



PMI RESEARCH & DEVELOPMENT

Study ZRHM-PK-05-JP **Clinical Study Report Appendix 16.1.6** **Randomization Scheme and Codes**

Study Title:	A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and nicotine gum
Short Title:	Nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Number:	ZRHM-PK-05-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):	16 November 2013
Principal Investigator and Affiliation:	F. Nobuoka, MD Ageo Medical Clinic 3133 Haraichi, Ageo City Saitama 362-0021, 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 Andrea Donelli, Clinical Scientist Nicola Lama, PhD, Biostatistician Patrick Picavet, MD, Medical Safety Officer
Version:	1.0
Date:	12 May 2015

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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16.1.6.1 RANDOMIZATION SCHEME AND CODES

The file: PMI_Covance_ZRHM-PK-05-JP_LIVE_9.00.000_SRL.txt, which is presented as the source in the footnote, is the LIVE randomization list provided by (b) (4)

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0001	Screen Failed	(b) (6)	49	Male					
JPN	AGE	0002	Randomized		61	Male	<= 0.6 mg	1068	17AUG2013 10:55 AM	Sequence 1 THS 2.2 Menthol – mCC	101
JPN	AGE	0003	Screen Failed		35	Male					
JPN	AGE	0004	Randomized		24	Male	> 0.6 - 1.0 mg	1095	17AUG2013 11:09 AM	Sequence 3 THS 2.2 Menthol – NRT gum	101
JPN	AGE	0005	Randomized		25	Male	> 0.6 - 1.0 mg	1087	17AUG2013 11:12 AM	Sequence 1 THS 2.2 Menthol – mCC	101
JPN	AGE	0006	Screen Failed		24	Male					
JPN	AGE	0007	Discontinued from Enrollment		41	Male	<= 0.6 mg				
JPN	AGE	0008	Screen Failed		38	Male					
JPN	AGE	0009	Screen Failed		30	Male					

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0010	Randomized	(b) (6)	23	Male	<= 0.6 mg	1022	17AUG2013 11:15 AM	Sequence 2 mCC – THS 2.2 Menthol	101
JPN	AGE	0011	Screen Failed		38	Male					
JPN	AGE	0012	Screen Failed		25	Male					
JPN	AGE	0013	Randomized		42	Male	<= 0.6 mg	1028	17AUG2013 11:16 AM	Sequence 2 mCC – THS 2.2 Menthol	101
JPN	AGE	0014	Screen Failed		37	Male					
JPN	AGE	0015	Screen Failed		37	Male					
JPN	AGE	0016	Screen Failed		50	Male					
JPN	AGE	0017	Randomized		42	Male	<= 0.6 mg	1035	17AUG2013 11:18 AM	Sequence 4 NRT gum – THS 2.2 Menthol	101
JPN	AGE	0018	Randomized		23	Male	<= 0.6 mg	1088	17AUG2013 11:19 AM	Sequence 3 THS 2.2 Menthol – NRT gum	102

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0019	Screen Failed	(b) (6)	44	Male					
JPN	AGE	0020	Screen Failed		36	Male					
JPN	AGE	0021	Screen Failed		26	Male					
JPN	AGE	0022	Randomized		23	Male	<= 0.6 mg	1108	17AUG2013 11:21 AM	Sequence 4 NRT gum – THS 2.2 Menthol	102
JPN	AGE	0023	Screen Failed		41	Male					
JPN	AGE	0024	Randomized		45	Male	<= 0.6 mg	1072	17AUG2013 11:22 AM	Sequence 1 THS 2.2 Menthol – mCC	102
JPN	AGE	0025	Randomized		36	Male	> 0.6 - 1.0 mg	1104	17AUG2013 11:24 AM	Sequence 2 mCC – THS 2.2 Menthol	102
JPN	AGE	0026	Screen Failed		47	Male					
JPN	AGE	0027	Randomized		24	Male	<= 0.6 mg	1115	17AUG2013 11:25 AM	Sequence 1 THS 2.2 Menthol – mCC	102



Randomization Scheme and Codes

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0028	Screen Failed	(b) (6)	46	Male					
JPN	AGE	0029	Screen Failed		31	Male					
JPN	AGE	0031	Randomized		23	Male	<= 0.6 mg	1106	07SEP2013 09:58 AM	Sequence 2 mCC – THS 2.2 Menthol	102
JPN	AGE	0032	Screen Failed		42	Male					
JPN	AGE	0033	Screen Failed		46	Male					
JPN	AGE	0034	Screen Failed		42	Male					
JPN	AGE	0035	Randomized		23	Male	> 0.6 - 1.0 mg	1030	07SEP2013 10:12 AM	Sequence 4 NRT gum – THS 2.2 Menthol	103
JPN	AGE	0036	Randomized		44	Male	<= 0.6 mg	1092	07SEP2013 10:13 AM	Sequence 3 THS 2.2 Menthol – NRT gum	103
JPN	AGE	0037	Screen Failed		24	Male					

