17 IEC/IRB Subject Information and Informed Consent Form Version 002 Approval Letter (Local Language)





16.1.3.18 IEC/IRB Subject Information and Informed Consent Form

There are 2 versions of the Subject Information and Informed Consent Form for the main study (1.0 and 2.0), 1 version (1.0) of the optional Bio-banking for Biomarkers and Risk Markers Informed Consent Form, and 1 version (1.0) of the optional Bio-banking for Transcriptomics Informed Consent Form. All versions are presented in this section.



16.1.3.18.1 IEC/IRB Subject Information and Informed Consent Form (English)



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM SHEET

Optional Bio-banking (Long-Term Storage) of Blood and
Urine Samples for Further Biomarker of exposure/Risk
Marker Research in Reduced Exposure Study Using THS
2.2 Menthol with 5 Days in a Confinement Setting and 85
Days in an Ambulatory Setting

Osaki Hospital Tokyo heart center

Study Number: ZRHM-07-JP
Version 1.0



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

Written Information and Informed Consent Form

This document states all necessary information that is useful for you to understand the contents of this optional research, which you are going to be participating, as well as your benefit and right. Please decide whether to participate in this optional research by your own free will after you have sufficiently understood the details of this optional research. If you have any question of this optional research, please contact us at any time. You will be able to take some time before your reply and are not expected to give us your answer within today. You can take home this Written Information with you to look into it thoughtfully, to have time to think it over or discuss with your family or friends before, and let us know your decision at a later date.

Should you have any questions, please ask the study physician ("Investigator"). You can ask the Investigator about any issue, which is in your opinion, related to the research.

Once you signed and dated this Informed Consent Form, in a presence of Investigator, you will receive one original which you will take home. When making the decision to participate in the research, it is important that you accept its course, its purpose, the planned procedures, and that you are ready to participate until the end of the research.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

1. Introduction

You have already agreed to participate in "Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new candidate of Modified Risk Tobacco Product (MRTP), on selected biomarkers of exposure (BoExp) compared to conventional cigarettes.

This form tells you about "Optional Bio-banking (Long-Term Storage) of Blood and Urine Samples for Further Biomarker of exposure /Risk Marker Research" (the optional research) which will be conducted in subjects who are already participating in the main study. This subject information and informed consent form is an addition to the main study form that you have already signed. The intention of this document is to ask you consent for collection, storage of blood and urine samples for long-term and for your consent to use these samples for further biomarker of exposure/risk marker analysis.

What is the biomarker of exposure /risk marker analysis?

Biomarkers can be described as substances measured in your body as the result of consumption of another substance (such as cigarette smoke). A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection.

Currently, we are in the process of investigating the list of potential biomarkers of exposure and risk markers to be assessed and we are not in a position to provide a definite list. Only additional biomarkers of exposure to smoke constituents or risk markers (biomarkers such as an example your level of lipids in your blood) might be assessed in your samples collected and stored for bio-banking in order to further investigate the results of the main study you are participating to.

No genetic or transcriptomics analysis will be performed on these samples taken for the long-term storage (also see Informed Consent for Optional Bio-banking [Long-Term Storage] of Blood Samples for Further Transcriptomic Research).

The investigator, or study staff, will go over this with you and answer any questions you may have regarding this optional part of the research. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given an original copy to keep. No one can force you to agree on this optional long-term storage of blood and urine samples for further biomarker/risk marker analysis. If you do not agree to participate, you can still continue to participate in the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

optional research. This form is not meant to replace the one for the main study, and the contents of the main study subject information apply to this optional research.

By signing this informed consent form you agree for collection, storage of blood and urine samples for long term and that further biomarker of exposure /risk marker analysis may be done on your samples.

This form may contain words you do not understand. Please ask the investigator or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this optional research.

Before you decide to take part, you must understand the purpose of this optional biomarker of exposure /risk marker analysis, how your participation may help you, any potential risks to you, and what is expected of you during procedures of this optional research. Even if you agree to participate in this optional research you are free to change your mind and stop at any time without penalty or loss of benefits which you would otherwise have.

2. Purpose of this optional research

The purpose of this optional research is to collect blood and urine samples and store them for long-term for further biomarker of exposure/risk marker analysis (for details of biomarker of exposure /risk marker analysis, please see above section).

If you consent to this optional research, six blood samples and thirty urine samples for further biomarker/risk marker analysis will be drawn. Specifically, two blood samples will be required from you at the beginning of the main study (Day 0), two samples at the end of the confinement period (Day 6) and two samples at the end of the ambulatory period (Day 90 Visit [Day 91]). In addition, 10 urine samples will be collected each from your 24 hour urine collection of Day 0, Day 5 and Day 90 Visit (Day 90). These samples will be sent to the designated laboratories listed below in Section 4 and will be stored for further biomarker/risk marker analysis.

3. What will happen to me if I take part?

If you consent to this optional research, the investigator will ask you to sign this informed consent form. By signing this form, you will give consent to this optional part of the research that is to give blood samples (six 5 ml tubes = 30 ml in total), and 30 urine samples (10 ml each, 300 ml in total) for long-term storage with the purpose of further biomarker of exposure /risk marker analysis. You will not be able to take part in this optional test unless you sign the consent form. In the unlikely case that there is a problem processing your sample, you will not be asked to give an additional sample.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

4. About samples

4.1 Sample Analysis and Storage

Your six blood samples and thirty urine samples will be shipped for storage and analysis to a laboratory contracted by the Sponsor (Philip Morris Products S.A.) which has experience in testing as well as retaining and storing samples such as these. The blood and urine samples will be stored in a dedicated repository for clinical samples in Germany and further analysed in a designated laboratory using appropriate methods.

Laboratory for storage:

Tel:

Fax:

Laboratory which will undertake the analysis will be required to follow the requirements as set out in this informed consent form.

4.2 Sample Access Rights

Your blood and urine samples when they leave the study site for analysis will not include your name or any other personal details that could identify you. However, unlike the long-term storage samples for transcriptomic analysis, links between you and codes on samples will not be removed (also see Informed Consent for Optional Bio-banking [Long-Term Storage] of Blood Samples for Further Transcriptomic Research).

4.3 Post-Optional Research Sample Handling

Samples will be transferred to the Sponsor's laboratories in Germany and laboratory which will perform the analysis. The samples will be destroyed when the maximum storage time has been reached (5 years for blood samples, and 2 years for urine samples) or no further analyses are possible (whichever is early). You should be aware that Philip Morris Products S.A. might not conduct all research immediately and that your samples may be studied at any time before they are destroyed.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

5. Expected Clinical advantages and risks

5.1 What are the possible disadvantages and risks of taking part?

Using a needle to remove blood from a vein is called “a blood draw.” During the study, it may be necessary to try more than once. A new needle will be used for each blood draw. Blood samples for long-term storage and urine samples for further biomarker of exposure /risk marker analysis will be taken six times during the study. You might feel pain or be light-headed from this. You may experience some temporary discomfort, bleeding, bruising, or rarely, infection, at the site of a needle stick you receive in the process of drawing blood samples.

5.2 What are the possible benefits of taking part?

There is no direct benefit to you by taking part in this optional research. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor the investigator will be contacted by the Sponsor in connection with the research or any information about the results of biomarker of exposure /risk marker analysis performed on the sample that you provide for this optional research.

6. Is taking part in this optional research voluntary?

Taking part in this optional research is voluntary. You may withdraw your consent to take part in it whilst you are involved in the research without affecting your participation in the main study, and without any penalty or loss of benefits to which you are entitled. To withdraw your consent, you must contact the investigator or site staff.

7. What if there is a problem?

The Sponsor has taken out an insurance policy for all subjects who consent to optional bio-banking (long-term storage) of blood and urine samples for further biomarker of exposure /risk marker research and will provide compensation should any deterioration of health which is directly attributable to the procedures for the optional research specified in the protocol.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

8. Can I change my mind?

You may withdraw your consent to the use of your blood and urine samples for this optional research whilst you are still undergoing study assessments until the end of the study by contacting the investigator or site staff.

If you withdraw your consent for further biomarker of exposure /risk marker analysis, you may request your blood and urine samples to be destroyed and no longer used in the research. However, the Sponsor shall be entitled to keep and use any research results obtained prior to your successful withdrawal of consent.

9. Will my taking part in this optional research be kept confidential?

Strict privacy and confidentiality procedures have been adopted for this research to keep your information safe. Your blood and urine samples when they leave the study site for analysis will not include your name or any other personal details that could identify you.

Sponsor may use other laboratories, investigators, commercial or academic third parties as Sponsor's "agents" to assist in this research. All such individuals are required to keep the data confidential.

10. What will happen with the results of this optional research?

This biomarker of exposure /risk marker analysis is not intended to provide you with clinical information. Although you have the right to access information in your medical records, the information that the Sponsor will maintain in their databases and create during biomarker of exposure /risk marker analysis is for research purposes only. Sponsor will not return any biomarker of exposure /risk marker analysis information to you or the investigator. Information resulting from the research will not be entered into your medical records. At some point, information about the results of the research may be published; however, you will not be identified in any such publication.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

11. Development for Commercial Gain

Any information resulting directly or indirectly from this biomarker of exposure /risk marker analysis, as well as any rights in law, diagnostic tests, drugs, or biological products developed or created directly or indirectly as a result of this research, are the exclusive property of the Sponsor (and its successors, if any) and may be used for commercial purposes anywhere in the world. By signing this form, you give up all and any rights you may have had to this property and these rights or any share of the profits that may be earned directly or indirectly as a result of this biomarker of exposure /risk marker analysis exclusively to the Sponsor. However, in signing this form and donating blood and urine samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

You will not be paid for consent for this optional research. You will not have to pay for any analyses related to this optional research.

12. Who is organising and funding the research?

The company sponsoring this optional assessment is Philip Morris Products S.A. (including agents, contractors or consultants).



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

13. Who has reviewed the research?

An independent ethics committee has reviewed the objectives and the proposed conduct of the main study and of this optional biomarker of exposure /risk marker analysis and has given a favourable opinion of it.

IRB is a committee, which has been established to assess whether or not the Clinical Study is conducted with respecting the participants' human rights and ensuring their safety, whether it is scientifically/ethically-valid and there is no problem in the Clinical Study Plan. IRB is required to consist of such as medical professionals (medical science and pharmaceutical science), some members other than medical professionals, and also independent members without interest from this Hospital. IRB performs to review the contents of Clinical Study Plan with taking patients' position into careful consideration. The President of our hospital is going to consult IRB members to get opinion concerning the implementation and continuation of the Clinical Study. At the same time, IRB is expected to advise their opinion to our President with reviewing the implementation and continuation of the Clinical Study from the scientific and ethical perspective.

We hereby certify the Clinical Study "Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting" including sample bio-banking has been reviewed and approved by the IRB that is established in Yasuda Hospital.

- ☐ Name : IRB, Yasuda Hospital
- ☐ Type of IRB : IRB established in Yasuda Hospital
- ☐ Founder : President, Yasuda Hospital
- ☐ Address : 1-13-9 Narimasu Itabashi-ku Tokyo, Japan
- ☐ Homepage Address: <http://www.yasudahosp.jp/>

You are entitled to view Procedure, list of board members, abstract record of this Institutional Review Board. The information is available at the study site. Please feel free to ask the Investigator (or site collaborator) for the information freely.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

14. Contact details

Please contact us at the following contact information desk if you have any question and/or consultations concerning sample bio-banking.

Hospital Name	Osaki Hospital Tokyo heart center
Information Desk	Osaki Hospital Tokyo heart center Clinical Research Coordinator
Contact person	
Telephone No.	

We ask for your kind understanding concerning sample bio-banking.

Please feel free to contact us if you have any question and/or issues need to be explained.

After due consideration, please sign the following Informed Consent Form as well as fill in the date of consent with your understanding and agreement for sample bio-banking. Please be sure to receive this Written Information and one original copy of Informed Consent Form you signed.

Thank you for taking time to read this information sheet.

Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

To President of Osaki Hospital Tokyo heart center

To be attached to the medical records

Informed Consent Form

I have received sufficient explanation and understood the contents of Optional Bio-banking (Long-Term Storage) of Blood and Urine Samples for Further Biomarker of exposure /Risk Marker Research in Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting and 85 Days in an Ambulatory Setting, therefore, I agree to participate in this analysis with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy

Name (Signature)

Please check

- ☐ I confirm that the optional bio-banking (long-term storage) of blood and urine samples for further biomarker of exposure /risk marker assessment has been explained to me and I have had the opportunity to ask questions and ample time to decide whether to participate. I know who to contact if I have any further questions.
- ☐ I confirm that I have read and understand the information sheet Japanese final version 1.0 dated 05 July 2013 for the biomarker of exposure/risk marker analysis.
- ☐ I understand that my participation is voluntary and agree to take part in this biomarker of exposure /risk marker analysis.
- ☐ I agree for collection and long-term storage of 30 ml blood and 300 ml urine.
- ☐ I agree that my blood sample can be used for the purposes of this further biomarker of exposure /risk marker assessment.
- ☐ I understand that if I withdraw my consent for biomarker of exposure /risk marker analysis, it will not be possible to destroy the data obtained from my samples.

I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Principal (Sub) Investigator

Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Seal

Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

To President of Osaki Hospital Tokyo heart center

For participants

Informed Consent Form

I have received sufficient explanation and understood the contents of Optional Bio-banking (Long-Term Storage) of Blood and Urine Samples for Further Biomarker of exposure /Risk Marker Research in Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting and 85 Days in an Ambulatory Setting, therefore, I agree to participate in this analysis with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy

Name (Signature)

Please check

- ☐ I confirm that the optional bio-banking (long-term storage) of blood and urine samples for further biomarker of exposure /risk marker assessment has been explained to me and I have had the opportunity to ask questions and ample time to decide whether to participate. I know who to contact if I have any further questions.
- ☐ I confirm that I have read and understand the information sheet Japanese final version 1.0 dated 05 July 2013 for the biomarker of exposure/risk marker analysis.
- ☐ I understand that my participation is voluntary and agree to take part in this biomarker of exposure /risk marker analysis.
- ☐ I agree for collection and long-term storage of 30 ml blood and 300 ml urine.
- ☐ I agree that my blood sample can be used for the purposes of this further biomarker of exposure /risk marker assessment.
- ☐ I understand that if I withdraw my consent for biomarker of exposure /risk marker analysis, it will not be possible to destroy the data obtained from my samples.

I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Principal (Sub) Investigator

Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Seal



Study Number: ZRHM-REXA-07-JP (Main Study)
Dated: 2013/DEC/06 (Ver. 2.0)

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM SHEET

A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting

(Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting)

Osaki Hospital Tokyo heart center



Study Number: ZRHM-REXA-07-JP (Main Study)
Dated: 2013/DEC/06 (Ver. 2.0)

Version 2.0

Study Number: ZRHM-REXA-07-JP (Main Study)
Dated: 2013/DEC/06 (Ver. 2.0)

Written Information and Informed Consent Form

This document states all necessary information that is useful for you to understand the contents of this clinical study, which you are going to be participating, as well as your benefit and right. Please decide whether to participate in this study by your own free will after you have sufficiently understood the details of this study. If you have any question of this study, please contact us at any time. You will be able to take some time before your reply and are not expected to give us your answer within today. You can take home this Written Information with you to look into it thoughtfully, to have time to think it over or discuss with your family or friends before, and let us know your decision at a later date.

Should you have any questions, please ask the study physician ("Investigator"). You can ask the Investigator about any issue, which is in your opinion, related to the study.

Once you signed and dated this Informed Consent Form, in a presence of the Investigator, you will receive one original which you will take home. When making the decision to participate in the study, it is important that you accept its course, its purpose, the planned procedures, and that you are ready to participate until the end of the study.

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1. Introduction

Cigarette smoking causes lung and heart disease and other serious diseases in smokers. There is no safe cigarette and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers cannot give up smoking or decide to continue smoking. To those smokers who are not able or not willing to quit, Philip Morris Products S.A. is developing alternative approaches by developing products with the potential to reduce the risks of tobacco-related diseases.

The product developed by Philip Morris Products S.A., and to be assessed in this study, is called Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol). With this product, the heating of the tobacco is maintained below 400°C, a temperature much lower than what is observed for menthol conventional cigarettes, which can reach 900°C. The THS 2.2 Menthol product comprises the following components: the THS Menthol Tobacco Stick (Menthol Tobacco Sticks), Tobacco Stick Holder, the Charger, a Cleaning Tool, a mains power supply, and a USB cable. The Tobacco Heating Device comprises everything in THS 2.2 Menthol except the Menthol Tobacco Stick. The function of the Holder is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 Minutes (allowing complete use of a single Menthol Tobacco Stick. Unlike menthol conventional cigarettes, the Menthol Tobacco Sticks do not burn down during their consumption and their lengths remain constant after use.

It is thought that by heating tobacco rather than burning it as in a normal cigarette it may be possible to reduce the harmful effects of smoking.

So far, no clinical studies have been conducted with the THS 2.2 Menthol. In previous clinical studies, tests on earlier versions of THS 2.2 Menthol showed no safety concerns. However, by participating to this study, you may experience risks and adverse reactions as described in the section 5, Expected Clinical advantages and risks.

Participants must be aware that there are no 'safe' cigarettes. Quitting smoking is the only method of reducing the risk of cancer, or any heart, blood vessels and lung diseases associated with smoking.

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2. Purpose of this study

The purpose of this study is a research to collect data on adult smoker using the newly developed Tobacco Heating System 2.2 Menthol.

The main purpose of the study is to evaluate the effect of a new candidate of modified risk tobacco product – Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) on selected biomarkers of exposure and selected risk markers compared to menthol conventional cigarettes with 5 days in a confinement setting and 85 days in an ambulatory setting. The term 'menthol conventional cigarette' refers to manufactured and commercially available menthol cigarettes and excludes hand-rolled cigarettes, cigars, pipes, and other nicotine-containing products. Biomarkers of exposure can be described as substances measured in your body as the result of consumption of another substance (such as cigarette smoke). For example you will intake carbon monoxide when you smoke. Carbon monoxide binds in your body to certain parts of your red blood cells called hemoglobin. The level of carbon monoxide bound to this hemoglobin will be measured among others in this study and is referred to as biomarker of exposure to carbon monoxide. Risk markers can be described as biological indicators of the body's response to exposure and indicate early biological changes, which if sustained, may go on to have pathological consequences. This study will also look at people's urge to smoke and any withdrawal symptoms; to gather information on the safety of using the new THS 2.2 Menthol product.

In addition, some analysis will be conducted in the study to assess human smoking behavior by way of Human Smoking Topography (HST) using the HST SODIM® device when using the THS 2.2 Menthol product compared to menthol conventional cigarettes. The impact of the HST SODIM® device on smoking behavior will also be assessed.

This study is not intended to recommend continued smoking.

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3. Study procedures

3.1 Information on Test Product

The product to be assessed in this study is called Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol).

THS 2.2 Menthol comprises the following components: Menthol Tobacco Stick, Holder, Charger, a Cleaning Tool, a mains power supply, and a USB cable:

Charger:		The function of the Charger (Model 4) is to recharge the Holder after use. It contains a battery with sufficient capacity to recharge the Holder approximately 20 times. It is a convenient size to carry around, and can itself be recharged from a mains power source.
Menthol Tobacco Stick		The function of the Holder (Model 4.2) is to heat the Menthol Tobacco Stick, delivering an aerosol to the user. The electrical heating is powered from an internal battery which delivers power for about 6 minutes (allowing complete use of a single Menthol Tobacco Stick)
Holder (Holder):		
THS Menthol Tobacco Stick (Menthol Tobacco Stick):		The Menthol Tobacco Stick (product code C3 Menthol) contains tobacco which, when heated, generates an aerosol. It is custom-designed to be used with the Holder.

So far, no clinical studies have been conducted with the THS 2.2 Menthol, however, a number of clinical studies have been conducted by Philip Morris International and Philip Morris USA from 2004 to 2012 with the previous version of the device (THS 1.0 and THS 2.1). All these studies showed reductions in exposure to selected smoke constituents in subjects who used the THS 1.0 or THS 2.1, as compared to subjects continuing smoking menthol conventional cigarettes. No safety concerns were to be reported from these studies.

3.2 Study Procedures

This is a randomized, 3-arm, ad libitum smoking study to compare the use of THS 2.2 Menthol product or smoking abstinence and smoking menthol conventional cigarettes. In total, approximately 160 female and male smoking, healthy, subjects will be randomized into the main study.

Please note: Ad libitum use means that you will be free to decide how many conventional cigarettes or product you wish to have. During the confinement period there are no restrictions in the number of menthol conventional cigarettes or Menthol Tobacco Sticks you smoke or use between 06:30 and 23:00, if you are randomized to menthol conventional cigarette arm or to THS 2.2 Menthol arm, respectively. However, if you are randomized to smoking abstinence arm, you will be asked to abstain from smoking or using any nicotine/tobacco-containing product up to 5 days during the confinement period. During the ambulatory period, there will be no restrictions in the number and time of menthol conventional cigarette or Menthol Tobacco Stick you use, if you are randomized to menthol conventional cigarette arm or to THS 2.2 Menthol arm.



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Subjects in the THS 2.2 Menthol arm will be instructed to exclusively use THS 2.2 Menthol and subjects in the Smoking abstinence arm will be instructed to remain abstinent from smoking with or without Nicotine Replacement Therapy. Subjects in the smoking abstinence arm may use NRT if considered necessary by the Investigator or if requested by the subject.

The entire study duration of your participation will be 123 to 150 days including a screening period of up to 28 days (4 weeks) prior to admission to the clinic (Day -30 to Day -3), a 9-day confinement period (afternoon of Day -2 to time of discharge of Day 6), a 85-day ambulatory period (from the time of Discharge of Day 6 to the time of Discharge on Day91) and a 28-day safety follow-up (after discharge on Day 91 to Day 119).

Screening period (Day -30 to Day -3)

The Screening period covers up to 4 weeks (Day -30 to Day -3) prior to Admission to the Site (afternoon of Day -2). A demonstration of the THS 2.2 Menthol product will be given by the site staff during the Screening Visit.

Confinement period (Day -2 to discharge on Day 6)

You will be in a confined setting for 9 days from Day -2 onwards as follows:

- The 1-day run-in period is defined as from Day -2 (Admission) until 06:29 of Day -1.

After admission and prior to enrolment at Day -2, as the last procedure of the eligibility assessments on that day, you will have a trial of the THS 2.2 Menthol product (using up to 3 Menthol Tobacco Sticks). If you are a female, the trial of the product will be done after pregnancy was excluded. You can only participate in the study if you are willing and able to use the product.

- The 2-day baseline period starts at 06:30 on Day -1 until 06:29 on Day 1.

Randomization to one of the following study arm will be performed by a computer program. You will be informed of the study arm to which you have been randomly selected prior to 06:30 on Day 1 of the study:

- THS 2.2 Menthol product (*ad libitum* use): subjects who will use the THS 2.2 Menthol product
 - Conventional Cigarette (*ad libitum* use): subject who will smoke their own single preferred brand of menthol conventional cigarettes
 - Smoking Abstinence: subjects who will abstain from smoking. If you are randomized to the smoking abstinence arm, you will be asked to abstain from smoking any nicotine/tobacco-containing product and you will not be provided with medication to support smoking abstinence. You will be provided with psychological support during the period of smoking abstinence.
- The 5 days exposure period in confinement is defined as from 06:30 of Day 1 until time of Discharge on Day 6.

During the exposure in confinement setting, you can smoke menthol conventional cigarettes or Menthol Tobacco Sticks between 06:30 and 23:00, if you are randomized to menthol conventional cigarette arm or to THS 2.2 Menthol arm, respectively. However, if you are randomized to smoking abstinence arm, you will be asked to abstain from smoking any nicotine/tobacco-containing product during this period.



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You will be discharged after 9 days confinement on Day 6, once you have completed all the procedures before Discharge on Day 6. Smoking is not allowed from Day 5, 23:01 until lung function test, blood draw for CYP2A6 activity, questionnaires to assess cough and withdrawal symptoms has been performed on Day 6.



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Ambulatory period (discharge on Day 6 to discharge on Day 91)

- The 85 days ambulatory period is defined as exposure period in ambulatory setting from the time of discharge on Day 6 until 23:00 on Day 90 and the Discharge Day from 23:01 on Day 90 until the time of discharge on Day 91

During the exposure in ambulatory setting, you will be asked to continue with your assigned product/regimen for 85 days. If you are allocated to the THS 2.2 Menthol arm, you will be instructed to exclusively use THS 2.2 Menthol and if you are allocated to the SA arm, you will be instructed to remain abstinent from smoking with or without NRT. If you are allocated to the SA arm, you may use NRT if considered necessary by the Investigator or if requested by you. NRT products will be used as per the product label, and they may be purchased at a pharmacy. You will be reimbursed. During the ambulatory period, you will be asked to complete a product use electronic diary to record any use of conventional cigarettes (menthol or non-menthol), Menthol Tobacco Sticks, nicotine replacement therapy, or other nicotine/tobacco-containing products.

You are required to make three visits (Day 30 Visit, Day 60 Visit, and Day 90 Visit) to the investigational site. Each visit will cover 2 consecutive days on site. The Day 30 Visit, Day 60 Visit and Day 90 Visit will take place from 08:00 AM on Day 30, Day 60 and Day 90 until all the assessments are finished on Day 31, Day 61 and Day 91, respectively.

You will be discharged from Day 90 Visit once you have completed all the safety procedures before Discharge on Day 91. Smoking will not be allowed from Day 90, 23:01 until lung function test, blood draw for CYP2A6 activity, and questionnaires to assess cough and withdrawal symptoms have been performed on Day 91.

The 28-day safety follow-up period (after the discharge on Day 91 until Day 119)

After the discharge, you will enter a 28-day safety follow-up period during which you will be asked to inform the site about any potential medical events you may experience. The site will also contact you to follow-up on any medical problems that has been reported by you during the study but have not been resolved before the discharge from the site.

Human Smoking Topography (HST)

As part of the main study described above, you will participate in a Human Smoking Topography procedure (for assessment of human smoking behaviours). Human smoking topography involves the measurement of each smoker's unique way of using THS 2.2 Menthol product or smoking menthol conventional cigarettes by employing a portable device named HST SODIM[®] device. The HST SODIM[®] device consists of a special holder which is placed between the smoker's mouth and the filter of the menthol conventional cigarette being smoked or THS 2.2 Menthol product being used and portable data logger. The holder is connected by 2 narrow tubes to a portable data logger/recording system which records among others such parameters as puff volume, number of puffs and puff duration. Smoking Topography will not be done if you are smoking menthol conventional cigarette that are incompatible with the HST SODIM[®] device (e.g. slim cigarettes).

At Day -1, the HST SODIM[®] device will be provided to the subjects who smoke menthol conventional cigarette compatible with it. If you are provided with the device, you will be asked to use it for every menthol conventional cigarettes smoked on all HST assessment days starting from Day 0 (in the case of malfunction, the device will be exchanged).

Thereafter, if you are randomized to menthol conventional cigarette arm or THS 2.2 Menthol arm, you will also be asked to use it on Day 1 and Day 4 of the confinement period for every

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product use. From Day 1 onwards, if you are randomized to smoking abstinence arm, you will not need to use it.

On Day 30 Visit, Day 60 Visit and Day 90 Visit, if you are randomized to menthol conventional cigarette or THS 2.2 Menthol group, you are asked to use HST SODIM[®] device every time you use THS 2.2 Menthol product or smoke menthol conventional cigarette: assessment of human smoking behavior will be performed for 4 hours on each Visit.