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0038	Screen Failed	(b) (6)	36	Male					
JPN	AGE	0039	Randomized		31	Male	<= 0.6 mg	1065	07SEP2013 10:15 AM	Sequence 1 THS 2.2 Menthol – mCC	103
JPN	AGE	0040	Randomized		30	Male	<= 0.6 mg	1042	07SEP2013 10:16 AM	Sequence 2 mCC – THS 2.2 Menthol	103
JPN	AGE	0041	Screen Failed		24	Male					
JPN	AGE	0042	Screen Failed		27	Male					
JPN	AGE	0043	Randomized		23	Male	<= 0.6 mg	1064	07SEP2013 10:17 AM	Sequence 2 mCC – THS 2.2 Menthol	103
JPN	AGE	0044	Screen Failed		35	Male					
JPN	AGE	0045	Randomized		23	Male	> 0.6 - 1.0 mg	1078	07SEP2013 10:18 AM	Sequence 1 THS 2.2 Menthol – mCC	103
JPN	AGE	0046	Screen Failed		24	Male					



Randomization Scheme and Codes

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization			Block #
								#	Date and Time	Sequence (Treatment)	
JPN	AGE	0047	Discontinued from Enrollment	(b) (6)	24	Male	<= 0.6 mg				
JPN	AGE	0048	Discontinued from Enrollment		24	Male	> 0.6 - 1.0 mg				
JPN	AGE	0049	Randomized		48	Male	<= 0.6 mg	1119	07SEP2013 10:20 AM	Sequence 1 THS 2.2 Menthol – mCC	104
JPN	AGE	0050	Randomized		25	Male	> 0.6 - 1.0 mg	1025	07SEP2013 10:21 AM	Sequence 2 mCC – THS 2.2 Menthol	104
JPN	AGE	0051	Randomized		24	Male	<= 0.6 mg	1011	07SEP2013 10:22 AM	Sequence 3 THS 2.2 Menthol – NRT gum	104
JPN	AGE	0052	Randomized		31	Male	<= 0.6 mg	1110	07SEP2013 10:23 AM	Sequence 1 THS 2.2 Menthol – mCC	104
JPN	AGE	0053	Screen Failed		25	Male					
JPN	AGE	0054	Randomized		25	Male	<= 0.6 mg	1017	07SEP2013 10:24 AM	Sequence 2 mCC – THS 2.2 Menthol	104
JPN	AGE	0055	Screen Failed		26	Male					

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0056	Screen Failed	(b) (6)	29	Male					
JPN	AGE	0057	Screen Failed		24	Male					
JPN	AGE	0058	Screen Failed		32	Male					
JPN	AGE	0059	Screen Failed		50	Male					
JPN	AGE	0060	Randomized		27	Female	> 0.6 - 1.0 mg	1103	22SEP2013 10:55 AM	Sequence 4 NRT gum – THS 2.2 Menthol	104
JPN	AGE	0061	Randomized		40	Female	<= 0.6 mg	1054	22SEP2013 10:59 AM	Sequence 3 THS 2.2 Menthol – NRT gum	105
JPN	AGE	0062	Screen Failed		38	Female					
JPN	AGE	0063	Randomized		35	Female	<= 0.6 mg	1053	22SEP2013 11:00 AM	Sequence 4 NRT gum – THS 2.2 Menthol	105
JPN	AGE	0064	Screen Failed		46	Female					



Randomization Scheme and Codes

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization			Block #
								#	Date and Time	Sequence (Treatment)	
JPN	AGE	0065	Screen Failed	(b) (6)	23	Female					
JPN	AGE	0066	Randomized		43	Female	> 0.6 - 1.0 mg	1027	22SEP2013 11:01 AM	Sequence 1 THS 2.2 Menthol – mCC	105
JPN	AGE	0067	Randomized		23	Female	> 0.6 - 1.0 mg	1058	22SEP2013 11:02 AM	Sequence 2 mCC – THS 2.2 Menthol	105
JPN	AGE	0068	Screen Failed		27	Female					
JPN	AGE	0069	Screen Failed		48	Female					
JPN	AGE	0070	Randomized		25	Female	> 0.6 - 1.0 mg	1047	22SEP2013 11:04 AM	Sequence 2 mCC – THS 2.2 Menthol	105
JPN	AGE	0071	Randomized		25	Female	<= 0.6 mg	1113	22SEP2013 11:05 AM	Sequence 1 THS 2.2 Menthol – mCC	105
JPN	AGE	0072	Randomized		29	Female	<= 0.6 mg	1098	22SEP2013 11:06 AM	Sequence 4 NRT gum – THS 2.2 Menthol	106
JPN	AGE	0073	Randomized		33	Female	<= 0.6 mg	1045	22SEP2013 11:07 AM	Sequence 2 mCC – THS 2.2 Menthol	106