Questionnaires and Visual Analogue Scales

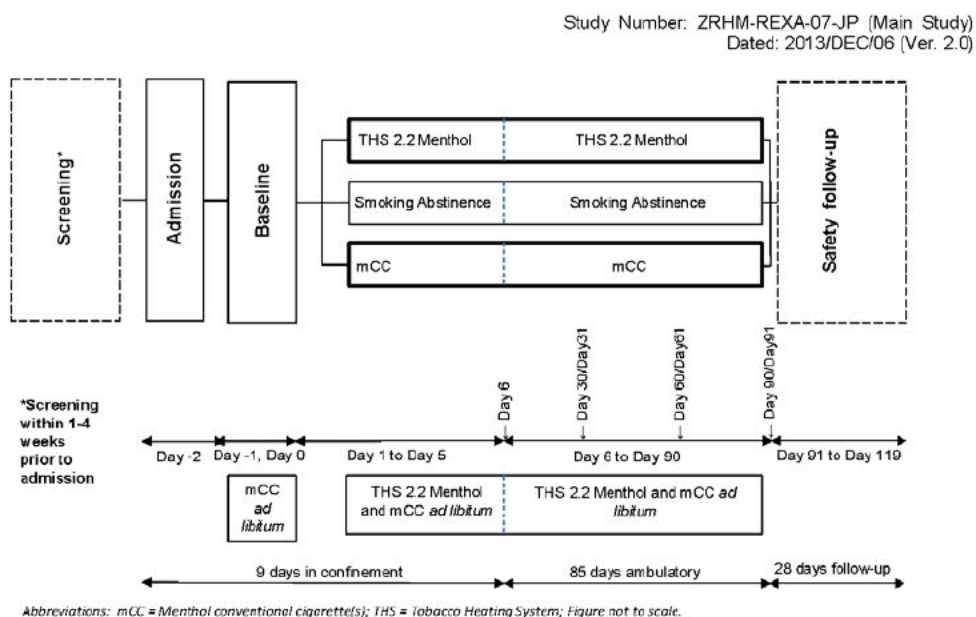
Throughout the study you will be asked to complete a variety of questionnaires and a visual analogue scale for cough assessment. The visual analogue scale requires that you make a mark on a line to indicate an answer to a question. The questionnaires and the visual analogue scale will be answered by you directly in an electronic device or on paper.

The study site staff will provide you with detailed instructions of how to use these tools. The questionnaires and the visual analogue scale will be reviewed for completeness by the site staff and you will be requested to complete any missing information.

Product Use Electronic Diary

This study has an ambulatory period, during which you will continue with your allocated product/regimen. During the ambulatory period, you will be asked to keep record of the number of products used (e.g. menthol and non-menthol conventional cigarettes, Menthol Tobacco Sticks, or any other tobacco / nicotine-products including NRT) on a daily basis from your time of discharge on Day 6 until 23:00 on Day 90 in this electronic diary. The electronic diary will be supplied by Sponsor and distributed to you by the study site staff on Day 6. The study site staff will provide you with detailed instructions of how to use the product use electronic diary before the Discharge on Day 6.

Study design of this study is shown in the below figure.





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Smoking Restrictions and Butts / Used Menthol Tobacco Sticks (Filters and Tobacco Plugs) Collection

Only smokers of menthol, commercially available and manufactured menthol conventional cigarettes with a maximum of 1 mg nicotine per cigarette are allowed into the study. This is an *ad libitum* product use study however the smoking can be restricted if, in the judgement of Investigator, more smoking can be dangerous to you.

During the exposure period (confinement and ambulatory setting), you will be assigned to either continue smoking menthol conventional cigarettes (from admission on site onwards, you must restrict to one preferred menthol conventional cigarettes) or to use exclusively the THS 2.2 Menthol product (which is explained within this information sheet) or abstain from smoking.

Confinement Period (9-days duration from Day -2 to Day 6)

During the confinement period, smoking will be allowed during the designated smoking times, from 06:30 to 23:00, except during study procedures.

Although this is an *ad libitum* smoking study, during this confinement period only, you will not have free access to your menthol conventional cigarettes or THS 2.2 Menthol product; these will be dispensed by the study site staff individually. Please inform the study site staff when you would like to smoke.

During the baseline period (Day -1 and Day 0), you will be allowed to continue smoking *ad libitum* your usual single preferred brand of menthol conventional cigarettes.

From Day 1 to Day 5, if you are randomised to the smoking abstinence arm, you will not be allowed to use any nicotine/tobacco-containing product during the exposure in confinement setting and you will not be provided with medication to support smoking abstinence.

From Day 1 to Day 5, if you are randomized to the THS 2.2 Menthol arm, you will not be allowed to smoke any menthol conventional cigarettes or use any other nicotine/tobacco containing products during the exposure in confinement setting. If smoking of conventional cigarettes (menthol or non-menthol) or use of any other nicotine/tobacco containing products is detected in this study arm, you may be withdrawn from the study at the discretion of investigator.

To avoid cross contamination between the three arms, users of the THS 2.2 Menthol product and of menthol conventional cigarettes must use separate rooms during the confinement period. Subjects allocated to the smoking abstinence arm should not have access to the smoking rooms.

In general, the performance of scheduled procedures has priority over your wish to smoke during the study. However this is different at Day 5 due to the assessment of the nicotine profile. If you want to smoke around the time of the blood draw, you should smoke first and the blood will be drawn after the cigarette has been smoked.

Smoking is not allowed from 23:00 on Day 5 until a lung function test, blood draw for CYP2A6 activity, and questionnaires to assess cough and withdrawal symptoms have been performed on the morning of Day 6

From Day 1 to Day 5, menthol conventional cigarettes butts will be collected for accountability only. From Day 1 to Day 5, the filters of all used THS Menthol Tobacco Sticks will be collected for subsequent analysis and accountability. From Day 1 to Day 5, the tobacco plug of all used THS Menthol Tobacco Sticks will be collected for subsequent visual inspection and accountability by the site staff.



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Ambulatory Period (85-days from discharge on Day 6 until 23:00 on Day 90)

During the exposure period in ambulatory setting, you will be asked to continue with your allocated product/regimen. However, you will be allowed to use medication to support smoking abstinence during the ambulatory period. But no medication supportive for smoking cessation other than NRT will be allowed in the study.

During the ambulatory period, there will be no smoking/product restriction except during the three visits on site on Day 30 Visit, Day 60 Visit, and Day 90 Visit: On Day 30, Day 60, and Day 90: product use will be allowed from 8:00 to 23:00 during the Visit. Smoking/product use before check-in on Day 30, Day 60 and Day 90 is not restricted. On Day 31, Day 61, product use will be allowed from 6:30. In the morning of Day 91 after the end of exposure ambulatory period (after 23:00 on Day 90), you will not be allowed to smoke until spirometry, assessment of cough and withdrawal symptom questionnaires and CYP2A6 assessment have been done on site.

During the ambulatory visit, you are free to smoke or use product anytime without asking the site staff. However, during the 4-hour of HST recording, you will be asked to inform the site staff whenever you smoke a menthol conventional cigarette or use a THS Menthol tobacco sticks if you are randomized to menthol conventional cigarette group or THS 2.2 Menthol group, and had received HST SODIM® device.

To avoid cross contamination between the three arms, users of the THS 2.2 Menthol product and of menthol conventional cigarettes must use separate rooms during the ambulatory visits. Subjects allocated to the smoking abstinence arm should not have access to the smoking rooms.

All tobacco plugs from Menthol Tobacco Sticks used after the check-in to the site until 23:00 on Day 30, Day 60, and Day 90, will be collected by the site staff for subsequent visual inspection.

If you are willing to make a quit attempt during the study you will be encouraged to do so at any time and you will be given adequate support from the site staff. You can quit smoking at any time during the course of the study. In case you quit, your study participation will be discontinued (this is applicable for all subjects during screening to the baseline period and for subjects allocated to THS 2.2 Menthol or conventional cigarette arms during the exposure period).



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Dietary Restrictions

A standard diet (in which caloric and fat content is controlled to avoid high-fat diet) will be designed by a dietician for the whole confinement period. In order to avoid any effect on assessment of biomarkers of exposure, grilled or pan-fried meat, pre-cooked smoked meats (e.g. tuna, ham, corned beef, bacon, sausage and meats) will not be permitted. In addition, alcohol, broccoli, brussels sprouts, cauliflower, grapefruit and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana, etc.) will not be allowed (except for the uptake of caffeine tablet for the study procedure). Consumption of quinine containing drinks (e.g. tonic water) is not allowed during the confinement period.

You are not allowed to bring your own food (including sweets or chewing gum, etc.) or beverages to the site. Meals will be served according to the agreed schedules. Consumption of water is allowed as desired.

During the ambulatory period, the above dietary restrictions are not applicable. However, 3 day prior to the Day 30 Visit, the Day 60 Visit, and the Day 90 Visit, you will be asked to refrain from consuming grapefruit or grapefruit-containing products, or quinine containing drinks (e.g., tonic water). Alcohol, broccoli, Brussels sprouts, cauliflower, grilled meat, xanthine-containing foods and beverages (e.g. coffee, tea, chocolate, cocoa, mate, guarana) will not be allowed on site during the ambulatory visits.

Fasting state has to be observed for at least 10 hours prior to blood draws for the following assessments:

- The safety laboratory at the Screening Visit, on Day 0, on Day 6, Day 31, Day 61, and Day 91
- The risk marker assessments in serum/plasma blood on day 0, day 6, Day 31, Day 61 and Day 91
- Serum/plasma bio-banking for further analysis of biomarkers of exposure and risk markers on Day 0 Day 6 and Day 91 (only if you consented: for details, please see the informed consent forms/subjects information sheets for bio-banking for further analysis of biomarkers of exposure and risk markers),
- Blood bio-banking for transcriptomics analysis on Day 0 Day 6 and Day 91 (only if you consented: for details, please see the informed consent forms/subjects information sheets for bio-banking for transcriptomics).

Concomitant Medication

No medication must be taken during the study from screening to time of discharge on Day 91 without prior consultation of the Investigator. The Investigator is responsible for your medical care during your participation in this study. Any decisions regarding the prescription of medication will be taken in your best interest.

During the ambulatory period, subjects in the SA arm may use NRT on the judgment of the Investigator or on request of the subject. No medication supportive for smoking cessation other than NRT will be allowed in the study.

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From the time of admission to the site, you must restrict yourself to smoking only your preferred single brand of menthol conventional cigarettes.

Confinement Period

During the run-in period (Admission to site until 06:30 of Day-1) and the baseline period (06:30 at Day-1 until 06:29 of Day 1), you will continue to smoke your single brand of commercially available menthol conventional cigarettes with a maximum of 1 mg nicotine per cigarette as written in the package.

Menthol conventional cigarettes will not be provided by Philip Morris Products S.A. or site staff. You will be asked to purchase your own preferred single brand menthol conventional cigarettes for the confinement period prior to Admission. You need to provide your anticipated amount of menthol conventional cigarettes for a total of 9 days plus four extra packs at Day -2 (Admission day) to the site staff.

The cigarette packs provided by you should not be opened and the cellophane wrapper should be intact. Each pack of cigarettes provided by you will be labelled. The unused menthol conventional cigarettes will be given back to you at discharge on Day 6.

THS 2.2 Menthol product will be provided by Philip Morris Products S.A..

Ambulatory Period

Menthol Tobacco Sticks for the ambulatory period will be supplied on Day 6 (before the Discharge), on Day 30 Visit and Day 60 Visit, and if needed, it will be delivered to you in between these visits (every two weeks). This delivery between the visits may be done by home-delivery and it will be organized by the site staff.

During the ambulatory visits, if you are in the THS 2.2 Menthol arm, you will have to return any empty packs and partially used packs of Menthol Tobacco Sticks you have used during the preceding weeks to the site for accountability.

All tobacco plugs from Menthol Tobacco Sticks used after check-in to the investigational site until 23:00 on Day 30, Day 60, and Day 90 will be collected in dedicated vials for subsequent analysis of potential combustion occurrences.

If you are allocated to the menthol conventional cigarette arm, you will be asked to buy your cigarettes directly from shops and bring an anticipated amount for the 2 days visit of the ambulatory period plus 2 extra packs. During the ambulatory visit, no collection of menthol conventional cigarette butts will be done.

If you are allocated to menthol conventional cigarette arm or THS 2.2 Menthol arm and had received HST SODIM® device, you will be asked to use HST SODIM® device for each menthol conventional cigarette or each THS Menthol tobacco sticks you have used during 4 hours on Day 30, Day 60 and Day 90.

During the ambulatory period, you will be asked to capture, from the time of Discharge on Day 6 to 23:00 on Day 90, the number of product you have used (e.g., menthol and non-menthol CC,

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Menthol Tobacco Sticks, or any other tobacco /nicotine-containing products including NRT) on a daily basis in the product use electronic diary. The product use electronic diary will be supplied by Sponsor and distributed to you by the study site collaborator.

3.3 Expected duration of your participation

The end of study is defined as the time of Discharge on Day 91 plus 28-day safety follow-up.

The entire study duration: 123 to 150 days

- Screening period: 1 to 28 days
- Confinement period: 9 days
- Ambulatory period: 85 days
- Safety follow-up period: 28 days

3.4 Expected number of subjects

A total of approximatively 160 subjects will be randomized to the study.

3.5 Withdrawal from the study / Termination of participation

You are free to withdraw from the study (stop your participation) at any time without any penalty. If you want to withdraw from the study, please inform Investigator of your withdrawal at any time. You will be questioned for the reason of premature withdrawal, although you are not obliged to disclose it.