Randomization Scheme and Codes

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0074	Randomized	(b) (6)	27	Female	<= 0.6 mg	1077	22SEP2013 11:08 AM	Sequence 1 THS 2.2 Menthol – mCC	106
JPN	AGE	0075	Randomized		36	Female	> 0.6 - 1.0 mg	1111	22SEP2013 11:09 AM	Sequence 2 mCC – THS 2.2 Menthol	106
JPN	AGE	0076	Randomized		26	Female	<= 0.6 mg	1079	22SEP2013 11:10 AM	Sequence 1 THS 2.2 Menthol – mCC	106
JPN	AGE	0077	Screen Failed		32	Female					
JPN	AGE	0078	Randomized		28	Female	<= 0.6 mg	1118	22SEP2013 11:11 AM	Sequence 3 THS 2.2 Menthol – NRT gum	106
JPN	AGE	0079	Screen Failed		47	Female					
JPN	AGE	0080	Screen Failed		28	Female					
JPN	AGE	0081	Screen Failed		24	Female					
JPN	AGE	0082	Randomized		39	Female	<= 0.6 mg	1037	22SEP2013 11:12 AM	Sequence 1 THS 2.2 Menthol – mCC	107

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0083	Randomized	(b) (6)	40	Female	<= 0.6 mg	1094	22SEP2013 11:13 AM	Sequence 4 NRT gum – THS 2.2 Menthol	107
JPN	AGE	0084	Randomized		26	Female	<= 0.6 mg	1006	22SEP2013 11:15 AM	Sequence 1 THS 2.2 Menthol – mCC	107
JPN	AGE	0085	Screen Failed		48	Female					
JPN	AGE	0086	Screen Failed		29	Female					
JPN	AGE	0087	Discontinued from Enrollment		30	Female	<= 0.6 mg				
JPN	AGE	0088	Screen Failed		33	Female					
JPN	AGE	0089	Randomized		41	Female	<= 0.6 mg	1026	12OCT2013 10:32 AM	Sequence 2 mCC – THS 2.2 Menthol	107
JPN	AGE	0090	Randomized		36	Female	<= 0.6 mg	1018	12OCT2013 10:39 AM	Sequence 2 mCC – THS 2.2 Menthol	108
JPN	AGE	0091	Screen Failed		37	Female					

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization			Block #
								#	Date and Time	Sequence (Treatment)	
JPN	AGE	0092	Discontinued from Enrollment	(b) (6)	25	Female	<= 0.6 mg				
JPN	AGE	0093	Randomized		32	Female	<= 0.6 mg	1036	12OCT2013 10:40 AM	Sequence 2 mCC – THS 2.2 Menthol	108
JPN	AGE	0094	Screen Failed		36	Female					
JPN	AGE	0095	Randomized		25	Female	> 0.6 - 1.0 mg	1105	12OCT2013 10:35 AM	Sequence 3 THS 2.2 Menthol – NRT gum	107
JPN	AGE	0096	Screen Failed		26	Female					
JPN	AGE	0097	Randomized		61	Female	<= 0.6 mg	1048	12OCT2013 10:41 AM	Sequence 1 THS 2.2 Menthol – mCC	108
JPN	AGE	0098	Screen Failed		43	Female					
JPN	AGE	0099	Screen Failed		55	Female					
JPN	AGE	0100	Screen Failed		29	Female					

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization			Block #
								#	Date and Time	Sequence (Treatment)	
JPN	AGE	0101	Screen Failed	(b) (6)	30	Female					
JPN	AGE	0102	Randomized		29	Female	<= 0.6 mg	1099	12OCT2013 10:36 AM	Sequence 2 mCC – THS 2.2 Menthol	107
JPN	AGE	0104	Screen Failed		28	Female					
JPN	AGE	0105	Randomized		42	Female	<= 0.6 mg	1061	12OCT2013 10:42 AM	Sequence 2 mCC – THS 2.2 Menthol	109
JPN	AGE	0106	Screen Failed		44	Female					
JPN	AGE	0107	Randomized		45	Female	<= 0.6 mg	1093	12OCT2013 10:37 AM	Sequence 1 THS 2.2 Menthol – mCC	108
JPN	AGE	0108	Discontinued from Enrollment		49	Female	<= 0.6 mg				
JPN	AGE	0109	Screen Failed		39	Female					
JPN	AGE	0110	Screen Failed		38	Female					