In addition, you will be withdrawn from the study for any of the following reasons even if you are willing to continue the participation:

- Any side effects or condition (including clinically significant changes in a laboratory which in the discretion of the Investigator does no longer justify the participation in this study)
- Positive pregnancy testing
- Withdrawal is considered by the Investigator to be in the best interest of the subject or the other subjects.
- The Sponsor or Investigator terminates the study. If the Sponsor or the Principal Investigator decides to prematurely terminate the study, the subject will be promptly informed and will follow the end of study procedures (safety assessments of discharge Day 6 then the 28 day safety follow-up period).
- Quit smoking during the study (this is applicable for all subjects during screening to the baseline period and for subjects allocated to THS 2.2 Menthol or CC arms during the exposure period).

You may be discontinued from the study for any of the following reasons:

- Lost to follow-up
- Concomitant treatment with non-authorized medication (in general, any concomitant medication should be discussed with the Investigator on an ongoing basis)



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- Non-compliance to the study procedures

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- The study may be terminated by the Sponsor at any time
- The study may be terminated by the Investigator or the Sponsor, in case of obtaining new data about the safety of the used product, or if the number or intensity of adverse events (any unfavourable and unintended medical event occurring in Subjects), in the Investigator's opinion, may influence the safety of the Subjects.

If the study is terminated, you will be informed about it, and appropriate measures to protect your health will be undertaken.

3.6 Schedule of events

Screening visit

- Informed consent for study participation and Informed consent for both bio-bankings (for further analysis of biomarkers of exposure and risk markers and for transcriptomics analysis)
- Information on the risk of smoking and advice on smoking cessation and debriefing on the product (you will be explained that THS 2.2 Menthol has not been demonstrated to be less harmful than menthol conventional cigarettes)
- Demographic data collected (gender, date of birth/age)
- Willingness to quit smoking within the next 3 months (you will be asked a question if you are planning to quit smoking during the next 3 months)
- Readiness to abstain from smoking for up to 90 days (you will be asked a question if you are ready to abstain from smoking for up to 90 days)
- Identification of current menthol conventional cigarette brand (the site staff will document brand name (s) with the nicotine and tar yields)
- Medical history/concomitant disease (any condition that started prior to and ended prior to Screening Visit and any ongoing condition)
- Prior medication and concomitant medication, including hormonal contraceptives, (taken by you within 4 weeks of Screening Visit)
- Smoking history
- Vital signs (blood pressure, heart rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Collection of blood and urine samples in order to perform laboratory tests (hematology, biochemistry – after at least 10 hours fasting period, a general urine test, serological tests for HIV, hepatitis B and C, test for the presence of addictive and narcotic substances, as well as nicotine metabolite in urine)
- Physical examination, including height, weight, calculation of your body mass index
- For female subjects urine pregnancy test and verification of contraceptive method used
- THS 2.2 Menthol product demonstration (the product will be demonstrated by the site staff)
- Chest X-rays (frontal and left lateral views will be taken: if not performed 6 months prior to Screening Visit): you will be referred for this procedure to a radiology unit
- Alcohol breath test screen (using an alcometer device)



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- A questionnaire for nicotine dependence (Fagerström Test for Nicotine Dependence)
- Lung function test: this will be done first without bronchodilator (salbutamol) inhalation and then with it. A small risk of an adverse reaction to this drug is possible (like the feeling of your heart beating faster (palpitations) or a tremor/slight shake). Any symptoms you may experience while using this drug should be reported to the study doctor immediately.
- Electrocardiogram (a painless tracing of your heart rate & rhythm – at least 10 minutes in supine position prior to recording)
- You will be asked to provide information of any unfavourable health or medical event, known as Adverse Events

Admission Day -2

- Collection of urine samples (for the presence of addictive and narcotic substances, as well as nicotine metabolite in urine, urine pregnancy tests for women)
- You will be asked about your concomitant diseases
- You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.
- Information on the risk of smoking and smoking cessation advice and debriefing on THS 2.2 Menthol
- Smoking history
- Alcohol breath test (using an alcometer device)
- Readiness to abstain from smoking for up to 90 days.
- Carbon monoxide breath test (measurement of the amount of carbon monoxide in the breath)
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Physical examination including weight, waist circumference, body mass index
- Identification of current menthol conventional cigarette brand (you will have to hand your menthol conventional cigarettes supply for the confinement period to the site staff, who will take a photograph of the front and of the side (bearing the tar and nicotine) for documentation.)
- Trial of THS 2.2 Menthol product (as the last procedure of the eligibility criteria you will have a trial of THS 2.2 Menthol [using up to 3 Menthol Tobacco Sticks])
- Immediately after the confirmation that you will participate to the study, you will be asked which product you would prefer to be randomized to, if you could choose your group (in reality, your study arm will be decided randomly and you cannot choose it).

Baseline Day -1

- Start of the 24-hour urine collection of Day -1 (each time you will urinate in to disposable containers which will then be handed over to the personnel of the Site). Site staff will provide detailed information concerning the method of urine collection.
- You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.



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- Carbon monoxide breath test (four times per day; first test to be performed 15 minutes prior to the first smoking event, the other tests to be done between 12:00–13:30, 16:00–17:30, and 20:00–21:30)
- Vital signs (blood pressure, heart rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Questionnaire of Smoking Urges - You will be asked to complete a questionnaire to indicate your desire to smoke.
- Modified Cigarette Evaluation Questionnaire – You will be asked to complete a questionnaire on how you evaluate the product
- Blood sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 20:00–21:30)
- All smoked menthol conventional cigarette butts will be collected for accountability.

Baseline Day 0

The following procedures will also be performed at Baseline Day 0:

- You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and on any concomitant medications.
- Start of the 24-hour urine collection of Day 0 (each time you will urinate in to disposable containers which will then be handed over to the personnel of the Site). Site personnel will provide detailed information concerning the method of urine collection.
- Collection of blood samples for Day 0 as follows:
 - Sample for hematology and biochemistry (safety samples - to ensure that you are fit and healthy to be enrolled in the study) - to be taken after at least 10 hours of fasting
 - Samples for risk marker analysis- to be taken after least 10 hours of fasting
 - Sample for Bio Banking for further analysis of biomarkers of exposure and risk markers (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition)
 - Sample for Bio Banking for further analysis of transcriptomics analysis (if you gave consent for this sample) (has to be done at least in 10 hours fasting condition)
 - Sample to measure the CYP2A6 activity, a biological entity involved in the metabolism of nicotine in your blood (has to be done prior to smoking)
 - Sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine):Sample of blood (between 16:00–17:30) 6 hours after the intake of caffeine tablet
 - Sample to measure carboxyhemoglobin (a measure of carbon monoxide levels in your blood) – (between 20:00–21:30)
 - Sample to measure the nicotine levels in your blood (between 20:00–21:30)
- Intake of a tablet of caffeine approximately 170 mg with 150 ml of water (to measure CYP1A2) (between 10:00–11:30)
- Lung function test – without bronchodilator (has to be done prior to smoking)
- Carbon monoxide breath test (four times per day; first test to be performed 15 minutes prior to the first smoking event, the other tests to be done between 12:00–13:30,



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16:00–17:30, and 20:00–21:30

- A sample of your urine will be taken or safety to ensure that you are fit and healthy to be enrolled in the study.
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement
- Human smoking topography (to assess your smoking behaviour) will be conducted only if you are provided with the HST SODIM® device. The device will be provided to the first 20 subjects who smoke menthol conventional cigarettes compatible with it. Please note the HST SODIM® device has to be used for all smoking events on Day 0 if you are provided with it.
- Human smoking topography questionnaire – if you are provided with the HST SODIM® device you will also be asked to answer a questionnaire to evaluate the use of HST on your smoking rituals.
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine / Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00)
- Questionnaire to evaluate product (Modified Cigarette Evaluation Questionnaire) and desire to smoke (Questionnaire of Smoking Urges) between 20:00–23:00.
- All smoked menthol conventional cigarettes butts will need to be collected for accountability.

Exposure period Day 1 to Day 5

- You will be notified of which study arm you have been randomly allocated to prior to 06:30 on the morning of Day 1.
- Support for smoking cessation if needed (SA arm only)
- Start of the 24-hour urine collection is on Day 1 until the morning of Day 6. (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection
- You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.
- Blood samples will be collected to measure values of Biomarkers in the blood. The Biomarkers in blood to be researched are known as carboxyhemoglobin, and nicotine and cotinine.
- Collection of blood samples as follows:
 1. Carboxyhemoglobin – Day 1 to Day 4, one blood sample in the evening between 20:00–21:30 each day. Day 5, one blood sample within 15 minutes prior to your first product use of the day and between 8:00–9:30 in the morning for subjects in the smoking abstinence arm, followed by a further three blood samples between 12:00–13:30, 16:00–17:30, and 20:00–21:30 for all subjects.
 2. Nicotine / Cotinine – Day 1 to Day 4, one blood sample in the evening between 20:00–21:30 each day. Day 5, THS 2.2 Menthol and menthol conventional cigarette arms only, one blood sample within 15 minutes prior to your first product



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use of the day followed by a further eight samples at 2 hour intervals. On Day 5 subjects randomised to smoking abstinence, one blood sample between 20:00–21:30.

- Blood samples will be collected to measure CYP1A2 activity (which is involved in the metabolism of caffeine): Sample of blood (between 16:00–17:30) 6 hours after the intake of caffeine tablet (Day 5 only).



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- Carbon monoxide breath test – four times per day; first test to be performed 15 minutes prior to the first smoking event and between 8:00–9:30 in the morning for subjects in smoking abstinence arm, the other tests to be done around between 12:00–13:30, 16:00–17:30, and 20:00–21:30 for all subjects (Day 1 to Day 5).
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement (Day 1 to Day 5).
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine / Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00) (Day 1 to Day 5)
- You will be asked to answer the HST questionnaire questions (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device) (Day 4 only)
- Questionnaire to evaluate product (Modified Cigarette Evaluation Questionnaire) (THS 2.2 Menthol and menthol conventional cigarette arms only) and desire to smoke (Questionnaire of Smoking Urges) between 20:00–23:00 (Day 1 to Day 5).
- Intake of a tablet of caffeine approximately 170 mg with 150 ml of water (to measure CYP1A2) (between 10:00–11:30) (Day 5 only).
- Human smoking topography (to assess your smoking behaviour) will be conducted only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (Day 1 and Day 4)
- Socio-economic Questionnaire (Day 4 only)

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will need to be collected (Day 1 to Day 5). In the THS 2.2 Menthol arm, subjects will be asked to collect every used filter and tobacco plugs into dedicated vials which will be provided by the staff.

Discharge Day 6

- Support for smoking cessation if needed (SA arm only)
- Collection of blood samples (including samples to measure a nicotine profile – two blood samples to be taken – the first one will be 20 hours after the start time of first product use on Day 5 and the second one will be 24 hours after the start time of first product use on Day 5. For smoking abstinence arm one blood sample will be taken between 08:00 – 09:30.)
- End of 24-hour urine collection started on Day 5
- Collection of blood and urine samples in order to perform laboratory tests (hematology, biochemistry – after at least 10 hours fasting period, a general urine test, urine pregnancy tests for women)
- Collection of blood samples for risk marker analysis- to be taken after least 10 hours of fasting
- Collection of blood and urine samples for long term storage for further analysis of biomarkers of exposure and risk-markers – after at least 10 hours fasting period, only if you



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consented.



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- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period, only if you consented.
- Collection of blood to measure CYP2A6 activity (has to be done prior to smoking)
- Physical examination including weight, body mass index
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking, but no later than 10:00)
- Lung function test: without bronchodilator (has to be done prior to smoking)
- Carbon monoxide breath test
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
- Electrocardiogram (at least 10 minutes in supine position prior to recording, a painless tracing of your heart rate & rhythm (ECG))
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol
- You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.
- Distribution of product use electronic diary (to be completed every day from the time of Discharge on Day 6 until 23:00 on Day 90: all Menthol Tobacco Sticks, menthol and non menthol conventional cigarette, and any tobacco nicotine containing products have to be recorded)
- Discharge (Day 6)

Please note that all used Menthol Tobacco Sticks from the THS 2.2 Menthol and menthol conventional cigarettes butts will need to be collected.

Ambulatory period: Day 30 Visit and Day 60 Visit (from 8:00 on Day 30/Day 60 until all assessments are finished on Day 31/Day 61)

- ◆ Day 30/Day 60
 - Opening of the Visit at 8:00
 - Support for smoking cessation if needed (SA arm only)
 - You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.
 - Human smoking topography (to assess your smoking behaviour) will be conducted for 4 hours only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product used in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (starts between 8:30 and 9:30)
 - Start of the 24-hour urine collection (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection (starts at 9:00 ± 20 min)
 - Carbon monoxide breath test
 - Collection of blood sample for carboxyhemoglobin



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- Collection of blood sample for Nicotine / Cotinine



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- Electrocardiogram (a painless tracing of your heart rate & rhythm – at least 10 minutes in supine position prior to recording)
 - Physical examination, including weight, calculation of your body mass index
 - Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement)
 - You will be asked to answer the HST questionnaire questions (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device)
 - Questionnaire to evaluate product (Modified Cigarette Evaluation Questionnaire) (THS 2.2 Menthol and menthol conventional cigarette arms only) and desire to smoke (Questionnaire of Smoking Urges)
 - All used tobacco plug from Menthol Tobacco Sticks from the THS 2.2 Menthol are collected in dedicated vials which will be provided by the staff for further analysis
- ◆ Day 31/Day 61
- Support for smoking cessation if needed (SA arm only)
 - You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.
 - Collection of blood and urine samples in order to perform laboratory tests (hematology, biochemistry)– after at least 10 hours fasting period- a general urine test, urine pregnancy tests for women
 - Collection of blood samples for risk marker analysis- to be taken after least 10 hours of fasting
 - End of 24-hour urine collection started on Day 30/Day 60
 - Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (no later than 10:00)
 - Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol
 - Discharge

Please note that all empty/partially empty packs of Menthol Tobacco Stick that you used since the last visit will need to be collected. You are asked not to throw away empty/partially empty packs of Menthol Tobacco Stick and to bring all empty/partially empty Menthol Tobacco Stick packs on Day 30/Day 60.



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Ambulatory period Day 90 Visit (from 8:00 until all assessments are finished on Day 91)

◆ Day 90

- Opening of the Visit at 8:00
- You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.
- Support for smoking cessation if needed (SA arm only)
- Human smoking topography (to assess your smoking behaviour) will be conducted for 4 hours only if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device. Please note the HST SODIM® device has to be used for all product uses in THS 2.2 Menthol and menthol conventional cigarette arms if you are provided with it (starts between 8:30 and 9:30)
- Start of the 24-hour urine collection (each time you will urinate into disposable containers which will then be handed over to the site staff). The site staff will provide detailed information concerning the method of urine collection (at 9:00 ± 20 min)
- Intake of a tablet of caffeine approximately 170 mg with 150 ml of water (to measure CYP1A2) (no later than 10:00)
- Carbon monoxide breath test
- Collection of blood sample for carboxyhemoglobin
- Collection of blood sample for Nicotine / Cotinine
- Sample to measure CYP1A2 activity (which is involved in the metabolism of caffeine): Sample of blood (between 15:00 – 16:00) 6 hours after the intake of caffeine tablet
- You will be asked to complete the HST questionnaire (if you are in the THS 2.2 Menthol or menthol conventional cigarette arm and provided with the HST SODIM® device)
- Questionnaire to evaluate product (Modified Cigarette Evaluation Questionnaire) (THS 2.2 and conventional cigarette arms only) and withdrawal symptoms (Questionnaire of Smoking Urges)
- A questionnaire for nicotine dependence
- All tobacco plugs of used Menthol Tobacco Sticks from the THS 2.2 Menthol are collected in dedicated vials which will be provided by the staff

◆ Day 91

- You will be asked to provide information on any unfavourable health or medical event, known as Adverse Events and any concomitant medications.
- Collection of blood to measure CYP2A6 activity (has to be done prior to smoking)
- Assessment of Cough (you will be asked to complete a questionnaire assessing your cough) and Minnesota Nicotine Withdrawal Scale (you will be asked to complete a questionnaire to evaluate signs and symptoms of withdrawal) (has to be done prior to smoking but no later than 10:00)
- Spirometry (measuring of your lung function) without bronchodilator. (has to be done prior to smoking).
- End of 24-hour urine collection started on Day 90
- Collection of blood and urine samples in order to perform laboratory tests (hematology, biochemistry – after at least 10 hours fasting period) a general urine test, urine pregnancy tests for women



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- Collection of blood samples for risk marker analysis- to be taken after least 10 hours of fasting
- Collection of blood sample for long term storage for further analysis of biomarkers of exposure and risk markers – after at least 10 hours fasting period, only if you consented.
- Collection of blood sample for long-term storage for further analysis of transcriptomics analysis – after at least 10 hours fasting period, only if you consented.
- Vital signs (blood pressure, pulse rate, respiratory rate: at least 5 minutes in supine position prior to measurement .
- Physical examination, including weight, waist circumference, calculation of your body mass index
- Electrocardiogram (a painless tracing of your heart rate & rhythm – at least 10 minutes in supine position prior to recording)
- Advice on the risk of smoking and advice on smoking cessation and debriefing on THS 2.2 Menthol
- Discharge

Please note that all empty/partially empty Menthol Tobacco Stick that you used since the last visit will need to be collected. You are asked not to throw away empty/partially empty Menthol Tobacco Stick packs and to bring all empty/partially empty Menthol Tobacco Stick packs on Day 90. You will have to return also the product use electronic diary to the site staff.

Safety Follow-up period

After you have completed the Day 91 assessments you will enter a 28-day safety follow-up period. If you experienced the product trial of THS 2.2 Menthol on the admission day and did not participated in the study, or discontinued study participation earlier than Day 91, you will be ask to complete the Day of Discharge safety assessments shown in the section of "Discharge Day 6", and will enter into the follow-up period. During this safety follow-up period you must inform the site of any new medical problems. The site will also contact you to follow-up on any medical problems that has been reported by you during the study but have not been resolved before the discharge from the site.

3.6.4 Early Termination

In case of early termination, safety procedures written in "Day of Discharge (Day 6)" will be performed.

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3.7 Sampling Handling and Storage

[Blood collection]

The maximal total volume of blood taken from you during the study will be around 290 ml, which includes all samples necessary for biomarker analysis and 50 ml for safety and repeated analysis, 30 ml of blood for long-term storage of the samples for future analysis of biomarkers of exposure and risk markers (only if additional consents are given) and 15 ml for long-term storage of samples for transcriptomics analysis (only if additional consents are given).

It is possible that you may feel some discomfort when the blood samples are being taken.

The blood samples collected will be analysed using a validated method by an appropriately equipped laboratory. The designated analytical laboratory will be responsible for keeping your samples until their subsequent destruction after the completion of Clinical Study Report. At all times throughout the study the security of your personal information will be maintained and you will remain anonymous.

The samples you provide will only be used for study related purposes, and no other analyses than study related analyses that has been described in this information sheet will be performed without you and the ethics committee's approval.

[Urine collection]

In the study, the spot urine samples (single urine samples) will be taken for, safety urine analysis, and the presence of addictive and narcotic substances, nicotine metabolites and pregnancy tests for women.

In this study, 24 hour urine collection will be performed. For 24 hour urine sample during the confinement period, you will empty your bladders shortly before 06:30 on the study days in confinement period as described above in the study schedule section. The collection period starts at 06:30 and ends the following day at 06:29. For 24 hour urine sample during ambulatory period, you will empty your bladder shortly before 09:00 and, then you will start collection of urine at 9:00 \pm 20 minutes on ambulatory visits for 24 hours until the next day. You will be given detailed instructions by the investigational site staff.

24 hour urine collection samples will be used to measure some biomarkers such as MHBMA, 3-HPMA, S-PMA as well as some risk markers. Monitoring these Biomarkers will show changes in your body that relate to the exposure of an organism to a chemical or biological changes associated with exposure.

During the sampling period, all urine passed must be collected. No urine must be passed into the toilet.



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[Bio-banking Long Term Storage of Blood or Urine]

Two separate consent forms (attached to this information sheet) are provided to you for collection and long-term storage of urine and blood samples for the purpose of additional future analysis of biomarkers or exposure and risk markers and transcriptomics. If you have given your consents for sample bio-banking for biomarker of exposure / risk markers and for transcriptomics (for details, please see information sheet for bio-banking of future analysis of biomarkers of exposure and risk markers and for transcriptomics) additional samples for long-term storage will be collected and stored as follows:

- Samples of urine (from the 24 hour urine collection that started on Day 0, Day 5 and Day 90) (300 ml in total)
- Samples of serum/plasma for biomarkers of exposure /risk markers (30 ml of blood total) on Day 0, Day 6 and Day 91. No genetic testing will be performed on these samples.
- Samples of blood for transcriptomics (15 ml of blood total,) on Day 0, Day 6, Day 91.

The samples intended for sample bio-banking will be kept frozen, separate from the other samples collected, and will be shipped to a central storage facility. After the completion of clinical study report, samples of plasma/serum and blood will be stored for a maximum of 5 years and samples of urine will be stored for a maximum of 2 years, and then they will be destroyed.

If you disagree for collection and long-term storage of the urine and blood samples, you will still be able to take part in the clinical study if you agree and sign the informed consent form for the study participation.

The facility at which the samples are stored will follow their procedures for destruction of banked samples if you withdraw your consent for sample bio-banking. However, for bio-banking for transcriptomics, it is impossible to destroy them after deletion of the link between your personal data and the blood sample (for details, please see information sheet for bio-banking for transcriptomics).

3.8 Probability to be allocated into each treatment

You will be randomized to one of the 3 study arms in a 2:1:1 ratio

- THS 2.2 Menthol Arm: ~80 subjects, *ad libitum* use of the product. Probability to be assigned to this arm is 50 per cent.
- Menthol conventional cigarette Arm: ~40 subjects, *ad libitum* use of their preferred menthol conventional cigarettes brand. Probability to be assigned to this arm is 25 per cent.
- Smoking abstinence Arm: ~40 subjects who will abstain from smoking. Probability to be assigned to this arm is 25 per cent.

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4. Subjects of this study

After you have received sufficient explanation about the study and have given the written consent for participation of the study, the followings will be assessed to confirm your eligibility in the study.

4.1 Who can participate in the study?

- Subject who has signed the ICF and is able to understand the information provided in the document.
- Subject is aged from 23 to 65 years (inclusive).
- Subject is Japanese.
- Subjects who in the opinion of the Investigator show no signs of significant disease on the basis of their medical history, physical examination, blood and urine laboratory tests and other tests results heart actions (ECG), chest X-ray, lung function test (spirometry), vital signs (blood pressure, breathing rate and heart rate).
- Subjects who currently smoke, based on self-reporting, and for the last 4 weeks have smoked at least 10 menthol conventional cigarettes per day. In addition, subjects must have smoked for at least the last three consecutive years and who do not plan to quit smoking in the next 3 months.
- Non-pregnant women using an acceptable contraceptive method (Your doctor can discuss the method(s) of birth control or contraception that is appropriate for you or acceptable for the study)
- Subjects ready and willing to use exclusively the THS 2.2 Menthol product for the duration of the study if randomized to this arm of the study
- Subjects who are ready to accept 90 days of smoking abstinence, if randomized to this arm.
- Subjects whose Body Mass Index (BMI) is greater than 18.5 and less than or equal to 32 kg/m² - BMI is calculated by dividing body mass (expressed in kilograms) by squared height (expressed in meters)

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4.2 Who cannot participate in the study?

- In the opinion of the Investigator cannot participate in the study for any clinically significant medical reason (e.g. subjects with chronic pulmonary obstructive disease or a history of heart attack)
- Have used nicotine replacement therapy, or nicotine products other than commercially available menthol conventional cigarettes (including electronic cigarettes), within 4 weeks prior to assessment.
- Participated in any other clinical study or medical experiment within the 3 month period prior to screening visit
- Within the 3 month period prior to the planned admission to the site donated blood or received blood or derivative products
- Have taken medication within 14 days of admission or within 5 half lives of the drug (whichever is longer), which has an impact on CYP1A2 or CYP2A6 activity. Examples of types of medications with effect on CYP1A2 and CYP2A6 may include the following; Antibiotics, Antidepressants, Neuroleptic, Antiepileptic, Antihypertensive, Hormonal contraceptives, Cholesterol lowering agents, Analgesic, Anti-diabetic. This list is not exhaustive and all taken medications should be discussed with the study team.
- If a subject has received any medication (prescribed or over-the-counter) within 14 days prior to Screening or prior to the Admission Day (Day -2), it will be decided at the discretion of the Investigator if these can potentially interfere with the study objectives or subject's safety.
- Are (or have been) employed in tobacco industry, or their close relatives (parent, sibling, children)
- Work for the Site or any other company involved in this study or their close relatives (parent, sibling, children)
- Have a limited legal capacity in order to give consent.
- Have previously participated in the same study at a different time.
- Are pregnant or breast-feeding women.
- The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in the study.
- The subject has a positive urine drug test.
- Positive serology test for human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C (smoking under this study may pose a significant risk to these individuals).

The final decision about subject's qualification is at the investigator's discretion which is based on the available information obtained during the screening.



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5. Expected Clinical advantages and risks

5.1 Anticipated Benefits

In Japan, research conducted by the Ministry of Health, Labour and Welfare has shown that 35.9% of male and 43.6% of female respondents over 20 years of age expressed the wish to quit smoking. In a large follow-up study of middle aged Japanese smokers, the predictors of smoking cessation were age, job, smoking habit, physical activity, health checkup participation, and health status. Advice on health risks associated with smoking and smoking cessation advice will be provided at Screening, at Admission, and at the Day of Discharge on Day 6, Day 30 Visit, Day 60 Visit and Day 90 Visit. Subjects who are motivated to quit smoking during the study will be referred to appropriate stop smoking services for continuing support. Subjects who participate in this study will also benefit from repeated, detailed health check-ups, which may help to uncover undiagnosed medical conditions.

5.2 Anticipated Risks and adverse reactions

1) Anticipated Foreseeable Risks due to Investigational Product (THS 2.2 Menthol) and reference product (menthol conventional cigarettes)

- For adverse reactions which THS 2.2 Menthol / menthol conventional cigarettes may cause, please refer to point "3) Adverse reactions" of this section.
- Change in smoking habits (e.g. smoking abstinence) due to study requirements may cause concomitant symptoms including anger, depression, hunger, anxiety, and difficulty to concentrate which are parts of the craving symptoms.
- During the ambulatory period, if you use nicotine replacement therapy (such as nicotine replacement therapy gum), you may experience the following side effects: Very common side-effects include runny nose, sneezing, watery eyes, nose bleeds. Common side-effects include headache, dizziness, cough, stomach discomfort, feeling sick, vomiting. Uncommon side-effects include chest palpitations, abnormal beating of the heart is a very rare side-effect.

2) Anticipated Foreseeable Risks due to Study Procedures

- Risks related to blood sampling, e.g. there is a possibility of excessive bleeding, fainting, hematoma, paresthesia, or infection.
- Risks related to chest X-rays: if you need to have a chest X-ray performed during the screening process for this study, the radiation exposure of a chest X-ray is equivalent to approximately 3 days natural background radiation exposure per X-ray.
- Risks related to drug application as part of testing procedures (lung function test) – for this procedure a short-acting bronchodilator (salbutamol: drug that will "open up" the lungs) will be used. A small risk of an adverse reaction to this drug is possible. Any symptoms you may experience whilst using this drug should be reported to the study doctor immediately.

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3) Adverse reactions

Cigarette smoking causes pulmonary and cardiovascular diseases and other serious diseases in smokers. In 2000 in Japan, the proportion of adult deaths due to smoking ranges from 20.0% to 24.9% in males and from 10.0% to 14.6% in females.