Randomization Scheme and Codes

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0111	Screen Failed	(b) (6)	25	Female					
JPN	AGE	0112	Discontinued from Enrollment		33	Female	<= 0.6 mg				
JPN	AGE	0113	Randomized		47	Female	<= 0.6 mg	1067	12OCT2013 10:44 AM	Sequence 1 THS 2.2 Menthol – mCC	109
JPN	AGE	0114	Screen Failed		24	Female					
JPN	AGE	0115	Discontinued from Enrollment		52	Female	<= 0.6 mg				
JPN	AGE	0116	Discontinued from Enrollment		47	Female	<= 0.6 mg				
JPN	AGE	0118	Screen Failed		34	Female					
JPN	AGE	0119	Randomized		28	Female	> 0.6 - 1.0 mg	1063	12OCT2013 10:45 AM	Sequence 3 THS 2.2 Menthol – NRT gum	108
JPN	AGE	0120	Randomized		26	Male	> 0.6 - 1.0 mg	1109	05NOV2013 10:12 AM	Sequence 4 NRT gum – THS 2.2 Menthol	108

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization			Block #
								#	Date and Time	Sequence (Treatment)	
JPN	AGE	0122	Discontinued from Enrollment	(b) (6)	33	Male	> 0.6 - 1.0 mg				
JPN	AGE	0123	Randomized		28	Male	> 0.6 - 1.0 mg	1059	05NOV2013 10:17 AM	Sequence 3 THS 2.2 Menthol – NRT gum	109
JPN	AGE	0124	Screen Failed		41	Male					
JPN	AGE	0125	Screen Failed		26	Male					
JPN	AGE	0126	Screen Failed		32	Male					
JPN	AGE	0127	Screen Failed		28	Male					
JPN	AGE	0128	Randomized		45	Male	> 0.6 - 1.0 mg	1003	05NOV2013 10:19 AM	Sequence 1 THS 2.2 Menthol – mCC	109
JPN	AGE	0129	Randomized		24	Male	> 0.6 - 1.0 mg	1062	05NOV2013 10:20 AM	Sequence 2 mCC – THS 2.2 Menthol	109
JPN	AGE	0130	Screen Failed		34	Male					



Randomization Scheme and Codes

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0131	Screen Failed	(b) (6)	47	Female					
JPN	AGE	0132	Randomized		44	Female	> 0.6 - 1.0 mg	1086	05NOV2013 10:22 AM	Sequence 4 NRT gum – THS 2.2 Menthol	109
JPN	AGE	0133	Screen Failed		35	Male					
JPN	AGE	0134	Randomized		37	Male	> 0.6 - 1.0 mg	1070	05NOV2013 10:23 AM	Sequence 1 THS 2.2 Menthol – mCC	110
JPN	AGE	0135	Randomized		44	Female	> 0.6 - 1.0 mg	1089	05NOV2013 10:25 AM	Sequence 2 mCC – THS 2.2 Menthol	110
JPN	AGE	0136	Randomized		32	Female	> 0.6 - 1.0 mg	1097	05NOV2013 10:26 AM	Sequence 1 THS 2.2 Menthol – mCC	110
JPN	AGE	0138	Screen Failed		52	Female					
JPN	AGE	0139	Randomized		39	Male	> 0.6 - 1.0 mg	1014	05NOV2013 10:28 AM	Sequence 2 mCC – THS 2.2 Menthol	110
JPN	AGE	0140	Randomized		24	Male	> 0.6 - 1.0 mg	1038	05NOV2013 10:29 AM	Sequence 2 mCC – THS 2.2 Menthol	111

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization			Block #
								#	Date and Time	Sequence (Treatment)	
JPN	AGE	0141	Discontinued from Enrollment	(b) (6)	25	Male	> 0.6 - 1.0 mg				
JPN	AGE	0142	Randomized		24	Male	> 0.6 - 1.0 mg	1100	05NOV2013 10:30 AM	Sequence 1 THS 2.2 Menthol – mCC	111
JPN	AGE	0143	Screen Failed		23	Male					
JPN	AGE	0144	Screen Failed		27	Male					
JPN	AGE	0145	Screen Failed		29	Male					
JPN	AGE	0146	Screen Failed		25	Male					
JPN	AGE	0147	Screen Failed		48	Male					
JPN	AGE	0148	Randomized		25	Female	> 0.6 - 1.0 mg	1071	05NOV2013 10:31 AM	Sequence 1 THS 2.2 Menthol – mCC	111
JPN	AGE	0149	Screen Failed		28	Male					

**Randomization Scheme and Codes**

Country	Site	Screening #	Current Subject Status	Date of Birth	Entry Age (Years)	Gender	Nicotine Level	Randomization		Sequence (Treatment)	Block #
								#	Date and Time		
JPN	AGE	0150	Screen Failed	(b) (6)	35	Male					
JPN	AGE	0151	Screen Failed		35	Male					
JPN	AGE	0152	Randomized		36	Male	> 0.6 - 1.0 mg	1007	05NOV2013 10:33 AM	Sequence 2 mCC – THS 2.2 Menthol	111

Note: mCC = menthol conventional cigarettes; NRT gum = Nicotine Replacement Therapy gum; THS = Tobacco Heating System.