Given the current state of knowledge of the THS 2.2 Menthol, at this stage, the harmfulness of THS 2.2 Menthol in terms of tobacco-related diseases is similar to that of menthol conventional cigarettes.

In the previous clinical study with THS 1.0, a predecessor to THS 2.2, an upper extremity deep vein thrombosis (a condition which involves formation of a thrombus [blood clot] in the blood vessel of arm) occurred in a subject who smoked 25 cigarettes per day on average for 20 years, as a serious adverse event possibly related to the study product. The investigator considered that the upper extremity deep vein thrombosis could be related to the travel which involved carrying heavy bag and immobilization of the subject arms. However, since cigarette smoking is a risk factor of deep vein thrombosis, the investigator concluded that the event is related to the study product. The upper extremity deep vein thrombosis resolved.

A smoker using the THS 2.2 Menthol may experience transient withdrawal symptoms (e.g. urge to smoke, irritability, anxiety feelings, restlessness, and difficulty concentrating) similar to observed during smoking cessation. Transient symptoms suggesting mild nicotine intoxication such as stimulant effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, increased ability to concentrate), gastric acid secretion, and vomiting center (nausea, vomiting).

Please correspond with the investigator or site staff in the case of having these or any other abnormal physical condition. Normal treatment is given to these symptoms.

5.3 Unforeseeable Risks

As with any new investigational product, there may be unforeseeable risks and hazards that could occur. Close monitoring and medical supervision are performed to detect any unforeseeable risk or safety signals at the earliest possibility. You will be informed of such risks on screening visit, admission day, and ambulatory visits.

6. Obtaining additional safety information

During the study, we will let you know whenever we get the information for any significant changes of the study plan, additional information for the risk profile of the Investigational Product, and information which may affect the subject's will. At that time, we will ask you for your intention whether or not you continue to participate in this study.

7. You may withdraw from this study at any time.

You may refuse to take part in this study without any penalty or detriment. In addition, you may terminate participation in this study, whenever you want, after you have consented to participate in this study. We guarantee that you will never get any detriment when you quit this study.

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8. Protection of Personal Information

Every valuable data of your cooperation and its relevant data for this study are going to be used for the development of the products. In addition, all those important data might be published at scientific meetings and/or in medical journals. In any cases, we assure you that we will always respect and keep your privacy, and also the hospital officials who are involved in this study and/or its related persons are committed not to disclose such information to outsiders.

In some cases, the study-related persons (e.g. Sponsor's staffs, Institutional Review Board members and Regulatory Agency staffs) review your medical records as for your treatment (including other departments' records and the duration before the study period). In such cases, these related persons have a duty to respect and keep your private information such as your name.

Signing the Informed Consent Form means that you agreed the direct access to your records. We give our assurance that your test samples such as your blood and/or urine sample will be used only for this study and never used for the other purpose. Then, every analyzed sample will be destroyed after completion of Clinical Study Report.

Additional data analyses not mentioned in the study might be performed with your collected data at a later time. If any additional analyses will be performed, they will fully be covered by data confidentiality, in the same way as the main analyses described in the protocol. By signing the Consent form at the end of this information sheet you are giving your permission for additional analysis of your data for study related purposes.

In order to maintain the confidentiality of the study for the Sponsor you will agree to keep all information relating to the conduct of the study confidential.

9. In the case of occurrence of Health hazards

The Sponsor is responsible for AEs and health damage of the subjects that are associated with the THS 2.2 Menthol product and with study procedures which are used during this study, except for AEs and health damage of the subjects caused by a negligent or an intentional misconduct and/or significant deviation to the Protocol of the Investigator or the clinical study site or the subjects. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

10. Fee for menthol conventional cigarettes, Investigational Product and Examination

The cost will be paid by the committed company for this study so that you don't need to pay for investigational product used for this study, while the cost for buying menthol conventional cigarettes will not be paid. The cost for examinations during this study will also be paid by the company.

As for the cost for tests not related to the study procedure, your health insurance and your co-payment would cover those expenses as usual.

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11. Compensation for cooperation

When you participate in this clinical study, for your effort and inconvenience for the scheduled visiting and admission, compensation will be offered by the hospital.

If you withdraw your participation during the study before completing all the schedules (including the ambulatory period), or in case of termination of the investigation for any cause, the full compensation amount may not be offered.

12. Duties of the participant

It is the duty of the Subject to conform to the recommendation and requirements of the study, observing the recommendations of the Investigator and the medical personnel of the Site, to observe restrictions resulting from study procedures, to treat the personnel of the Site and other Subjects of the study with respect, provide reliable information related to the participation in the study, as well as to report to the Site on time. During the stay at the Site, the Subjects are not allowed to invite guests and must not leave the Site premises, with the exception of rooms dedicated for smoking or for the organized strolls under medical supervision. Taking pictures and making recordings at the Site is strictly prohibited or else one will be immediately excluded from the study. Participants staying at the Site must observe the Site Regulations that will be provided to you.

If you have been consulting in the other hospital or other department in the study site, or will consult in the other doctor during the study period, you must contact the investigator (or study collaborator). Information such as your participation in the study and medication(s) to be avoided during the study will be provided to the other doctor(s) by the investigator. The investigator may contact the other doctor(s) and request for information required in the study such as your medical treatment.

You should not take any medication during the study without prior informing the Investigator (or study collaborator). Please correspond with the investigator (or study collaborator) in the case of having abnormal physical condition.

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13. Institutional Review Board (IRB) Approval

IRB is a committee, which has been established to assess whether or not the Clinical Study is conducted with respecting the participants' human rights and ensuring their safety, whether it is scientifically/ethically-valid and there is no problem in the Clinical Study Plan. IRB is required to consist of such as medical professionals (medical science and pharmaceutical science), some members other than medical professionals, and also independent members without interest from this Hospital. IRB performs to review the contents of Clinical Study Plan with taking patients' position into careful consideration. The President of our hospital is going to consult IRB members to get opinion concerning the implementation and continuation of the Clinical Study. At the same time, IRB is expected to advise their opinion to our President with reviewing the implementation and continuation of the Clinical Study from the scientific and ethical perspective.

We hereby certify that this Clinical Study has been reviewed and approved by the IRB that is established in Yasuda Hospital.

- ☐ Name : IRB, Yasuda Hospital
- ☐ Type of IRB : IRB established in Yasuda Hospital
- ☐ Founder : President, Yasuda Hospital
- ☐ Address : 1-13-9 Narimasu Itabashi-ku Tokyo, Japan
- ☐ Homepage Address: <http://www.yasudahosp.jp/>

You are entitled to view Procedure, list of board members, abstract record of this Institutional Review Board. The information is available at the study site. Please feel free to ask the Information Desk for the information freely.

14. Name, Title and Contact information of Principal and Sub-Investigator

This Clinical Study is conducted by the following Principal Investigator and Sub-Investigator

「Principal Investigator」

Masahiro Endo

President of Osaki Hospital Tokyo Heart Center and Head of Clinical Pharmacology
Research Laboratory

+81-3-5789-8115



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「Sub-Investigator」

Study Number: ZRHM-REXA-07-JP (Main Study)
Dated: 2013/DEC/06 (Ver. 2.0)**15. Counseling Counter for this study**

Please contact us at the following contact information desk if you have any question and/or consultations concerning this Clinical Study.

Hospital Name	Osaki Hospital Tokyo heart center
Information Desk	Osaki Hospital Tokyo heart center Clinical Research Coordinator
Contact person	
Telephone No.	

We ask for your kind understanding concerning this Clinical Study and Investigational product. Please feel free to contact us if you have any question and/or issues need to be explained. After due consideration, please sign the following Informed Consent Form as well as fill in the date of consent with your understanding and agreement for this Clinical Study. Please be sure to receive this Written Information and one original of Informed Consent Form you signed.



Study Number: ZRHM-REXA-07-JP (Main Study)
Dated: 2013/DEC/06 (Ver. 2.0)

To President of Osaki Hospital Tokyo heart center

To be attached to the medical records

Informed Consent Form

I have received sufficient explanation and understood the contents of this study "Reduced exposure study using THS 2.2 with 5 days in a confinement setting and 85 days in an ambulatory setting", therefore, I agree to participate in this study with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy (hh:mm a.m./p.m.)

Name (Signature)

Please check

- ☐ I am currently a smoker and have no plan or intent to cease smoking within the next three months, except when I am assigned to the abstinence group.
- ☐ I am aware that smoking may cause lung cancer, or worsen the risk of myocardial infarction, stroke or aggravation of emphysema, that tobacco smoke could negatively impact people in my vicinity, children and infants or the aged in particular, that I need to exercise caution not to disturb other persons, and that smoking dependency may result from nicotine, although its degree varies from one person to another.
- ☐ I have been exhaustively informed by Dr Endo, to be filled out by Investigator, legibly, in print) about the purposes of this study, type and character of the medical experiment and about the risk and benefits related to participation in this study.
- ☐ I agree for my blood and urine samples to be collected for safety and biomarker analysis.
- ☐ I have received one original of "Subject Information and Informed Consent Form" (version 2.0 dated 06-DEC-2013).
- ☐ I understand that relevant sections of my medical notes will be reviewed by representatives of Philip Morris Products S.A., auditors and regulatory authorities where it is relevant to my taking part in the study.
- ☐ I give permission for these individuals to have access to my records.
- ☐ I have been informed about the conditions of the third party insurance of the Sponsor for damages incurred as a result of participation in this study, and I accept them.
- ☐ I have had the opportunity to ask questions related to the medical experiment and I have received satisfactory answers to all of them.
- ☐ I agree for my blood samples to be collected in order to rule out infection with HIV virus, Hepatitis C virus and Hepatitis B surface antigen.
- ☐ I know my rights and my obligations resulting from my participation in the study.
- ☐ By signing this document I do not lose any rights to which I am entitled according to Japanese law.
- ☐ I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation.
- ☐ I have read all the information contained in above "Subject Information and Informed Consent Form" (version 2.0 dated 06-DEC-2013).
- ☐ I hereby confirm my informed and voluntary consent to participation in the said study. At the same time I know that at any time I may cease smoking or withdraw from further participation in this study, without providing a reason.
- ☐ I accept all study procedures (except for long-term storage of blood and urine samples) and requirements and obligations resulting from study participation.

I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy
(hh:mm a.m./p.m.)

Osaki Hospital Tokyo heart center
Hospital

Clinical Pharmacology Research Laboratory
Department

President
Title

Principal (Sub) Investigator

Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy
(hh:mm a.m./p.m.)

Osaki Hospital Tokyo heart center
Hospital

Department

Title

CRC

Seal



Study Number: ZRHM-REXA-07-JP (Main Study)
Dated: 2013/DEC/06 (Ver. 2.0)

To President of Osaki Hospital Tokyo heart center

For participants

Informed Consent Form

I have received sufficient explanation and understood the contents of this study "Reduced exposure study using THS 2.2 with 5 days in a confinement setting and 85 days in an ambulatory setting", therefore, I agree to participate in this study with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy (hh:mm a.m./p.m.)

Name (Signature)

Please check

- ☐ I am currently a smoker and have no plan or intent to cease smoking within the next three months, except when I am assigned to the abstinence group.
- ☐ I am aware that smoking may cause lung cancer, or worsen the risk of myocardial infarction, stroke or aggravation of emphysema, that tobacco smoke could negatively impact people in my vicinity, children and infants or the aged in particular, that I need to exercise caution not to disturb other persons, and that smoking dependency may result from nicotine, although its degree varies from one person to another.
- ☐ I have been exhaustively informed by Dr Endo, to be filled out by Investigator, legibly, in print) about the purposes of this study, type and character of the medical experiment and about the risk and benefits related to participation in this study.
- ☐ I agree for my blood and urine samples to be collected for safety and biomarker analysis.
- ☐ I have received one original of "Subject Information and Informed Consent Form" (version 2.0 dated 06-DEC-2013).
- ☐ I understand that relevant sections of my medical notes will be reviewed by representatives of Philip Morris Products S.A., auditors and regulatory authorities where it is relevant to my taking part in the study.
- ☐ I give permission for these individuals to have access to my records.
- ☐ I have been informed about the conditions of the third party insurance of the Sponsor for damages incurred as a result of participation in this study, and I accept them.
- ☐ I have had the opportunity to ask questions related to the medical experiment and I have received satisfactory answers to all of them.
- ☐ I agree for my blood samples to be collected in order to rule out infection with HIV virus, Hepatitis C virus and Hepatitis B surface antigen.
- ☐ I know my rights and my obligations resulting from my participation in the study.
- ☐ By signing this document I do not lose any rights to which I am entitled according to Japanese law.
- ☐ I agree to keep confidential all information relating to the study product (THS 2.2 Menthol), including the product design, specifications and method of operation.
- ☐ I have read all the information contained in above "Subject Information and Informed Consent Form" (version 2.0 dated 06-DEC-2013).
- ☐ I hereby confirm my informed and voluntary consent to participation in the said study. At the same time I know that at any time I may cease smoking or withdraw from further participation in this study, without providing a reason.
- ☐ I accept all study procedures (except for long-term storage of blood and urine samples) and requirements and obligations resulting from study participation.

I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy
(hh:mm a.m./p.m.)

Osaki Hospital Tokyo heart center
Hospital

Clinical Pharmacology Research Laboratory
Department

President
Title

Principal (Sub) Investigator

Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy
(hh:mm a.m./p.m.)

Osaki Hospital Tokyo heart center
Hospital

Department

Title

CRC

Seal



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM SHEET

Optional Bio-banking (Long-Term Storage) of Blood and
Urine Samples for Further Biomarker of exposure/Risk
Marker Research in Reduced Exposure Study Using THS
2.2 Menthol with 5 Days in a Confinement Setting and 85
Days in an Ambulatory Setting

Osaki Hospital Tokyo heart center

Study Number: ZRHM-07-JP
Version 1.0



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

Written Information and Informed Consent Form

This document states all necessary information that is useful for you to understand the contents of this optional research, which you are going to be participating, as well as your benefit and right. Please decide whether to participate in this optional research by your own free will after you have sufficiently understood the details of this optional research. If you have any question of this optional research, please contact us at any time. You will be able to take some time before your reply and are not expected to give us your answer within today. You can take home this Written Information with you to look into it thoughtfully, to have time to think it over or discuss with your family or friends before, and let us know your decision at a later date.

Should you have any questions, please ask the study physician ("Investigator"). You can ask the Investigator about any issue, which is in your opinion, related to the research.

Once you signed and dated this Informed Consent Form, in a presence of Investigator, you will receive one original which you will take home. When making the decision to participate in the research, it is important that you accept its course, its purpose, the planned procedures, and that you are ready to participate until the end of the research.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

1. Introduction

You have already agreed to participate in "Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting" (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new candidate of Modified Risk Tobacco Product (MRTP), on selected biomarkers of exposure (BoExp) compared to conventional cigarettes.

This form tells you about "Optional Bio-banking (Long-Term Storage) of Blood and Urine Samples for Further Biomarker of exposure /Risk Marker Research" (the optional research) which will be conducted in subjects who are already participating in the main study. This subject information and informed consent form is an addition to the main study form that you have already signed. The intention of this document is to ask you consent for collection, storage of blood and urine samples for long-term and for your consent to use these samples for further biomarker of exposure/risk marker analysis.

What is the biomarker of exposure /risk marker analysis?

Biomarkers can be described as substances measured in your body as the result of consumption of another substance (such as cigarette smoke). A risk marker is a biological characteristic which is associated with increased risk of certain disease or infection.

Currently, we are in the process of investigating the list of potential biomarkers of exposure and risk markers to be assessed and we are not in a position to provide a definite list. Only additional biomarkers of exposure to smoke constituents or risk markers (biomarkers such as an example your level of lipids in your blood) might be assessed in your samples collected and stored for bio-banking in order to further investigate the results of the main study you are participating to.

No genetic or transcriptomics analysis will be performed on these samples taken for the long-term storage (also see Informed Consent for Optional Bio-banking [Long-Term Storage] of Blood Samples for Further Transcriptomic Research).

The investigator, or study staff, will go over this with you and answer any questions you may have regarding this optional part of the research. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given an original copy to keep. No one can force you to agree on this optional long-term storage of blood and urine samples for further biomarker/risk marker analysis. If you do not agree to participate, you can still continue to participate in the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

optional research. This form is not meant to replace the one for the main study, and the contents of the main study subject information apply to this optional research.

By signing this informed consent form you agree for collection, storage of blood and urine samples for long term and that further biomarker of exposure /risk marker analysis may be done on your samples.

This form may contain words you do not understand. Please ask the investigator or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this optional research.

Before you decide to take part, you must understand the purpose of this optional biomarker of exposure /risk marker analysis, how your participation may help you, any potential risks to you, and what is expected of you during procedures of this optional research. Even if you agree to participate in this optional research you are free to change your mind and stop at any time without penalty or loss of benefits which you would otherwise have.

2. Purpose of this optional research

The purpose of this optional research is to collect blood and urine samples and store them for long-term for further biomarker of exposure/risk marker analysis (for details of biomarker of exposure /risk marker analysis, please see above section).

If you consent to this optional research, six blood samples and thirty urine samples for further biomarker/risk marker analysis will be drawn. Specifically, two blood samples will be required from you at the beginning of the main study (Day 0), two samples at the end of the confinement period (Day 6) and two samples at the end of the ambulatory period (Day 90 Visit [Day 91]). In addition, 10 urine samples will be collected each from your 24 hour urine collection of Day 0, Day 5 and Day 90 Visit (Day 90). These samples will be sent to the designated laboratories listed below in Section 4 and will be stored for further biomarker/risk marker analysis.

3. What will happen to me if I take part?

If you consent to this optional research, the investigator will ask you to sign this informed consent form. By signing this form, you will give consent to this optional part of the research that is to give blood samples (six 5 ml tubes = 30 ml in total), and 30 urine samples (10 ml each, 300 ml in total) for long-term storage with the purpose of further biomarker of exposure /risk marker analysis. You will not be able to take part in this optional test unless you sign the consent form. In the unlikely case that there is a problem processing your sample, you will not be asked to give an additional sample.



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4. About samples

4.1 Sample Analysis and Storage

Your six blood samples and thirty urine samples will be shipped for storage and analysis to a laboratory contracted by the Sponsor (Philip Morris Products S.A.) which has experience in testing as well as retaining and storing samples such as these. The blood and urine samples will be stored in a dedicated repository for clinical samples in Germany and further analysed in a designated laboratory using appropriate methods.

Laboratory for storage:

Tel:

Fax:

Laboratory which will undertake the analysis will be required to follow the requirements as set out in this informed consent form.

4.2 Sample Access Rights

Your blood and urine samples when they leave the study site for analysis will not include your name or any other personal details that could identify you. However, unlike the long-term storage samples for transcriptomic analysis, links between you and codes on samples will not be removed (also see Informed Consent for Optional Bio-banking [Long-Term Storage] of Blood Samples for Further Transcriptomic Research).

4.3 Post-Optional Research Sample Handling

Samples will be transferred to the Sponsor's laboratories in Germany and laboratory which will perform the analysis. The samples will be destroyed when the maximum storage time has been reached (5 years for blood samples, and 2 years for urine samples) or no further analyses are possible (whichever is early). You should be aware that Philip Morris Products S.A. might not conduct all research immediately and that your samples may be studied at any time before they are destroyed.



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5. Expected Clinical advantages and risks

5.1 What are the possible disadvantages and risks of taking part?

Using a needle to remove blood from a vein is called "a blood draw." During the study, it may be necessary to try more than once. A new needle will be used for each blood draw. Blood samples for long-term storage and urine samples for further biomarker of exposure /risk marker analysis will be taken six times during the study. You might feel pain or be light-headed from this. You may experience some temporary discomfort, bleeding, bruising, or rarely, infection, at the site of a needle stick you receive in the process of drawing blood samples.

5.2 What are the possible benefits of taking part?

There is no direct benefit to you by taking part in this optional research. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor the investigator will be contacted by the Sponsor in connection with the research or any information about the results of biomarker of exposure /risk marker analysis performed on the sample that you provide for this optional research.

6. Is taking part in this optional research voluntary?

Taking part in this optional research is voluntary. You may withdraw your consent to take part in it whilst you are involved in the research without affecting your participation in the main study, and without any penalty or loss of benefits to which you are entitled. To withdraw your consent, you must contact the investigator or site staff.

7. What if there is a problem?

The Sponsor has taken out an insurance policy for all subjects who consent to optional bio-banking (long-term storage) of blood and urine samples for further biomarker of exposure /risk marker research and will provide compensation should any deterioration of health which is directly attributable to the procedures for the optional research specified in the protocol.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

8. Can I change my mind?

You may withdraw your consent to the use of your blood and urine samples for this optional research whilst you are still undergoing study assessments until the end of the study by contacting the investigator or site staff.

If you withdraw your consent for further biomarker of exposure /risk marker analysis, you may request your blood and urine samples to be destroyed and no longer used in the research. However, the Sponsor shall be entitled to keep and use any research results obtained prior to your successful withdrawal of consent.

9. Will my taking part in this optional research be kept confidential?

Strict privacy and confidentiality procedures have been adopted for this research to keep your information safe. Your blood and urine samples when they leave the study site for analysis will not include your name or any other personal details that could identify you.

Sponsor may use other laboratories, investigators, commercial or academic third parties as Sponsor's "agents" to assist in this research. All such individuals are required to keep the data confidential.

10. What will happen with the results of this optional research?

This biomarker of exposure /risk marker analysis is not intended to provide you with clinical information. Although you have the right to access information in your medical records, the information that the Sponsor will maintain in their databases and create during biomarker of exposure /risk marker analysis is for research purposes only. Sponsor will not return any biomarker of exposure /risk marker analysis information to you or the investigator. Information resulting from the research will not be entered into your medical records. At some point, information about the results of the research may be published; however, you will not be identified in any such publication.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

11. Development for Commercial Gain

Any information resulting directly or indirectly from this biomarker of exposure /risk marker analysis, as well as any rights in law, diagnostic tests, drugs, or biological products developed or created directly or indirectly as a result of this research, are the exclusive property of the Sponsor (and its successors, if any) and may be used for commercial purposes anywhere in the world. By signing this form, you give up all and any rights you may have had to this property and these rights or any share of the profits that may be earned directly or indirectly as a result of this biomarker of exposure /risk marker analysis exclusively to the Sponsor. However, in signing this form and donating blood and urine samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

You will not be paid for consent for this optional research. You will not have to pay for any analyses related to this optional research.

12. Who is organising and funding the research?

The company sponsoring this optional assessment is Philip Morris Products S.A. (including agents, contractors or consultants).



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

13. Who has reviewed the research?

An independent ethics committee has reviewed the objectives and the proposed conduct of the main study and of this optional biomarker of exposure /risk marker analysis and has given a favourable opinion of it.

IRB is a committee, which has been established to assess whether or not the Clinical Study is conducted with respecting the participants' human rights and ensuring their safety, whether it is scientifically/ethically-valid and there is no problem in the Clinical Study Plan. IRB is required to consist of such as medical professionals (medical science and pharmaceutical science), some members other than medical professionals, and also independent members without interest from this Hospital. IRB performs to review the contents of Clinical Study Plan with taking patients' position into careful consideration. The President of our hospital is going to consult IRB members to get opinion concerning the implementation and continuation of the Clinical Study. At the same time, IRB is expected to advise their opinion to our President with reviewing the implementation and continuation of the Clinical Study from the scientific and ethical perspective.

We hereby certify the Clinical Study "Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting" including sample bio-banking has been reviewed and approved by the IRB that is established in Yasuda Hospital.

- ☐ Name : IRB, Yasuda Hospital
- ☐ Type of IRB : IRB established in Yasuda Hospital
- ☐ Founder : President, Yasuda Hospital
- ☐ Address : 1-13-9 Narimasu Itabashi-ku Tokyo, Japan
- ☐ Homepage Address: <http://www.yasudahosp.jp/>

You are entitled to view Procedure, list of board members, abstract record of this Institutional Review Board. The information is available at the study site. Please feel free to ask the Investigator (or site collaborator) for the information freely.



Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

14. Contact details

Please contact us at the following contact information desk if you have any question and/or consultations concerning sample bio-banking.

Hospital Name	Osaki Hospital Tokyo heart center
Information Desk	Osaki Hospital Tokyo heart center Clinical Research Coordinator
Contact person	
Telephone No.	

We ask for your kind understanding concerning sample bio-banking.

Please feel free to contact us if you have any question and/or issues need to be explained.

After due consideration, please sign the following Informed Consent Form as well as fill in the date of consent with your understanding and agreement for sample bio-banking. Please be sure to receive this Written Information and one original copy of Informed Consent Form you signed.

Thank you for taking time to read this information sheet.

Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

To President of Osaki Hospital Tokyo heart center

To be attached to the medical records

Informed Consent Form

I have received sufficient explanation and understood the contents of Optional Bio-banking (Long-Term Storage) of Blood and Urine Samples for Further Biomarker of exposure /Risk Marker Research in Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting and 85 Days in an Ambulatory Setting, therefore, I agree to participate in this analysis with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy

Name (Signature)

Please check

- ☐ I confirm that the optional bio-banking (long-term storage) of blood and urine samples for further biomarker of exposure /risk marker assessment has been explained to me and I have had the opportunity to ask questions and ample time to decide whether to participate. I know who to contact if I have any further questions.
- ☐ I confirm that I have read and understand the information sheet Japanese final version 1.0 dated 05 July 2013 for the biomarker of exposure/risk marker analysis.
- ☐ I understand that my participation is voluntary and agree to take part in this biomarker of exposure /risk marker analysis.
- ☐ I agree for collection and long-term storage of 30 ml blood and 300 ml urine.
- ☐ I agree that my blood sample can be used for the purposes of this further biomarker of exposure /risk marker assessment.
- ☐ I understand that if I withdraw my consent for biomarker of exposure /risk marker analysis, it will not be possible to destroy the data obtained from my samples.

I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Principal (Sub) Investigator

Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Seal

Study Number: ZRHM-REXA-07-JP (Bio-banking for BoEXP/Risk markers)
Dated: 2013/07/05 (Ver. 1.0)

To President of Osaki Hospital Tokyo heart center

For participants

Informed Consent Form

I have received sufficient explanation and understood the contents of Optional Bio-banking (Long-Term Storage) of Blood and Urine Samples for Further Biomarker of exposure /Risk Marker Research in Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting and 85 Days in an Ambulatory Setting, therefore, I agree to participate in this analysis with my own free will.

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Name (Signature)

Please check

- ☐ I confirm that the optional bio-banking (long-term storage) of blood and urine samples for further biomarker of exposure /risk marker assessment has been explained to me and I have had the opportunity to ask questions and ample time to decide whether to participate. I know who to contact if I have any further questions.
- ☐ I confirm that I have read and understand the information sheet Japanese final version 1.0 dated 05 July 2013 for the biomarker of exposure/risk marker analysis.
- ☐ I understand that my participation is voluntary and agree to take part in this biomarker of exposure /risk marker analysis.
- ☐ I agree for collection and long-term storage of 30 ml blood and 300 ml urine.
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I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Principal (Sub) Investigator

Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Seal



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

PARTICIPANT INFORMATION AND INFORMED CONSENT FORM SHEET

Optional Bio-banking (Long-Term Storage) of Blood
Samples for Further Transcriptomic Research
in Reduced Exposure Study Using THS 2.2 Menthol with 5
Days in a Confinement Setting and 85 Days in an
Ambulatory Setting

Osaki Hospital Tokyo heart center

Study Number: ZRHM-07-JP
Version 1.0



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

Written Information and Informed Consent Form

This document states all necessary information that is useful for you to understand the contents of this research, which you are going to be participating, as well as your benefit and right. Please decide whether to participate in this optional research by your own free will after you have sufficiently understood the details of this analysis. If you have any question of this optional research, please contact us at any time. You will be able to take some time before your reply and are not expected to give us your answer within today. You can take home this Written Information with you to look into it thoughtfully, to have time to think it over or discuss with your family or friends before, and let us know your decision at a later date.