Source: PMI_Covance_ZRHM-PK-05-JP_LIVE_9.00.000_SRL.txt SDTM.DM SDTM.SUPPDM SDTM.DS SDTM.FA

Path: /cvn/projects/prj/development/000000106326/dev/listings/l_rand.sas

Program Run: 23FEB15 cvn_jhardman Program Status: FINAL

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16.1.6.2 BIOSTATISTICAL ADDENDUM TO IXRS

(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4)	Project Code: COVNCPK05JP01	Version: 3.0

<div style="background-color: #cccccc; height: 250px; width: 100%;"></div>	<p>PMI <u>Protocol: ZRHM-PK-05-JP</u> <u>(Covance)</u></p> <p>Biostatistical Addendum Subject Randomization List (BA-S)</p>
	<div style="display: flex;"> <div style="flex: 1;"> <p>Web: E-mail: Phone: Facsimile: Mail:</p> </div> <div style="flex: 2; background-color: #cccccc; height: 150px; width: 100%;"></div> </div>

Confidentiality Statement

This document contains information that is confidential and proprietary, and is not for distribution beyond the (b) (4) (b) (4) and/or the Client organization designated on title page.

(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4) Project Code: COVNCPK05JP01		Version: 3.0

Change History

Document	Version	Author	Date	Description
Initial	1.0	M. Baldwin	06-Mar-2013	This document captures the requirements for creation of the Subject Randomization List for Protocol ZRHM-PK-05-JP (COVNCPK05JP01). Creation of this document began on 04-Mar-2013.
Revision	2.0	M. Baldwin	18-Apr-2013	Protocol updated to PMI ZRHM-PK-05-JP (Covance) (front page only). Sections 4.2 and 4.3.1 were updated due to a change in the sample size / allocation ratio / treatment group caps. The subject randomization list is not being regenerated as a result of these changes (the lists generated from BA-S v1.0 will be utilized for this study).
Revision	3.0	K. Vanner	04-Feb-2015	Revised to include additional recipient of LIVE Subject Randomization List. Updates to this document include: <ul style="list-style-type: none"> - Approvers updated in BA-S Approval Signatures section - Section 1.3 added to include BA-S v3.0 timelines - Note added in Section 5 to indicate Sections 5.1-5.3 refer to BA-S v1.0 only and are not to be resent as part of BA-S v3.0 - Section 6.4 added to include approval requirements for BA-S v3.0 Note: the Subject Randomization List will not be re-generated as a result of this revision.

Any changes, after approval, either requested by the Client or (b) (4) will be captured in an amendment to this document. Each amendment requires approval signatures by both the Client and (b) (4) before any changes are implemented. Approved changes may require renegotiation and reassessment of the cost, resource, and schedule commitments for this project. Versions will increment by 1 (i.e. Version 1.0 to 2.0 to 3.0, etc.).

BA-S Approval Signatures

Altac CT utilizes a document management system to record the approval of the internal design team. The (b) (4) signatures below represent the collective team approval.

By signing below, I agree that this document represents my best understanding of the requirements and an accurate interpretation of the Protocol for the project described within and is in line with my expectations.

(b) (4)

Dr Nicola Lama

PRINT NAME

PMI Staff Scientist / Statistics

TITLE

SIGNATURE

05 FEB 2015

DATE

Andrew Hedge

PRINT NAME

Covance Principal Statistician

TITLE

SIGNATURE

04 FEB 2015

DATE

(b) (4)

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(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4)	Project Code: COVNCPK05JP01	Version: 3.0

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(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4)	Project Code: COVNCPK05JP01	Version: 3.0

1. Timelines

1.1	Version 1.0 Milestone Dates / Timelines	
1	BA-S Approval Date:	06-Mar-2013
2	Pre-load DUMMY List Provided to Client / Designee:	26-Mar-2013
3	Pre-load DUMMY List Provided to Additional Client / Designee:	26-Mar-2013
4	Client / Designee Approval of Pre-load DUMMY List:	29-Mar-2013
5	Additional Client / Designee Approval of Pre-load DUMMY List:	29-Mar-2013
1.2	Version 2.0 Milestone Dates / Timelines	
1	BA-S Approval Date:	17-Apr-2013
1.3	Version 3.0 Milestone Dates / Timelines	
1	BA-S Approval Date:	04-Feb-2015
2	Pre-load LIVE List Provided to Client / Designee:	06-Feb-2015
3	Client / Designee Approval of LIVE list:	Not Applicable

2. Purpose

The Biostatistical Addendum – Subject Randomization List (BA-S) document captures the requirements related to the generation of a subject randomization schedule to be utilized for the randomization of subjects in (b) (4) IXR system for a given study.

3. General Requirements

3.1	General Requirements	
1	Version of the List(s):	Initial
2	Number of Randomization Lists Generated / Provided:	1
	Note: This number refers to the number of files to be produced for loading into the IXRS. If the overall file (list) includes sub-lists (e.g. for individual strata, cohorts, subject replacements), then the overall number of randomization lists to be loaded into the IXRS is 1 (one) list (this number does not refer to sub-lists which will be concatenated into a single overall list).	
3	Purpose Statement:	To generate subject randomization list(s).
4	Forced Randomization:	Allowed - Scrambled Rand List Required Note: this is not forced randomization due to medication unavailability, but rather to obtain the required treatment balance. Refer to the URS Randomization Module for details.

(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4)	Project Code: COVNCPK05JP01	Version: 3.0

4. Subject Randomization List Details

4.1 File Configuration													
1	File Format:	ASCII comma delimited (.txt)											
	Note: This file format refers to list(s) that are to be generated for loading into the IXRS and provided for approval (see Section 5); this does <u>not</u> refer to file formats relating to Live data transfers (mid / end of study) that will be described / captured in a separate Data Transfer specification document (with other file formats available).												
2	Sorting:	Sorted ascending by Sequence Number (RandNo is Scrambled)											
3	Subject Randomization List File Names*:	DUMMY Subject Randomization List: - PMI_Covance_ZRHM-PK-05-JP_DUMMY_9.XX.YYY_SRL.txt LIVE Subject Randomization List: - PMI_Covance_ZRHM-PK-05-JP_LIVE_9.XX.YYY_SRL.txt											
* Filename versioning 9.XX.YYY: - 9(b) (4) internal reference code for Subject Randomization List - XX = 00, 01, 02, etc. refers to Client versions of Subject Randomization Lists generated / sent for approval and version of BA-S - YYY = 000, 001, 002, etc. refers to internal (b) (4) versions generated to provide a Subject Randomization List that has passed internal testing and ready for Client approval													
4.2 Treatment Group Definitions													
	Treatment Group (Treatment)	Treatment Group Description (TrtDC)	<table border="1"> <thead> <tr> <th>Treatment Group Allocation Ratio in List*</th> <th>Actual Treatment Group Allocation Ratio in Study*</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>22</td> </tr> <tr> <td>2</td> <td>22</td> </tr> <tr> <td>3</td> <td>9</td> </tr> <tr> <td>4</td> <td>9</td> </tr> </tbody> </table>	Treatment Group Allocation Ratio in List*	Actual Treatment Group Allocation Ratio in Study*	1	22	2	22	3	9	4	9
Treatment Group Allocation Ratio in List*	Actual Treatment Group Allocation Ratio in Study*												
1	22												
2	22												
3	9												
4	9												
	1	Sequence 1 THS 2.2 Menthol – mCC											
	2	Sequence 2 mCC – THS 2.2 Menthol											
	3	Sequence 3 THS 2.2 Menthol – NRT gum											
	4	Sequence 4 NRT gum – THS 2.2 Menthol											
* Notes: - Overall sample size = 62; overall allocation ratio 22:22:9:9 (for Treatments 1:2:3:4 respectively) to be achieved by utilizing treatment caps. - The list will be generated utilizing a block size 6 in a 2:2:1:1 ratio. - 9 complete blocks will result in 18:18:9:9 records. - After the 9 th block is complete, the treatment cap (of 9) for Treatments 3 and 4 will have been reached. - The IXRS will subsequently assign the 2xTreatment 1 and 2xTreatment 2 records in the 10 th and 11 th blocks in order to achieve the overall required treatment group ratio 22:22:9:9. - See URS for details on this functionality.													
4.3 List Structure / Content													
1	Maximum Number of Subjects to be Randomized:	62											
2	Block Size:	6											
3	Overall Number of Randomization Numbers:	120											
4	Overall Number of Blocks:	20											
5	Overall Number of Randomization Numbers per Treatment Group:	1=40; 2=40; 3=20; 4=20											

(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4) Project Code: COVNCPPK05JP01		Version: 3.0

4.4 Stratum Definitions				
Study-level randomization – stratification not required.				
4.5	Randomization List Format * Note (Loaded in IXRS): <ul style="list-style-type: none"> Per (b) (4) standards, only certain variables are required to be loaded into the IXRS. Non-loaded variables (such as TrialID, StratDC, TrtDC, etc.) are already contained within the IXRS, and hence can still be included in Live data transfers as required. Also note that BlockNo will only be loaded if required by the IXRS for dynamic allocation of blocks. 			
Column No.	Column Header	Format	Description	* Loaded in IXRS
1	TrialID	Text	ZRHM-PK-05-JP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2	SeqNo	5 digits (numeric)	Sequence Number (unique) Overall Sequence Number range: 10001-10120	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3	RandNo	4 digits (numeric)	Randomization Number (unique) Overall Randomization Number range: 1001-1120 (scrambled)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4	Treatment	1 digit(s) (numeric)	Treatment Identifier; based on Treatment Group Definitions in Section 4.2	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
5	TrtDC	Text	Treatment Description; based on Treatment Group Definitions in Section 4.2	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
6	BlockNo	3 digits (numeric)	Block Number Overall Block Number range: 101-120	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

File Example: To note, the sample below is for illustrative purposes and was not taken from the LIVE list.

TrialID,SeqNo,RandNo,Treatment,TrtDC,BlockNo
 ZRHM-PK-05-JP,10001,1009,4,Sequence 4 NRT gum – THS 2.2 Menthol,101
 ZRHM-PK-05-JP,10002,1078,1,Sequence 1 THS 2.2 Menthol – mCC,101
 ZRHM-PK-05-JP,10003,1054,3,Sequence 3 THS 2.2 Menthol – NRT gum,101
 ZRHM-PK-05-JP,10004,1055,2,Sequence 2 mCC – THS 2.2 Menthol,101
 ZRHM-PK-05-JP,10005,1108,2,Sequence 2 mCC – THS 2.2 Menthol,101
 ZRHM-PK-05-JP,10006,1085,1,Sequence 1 THS 2.2 Menthol – mCC,101

ZRHM-PK-05-JP,10115,1104,3,Sequence 3 THS 2.2 Menthol – NRT gum,120
 ZRHM-PK-05-JP,10116,1064,1,Sequence 1 THS 2.2 Menthol – mCC,120
 ZRHM-PK-05-JP,10117,1081,2,Sequence 2 mCC – THS 2.2 Menthol,120
 ZRHM-PK-05-JP,10118,1007,4,Sequence 4 NRT gum – THS 2.2 Menthol,120
 ZRHM-PK-05-JP,10119,1040,2,Sequence 2 mCC – THS 2.2 Menthol,120
 ZRHM-PK-05-JP,10120,1033,1,Sequence 1 THS 2.2 Menthol – mCC,120

(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4)	Project Code: COVNCPK05JP01	Version: 3.0

5. Approval Requirements

List Delivery and Approval Information:		
<p>(b) (4) will generate (in parallel) <u>both</u> a LIVE and a DUMMY Subject Randomization List with each utilizing a different starting seed to ensure that the lists are identical in structure but non-identical with respect to Treatment Group ordering.</p> <ul style="list-style-type: none"> LIVE Subject Randomization List: list to be loaded into the Live IXRS; note this list can only be approved by an Unblinded Recipient (who is also privy to the file structure (e.g. treatment identifiers / block size)). DUMMY Subject Randomization List: list used for IXRS development and (b) (4) / Client User Acceptance Testing; note this list can be approved by any Blinded or Unblinded Recipient who is privy to the file structure (e.g. treatment identifiers / block size). <p>Note:</p> <ul style="list-style-type: none"> (b) (4) policy does not allow the sending of LIVE lists via Email. The (b) (4) list generation standard fee covers 1xPre-Load Approval (Required) plus 1xPost-Load Approval (Optional). A cost of \$500 will be incurred for each additional Pre- or Post-Load Approval / Recipient. 		
Approval Requirements – BA-S v1.0		
Internal Note: Items in sections 5.1-5.3 are not to be resent; see below starting with Section 5.4 for Additional Recipient for BA-S v3.0		
5.1	Pre-Load Approval of DUMMY and/or LIVE list (Required): Prior to the LIVE list(s) being loaded into the IXRS, (b) (4) policy requires a Client (or designee) to provide a Pre-Load Approval of the generated DUMMY or LIVE list.	
1	A copy of the <u>pre-load</u> file(s) will be sent to the Client (or designee) for verification / approval:	<input checked="" type="checkbox"/> Approval required
2	Version of the <u>pre-load</u> file(s) to be approved:	DUMMY list(s) PMI_Covance_ZRHM-PK-05-JP_DUMMY_9.XX.YYY_SRL.txt
3	Security Assessment:	Password Protected .zip file: PMI_Covance_ZRHM-PK-05-JP_PreLoad_DUMMY_SRL_<YYYYMMDD>.zip
4	Route of Delivery:	Email
5	Recipient Details:	Name: Dr Nicola Lama Title: Staff Scientist / Statistics Company: Philip Morris International Address: c/o Philip Morris Product S.A. Quai Jeanrenaud 5, 2000 Neuchatel Switzerland Phone: +41 58 242 2694 Mobile: +41 79 700 9374 Email: Nicola.Lama@pmi.com
6	The pre-load file must be approved in writing prior to the data being loaded into the IXRS. Failure to do so can adversely affect the go-live date of the IXRS.	

(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4)	Project Code: COVNCPK05JP01	Version: 3.0

5.2 Additional Pre-Load Approval / Recipient of DUMMY and/or LIVE list(s) (Optional): each additional Pre-Load Approval / Recipient to Section 5.1 will incur a cost of \$500 per Recipient.		
1	A copy of the <u>pre-load</u> file(s) will also be sent to the Client (or designee):	<input type="checkbox"/> Not required <input checked="" type="checkbox"/> For Approval (additional to Section 5.1 above) <input type="checkbox"/> Recipient only (without approval)
2	Timing:	In parallel to Pre-Load Approval in Section 5.1
3	Version of the <u>pre-load</u> file(s) to be approved:	DUMMY list(s) PMI_Covance_ZRHM-PK-05-JP_DUMMY_9.XX.YYY_SRL.txt
4	Security Assessment:	Password Protected .zip file: PMI_Covance_ZRHM-PK-05-JP_PreLoad_DUMMY_SRL_<YYYYMMDD>.zip
5	Route of Delivery:	Email
6	Recipient Details:	Name: Andrew Hedge Title: Principal Statistician Company: Covance Clinical Research Unit Address: Springfield House Hyde Street Leeds LS2 9LH Phone: 44 (0)113 237 3500 DDI: 44 (0)113 241 6716 Email: andrew.hedge@covance.com
7	In the case of additional approval(s) being required, the pre-load file must be approved in writing (by each additional approver) prior to the data being loaded into the IXRS. Failure to do so can adversely affect the go-live date of the IXRS.	
5.3 Post-Load Approval of LIVE list (Optional): Following the required pre-load approval, the LIVE list(s) will be imported into the Live IXRS production environment and verified for accuracy; once complete, a Post-Load Approval may be required to verify the accuracy of the LIVE list loaded into the IXRS. Note that: <ul style="list-style-type: none"> - The LIVE Subject Randomization List is extracted directly from the IXRS (post-load) and will only contain those variables that were required to be loaded into the IXRS. - The file will be provided as ASCII text file only, using the (b) (4) filename convention. - (b) (4) policy does not allow the sending of LIVE lists via Email; Unblinded Recipient only. 		
1	A copy of the <u>post-load</u> file will be sent to the Client (or designee) for verification / approval:	<input checked="" type="checkbox"/> Client waives review (not required) <input type="checkbox"/> Approval required <input type="checkbox"/> Recipient only (without approval)

(b) (4)	Biostatistical Addendum-Subject Randomization List(BA-S)	Template v2.0 – SOP 30.7-8 Form 3b
Name of Client: PMI / Covance		Protocol Number: ZRHM-PK-05-JP
(b) (4)	Project Code: COVNCPK05JP01	Version: 3.0

Approval Requirements – BA-S v3.0		
5.4 Additional Approval / Recipient of DUMMY and/or LIVE list(s) (Optional): each additional Approval / Recipient to Section 5.1 will incur a cost of \$500 per Recipient.		
1	A copy of the <u>pre-load</u> file(s) will also be sent to the Client (or designee):	<input type="checkbox"/> Not required <input type="checkbox"/> For Approval (additional to Section 5.1 above) <input checked="" type="checkbox"/> Recipient only (without approval)
2	Version of the <u>pre-load</u> file(s) to be received:	LIVE list(s) PMI_Covance_ZRHM-PK-05-JP_LIVE_9.XX.YYY_SRL.txt
3	Security Assessment:	Password Protected .zip file: PMI_Covance_ZRHR_ZRHM_Studies_PreLoad_LIVE_SRL_<YYYYMMDD>.zip Note: zip file to contain all x8 LIVE lists relating to the below protocols: <ul style="list-style-type: none"> - ZRHR-PK-01-EU - ZRHR-PK-02-JP - ZRHR-REXC-03-EU - ZRHR-REXC-04-JP - ZRHM-PK-05-JP - ZRHM-PK-06-US - ZRHM-REXA-07-JP - ZRHM-REXA-08-US
4	Route of Delivery:	Covance sFTP / (b) (4) (b) (4) IVE
5	LIVE List Recipient Details:	Name: Andrew Hedge Title: Principal Statistician Company: Covance Clinical Research Unit Address: Springfield House Hyde Street Leeds LS2 9LH Phone: 44 (0)113 237 3500 DDI: 44 (0)113 301 3759 Email: andrew.hedge@covance.com