Should you have any questions, please ask the study physician ("Investigator"). You can ask the Investigator about any issue, which is in your opinion, related to the research.

Once you signed and dated this Informed Consent Form, in a presence of Investigator, you will receive one original which you will take home. When making the decision to participate in the research, it is important that you accept its course, its purpose, the planned procedures, and that you are ready to participate until the end of the research.



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

1. Introduction

You have already agreed to participate in “Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting” (the main study), involving the new Tobacco Heating System (THS) 2.2 for the evaluation of the effects of THS 2.2, a new candidate of modified risk tobacco product (MRTP), on selected biomarkers of exposure (BoExp) compared to conventional cigarettes.

This form tells you about “Optional Bio-banking (Long-Term Storage) of Blood Samples for further Transcriptomic Research” (the optional research) which will be conducted in subjects who are already participating in the main study. This subject information and informed consent form is an addition to the main study form that you have already signed. The intention of this document is to ask you consent for collection, storage of blood samples for long-term and for your consent to use these samples for transcriptomic testing.

What is the transcriptomic testing?

Cells are the building blocks of the human body and each type of cell is specially adapted to its specific function in the body. All cells contain proteins. One of the roles of the family of biological molecules ribonucleic acid (RNA) is to help make these proteins. The optional measurements (transcriptomic testing) described here will involve the determination of the number and quality of that RNA, in all its forms, in blood samples from healthy subjects to understand if the harmful effect of smoking conventional cigarettes on the function of cells could be decreased when switching to the THS 2.2 test product. This transcriptomic testing will help understand how people respond to different exposure types (i.e., conventional cigarette versus test product).

Transcriptomic testing is different from genetic testing done for the purpose of diagnosing a person with a certain disease, or for risk for developing a certain disease.

The investigator, or study staff, will go over this with you and answer any questions you may have regarding this optional part of the research. If you agree to volunteer, you will be asked to sign and date this consent form and you will be given an original copy to keep. No one can force you to agree on this optional long-term storage of blood samples for further transcriptomic testing. If you do not agree to participate, you can still continue to participate in the main study. You must have reviewed and signed the main study informed consent before you review this subject information sheet for the optional research. This form is not meant to replace the one for the main study, and the content of the main study subject information applies to this optional transcriptomic testing.



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

By signing this informed consent form you agree for collection, storage of blood samples for long term and that transcriptomic testing may be done on your samples of blood.

This form may contain words you do not understand. Please ask the investigator or study staff to explain any words or information you do not clearly understand before agreeing to volunteer for this optional research.

Before you decide to take part, you must understand the purpose of this optional transcriptomic testing, how your participation may help you, any potential risks to you, and what is expected of you during this sub-research. Even if you agree to participate in this optional research you are free to change your mind and stop at any time without penalty or loss of benefits which you would otherwise have.

2. Purpose of this optional research

The purpose of this optional research is to collect blood samples and store them for long-term for future transcriptomic testing (for details of transcriptomic testing, please see above section).

If you consent to this optional research, three blood samples for transcriptomic testing will be drawn. Specifically, one blood sample will be required from you at the beginning of the main study (Day 0), one at the end of the confinement period (Day 6), and one at the end of the ambulatory period (Day 90 Visit [Day 91]). These samples will be sent to the designated laboratories listed below in Section 4 and will be stored for further transcriptomic testing to investigate how subject's RNA (for explanation of RNA, please see above section) is effected by using the THS 2.2 product in comparison to smoking conventional cigarettes and smoking abstinence during the stay at the clinic site and ambulatory period.

3. What will happen to me if I take part?

If you consent to this optional research, the study doctor will ask you to sign this informed consent form. By signing this form, you will give consent to this optional part of the research that is to give blood samples (three 5 ml tubes = 15 ml in total) for long-term storage with the purpose of transcriptomic testing. You will not be able to take part in this optional test unless you sign the consent form. In the unlikely case that there is a problem processing your sample, you will not be asked to give an additional sample.



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
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4. About samples

4.1 Sample Analysis and Storage

Your three blood samples will be shipped for storage and analysis to a laboratory contracted by the Sponsor (Philip Morris Products S.A.) which has experience in testing as well as retaining and storing samples such as these. The blood samples will be stored in a dedicated repository for clinical samples in Germany and further analysed in a designated laboratory using appropriate methods.

Laboratory for storage:

(b) (4)

Tel: (b) (4)

Fax: (b) (4)

Laboratory which will undertake the analysis will be required to follow the requirements as set out in this informed consent form.

4.2 Sample Access Rights

Your blood samples when they leave the study site for analysis will not include your name or any other personal details that could identify you. All blood samples will be coded and the link between you and the code will be removed once all checks of the sample and related research paperwork are complete. It will happen before the samples are sent to the laboratories.

Once the link has been removed it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymisation is intended to prevent your re-identification. As anonymised samples and associated data are not traceable back to you, it is not possible to undertake actions such as sample destruction, even at your request if this one is done after removal of the list. Only your study doctor or site staff will be able to trace the samples back to you, and only until the time at which the samples are sent to the laboratories.



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

4.3 Post-Optional Research Sample Handling

Samples will be transferred to the Sponsor's laboratories in Germany and laboratory which will perform the analysis. The samples will be destroyed when the maximum storage time has been reached (5 years) or no further analyses are possible (whichever is early). You should be aware that Philip Morris Products S.A. might not conduct all research immediately and that your samples may be studied at any time before they are destroyed.

5. Expected Clinical advantages and risks

5.1 What are the possible disadvantages and risks of taking part?

Using a needle to remove blood from a vein is called "a blood draw." During the study, it may be necessary to try more than once. A new needle will be used for each blood draw. Blood samples for long-term storage for further transcriptomic testing will be taken three times during the study. You might feel pain or be light-headed from this. You may experience some temporary discomfort, bleeding, bruising, or rarely, infection, at the site of a needle stick you receive in the process of drawing blood samples.

5.2 What are the possible benefits of taking part?

There is no direct benefit to you by taking part in this optional research. However, your participation may help to increase the knowledge and understanding of medical conditions and how different people respond to the study products.

Neither you nor the investigator will be contacted by the Sponsor in connection with the research or any information about the results of transcriptomic tests performed on the sample that you provide for this optional research.

6. Is taking part in this optional research voluntary?

Taking part in this optional research is voluntary. You may withdraw your consent to take part in it whilst you are involved in the research without affecting your participation in the main study, and without any penalty or loss of benefits to which you are entitled. To withdraw your consent, you must contact the investigator or site staff.



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

7. What if there is a problem?

The Sponsor has taken out an insurance policy for all subjects who consent to optional bio-banking (long-term storage) of blood samples for further transcriptomic research and will provide compensation should any deterioration of health which is directly attributable to the procedures for the optional research specified in the protocol.

8. Can I change my mind?

You may withdraw your consent to the use of your blood samples for this optional research whilst you are still undergoing study assessments until the end of the study by contacting the investigator or site staff.

The investigator will keep records that link your personal information with your coded blood sample and health information until all the information about the samples has been checked at the end of the research. Then, the link will be removed. If you withdraw your consent for transcriptomic analysis prior to deletion of the link, you may request your blood samples to be destroyed and no longer used in the research. After these records linking your identity to your sample have been checked and subsequently destroyed, it will no longer be possible for the researchers to destroy your sample and the related data if you withdraw your consent since the samples have been anonymized.

The Sponsor shall be entitled to keep and use any research results obtained prior to your successful withdrawal of consent.

9. Will my taking part in this optional research be kept confidential?

Strict privacy and confidentiality procedures have been adopted for this research to keep your information safe. Your blood samples when they leave the study site for analysis will not include your name or any other personal details that could identify you.

Sponsor may use other laboratories, investigators, commercial or academic third parties as Sponsor's "agents" to assist in this research. All such individuals are required to keep the data confidential.



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10. What will happen with the results of this optional assessment?

This transcriptomic research is not intended to provide you with clinical information. Although you have the right to access information in your medical records, the information that the Sponsor will maintain in their databases and create during transcriptomic testing is for research purposes only. The Sponsor will not return any transcriptomic information to you or the investigator. Information resulting from the research will not be entered into your medical records. At some point, information about the results of the research may be published; however, you will not be identified in any such publication as your samples are anonymized.

11. Development for Commercial Gain

Any information resulting directly or indirectly from this transcriptomic research, as well as any rights in law, diagnostic tests, drugs, or biological products developed or created directly or indirectly as a result of this research, are the exclusive property of the Sponsor (and its successors, if any) and may be used for commercial purposes anywhere in the world. By signing this form, you give up all and any rights you may have had to this property and these rights or any share of the profits that may be earned directly or indirectly as a result of this transcriptomic research exclusively to the Sponsor. However, in signing this form and donating blood samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

You will not be paid for consent for this optional research. You will not have to pay for any analyses related to this optional research.

12. Who is organising and funding the research?

The company sponsoring this optional assessment is Philip Morris Products S.A. (including agents, contractors or consultants).



Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

13. Who has reviewed the research?

An independent ethics committee has reviewed the objectives and the proposed conduct of the main study and of this optional transcriptomic research and has given a favourable opinion of it.

IRB is a committee, which has been established to assess whether or not the Clinical Study is conducted with respecting the participants' human rights and ensuring their safety, whether it is scientifically/ethically-valid and there is no problem in the Clinical Study Plan. IRB is required to consist of such as medical professionals (medical science and pharmaceutical science), some members other than medical professionals, and also independent members without interest from this Hospital. IRB performs to review the contents of Clinical Study Plan with taking patients' position into careful consideration. The President of our hospital is going to consult IRB members to get opinion concerning the implementation and continuation of the Clinical Study. At the same time, IRB is expected to advise their opinion to our President with reviewing the implementation and continuation of the Clinical Study from the scientific and ethical perspective.

We hereby certify the Clinical Study "Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 Days in an ambulatory setting" including sample bio-banking has been reviewed and approved by the IRB that is established in Yasuda Hospital.

- ☐ Name : IRB, Yasuda Hospital
- ☐ Type of IRB : IRB established in Yasuda Hospital
- ☐ Founder : President, Yasuda Hospital
- ☐ Address : 1-13-9 Narimasu Itabashi-ku Tokyo, Japan
- ☐ Homepage Address: <http://www.yasudahosp.jp/>

You are entitled to view Procedure, list of board members, abstract record of this Institutional Review Board. The information is available at the study site. Please feel free to ask the Investigator (or site collaborator) for the information freely.

Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)**14. Contact details**

Please contact us at the following contact information desk if you have any question and/or consultations concerning sample bio-banking.

Hospital Name	Osaki Hospital Tokyo heart center
Information Desk	Osaki Hospital Tokyo heart center Clinical Research Coordinator
Contact person	
Telephone No.	

We ask for your kind understanding concerning sample bio-banking.

Please feel free to contact us if you have any question and/or issues need to be explained.

After due consideration, please sign the following Informed Consent Form as well as fill in the date of consent with your understanding and agreement for sample bio-banking. Please be sure to receive this Written Information and one original copy of Informed Consent Form you signed.

Thank you for taking time to read this information sheet.

Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

To President of Osaki Hospital Tokyo heart center

To be attached to the medical records

Informed Consent Form

I have received sufficient explanation and understood the contents of Optional Bio-banking (Long-Term Storage) of Blood Samples for Further Transcriptomic Research in Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting and 85 Days in an Ambulatory Setting, therefore, I agree to participate in this analysis with my own free will.

Only your handwriting is acceptable.

dd/MMM/yyyy

Name (Signature)

Please check

- ☐ I confirm that the optional bio-banking (long-term storage) of blood samples for further transcriptomic assessment has been explained to me and I have had the opportunity to ask questions and ample time to decide whether to participate. I know who to contact if I have any further questions.
- ☐ I confirm that I have read and understand the information sheet Japanese final version 1.0 dated 05 July 2013 for the transcriptomic analysis.
- ☐ I understand that my participation is voluntary and agree to take part in this transcriptomic analysis.
- ☐ I agree for collection and long-term storage of 15 ml blood.
- ☐ I agree that my blood sample can be used for the purposes of this transcriptomic assessment.
- ☐ I understand that the link between myself and my transcriptomic blood sampling will be destroyed at the end of the study and before sending the blood samples to the laboratories.
- ☐ I understand that if I withdraw my consent for the transcriptomic assessment, it will not be possible to destroy both my blood samples and the data obtained from my samples from deletion of the link between my personal data and the blood sample.

I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

Principal (Sub) Investigator

Seal

Collaborator Signature or Printed name/Seal

dd/MMM/yyyy

Osaki Hospital Tokyo heart center
Hospital

Department

Title

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Study Number: ZRHM-REXA-07-JP (Bio-banking for Transcriptomics)
Dated: 2013/07/05 (Ver. 1.0)

To President of Osaki Hospital Tokyo heart center

For participants

Informed Consent Form

I have received sufficient explanation and understood the contents of Optional Bio-banking (Long-Term Storage) of Blood Samples for Further Transcriptomic Research in Reduced Exposure Study Using THS 2.2 Menthol with 5 Days in a Confinement Setting and 85 Days in an Ambulatory Setting, therefore, I agree to participate in this analysis with my own free will.

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I have performed sufficient explanation to the above-mentioned participant.

Principal (Sub) Investigator Signature or Printed name/Seal

dd/MMM/yyyy

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16.1.3.18.2 IEC/IRB Subject Information and Informed Consent Form (Local Language)





