



PMI RESEARCH & DEVELOPMENT

Study ZRHM-REXA-08-US **Clinical Study Report Appendix 16.1.9** **Bioanalytical Documentation**

Study Title:	A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently 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 86 days in an ambulatory setting ZRHM-REXA-08-US
Study Number:	ZRHM-REXA-08-US
Product Name:	Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol)
Study Initiated (first subject screened):	17 December 2013
Study Completed (last subject last visit):	12 October 2014
Principal Investigator and Affiliation:	Dr William Lewis, Covance Dallas Site 1341 W. Mockingbird Ln., Suite 400E Dallas, TX 75247 Dr H. Frank Farmer, Covance Daytona Beach Site 1900 Mason Ave., Suite 140 Daytona Beach, FL 32117
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 Guillaume de La Bourdonnaye, MEng, MSc, Biostatistician Andrea Donelli, Clinical Scientist Ruben Rosoky, MD PhD MFPM, Medical Safety Officer
Version:	1.0
Date:	25 May 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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16.1.9 BIOANALYTICAL DOCUMENTATION

16.1.9.1 STANDARDIZATION AND LABORATORY REFERENCE RANGES



(b) (4)

08-Nov-13

<u>Test Name</u>	<u>Test Number</u>	<u>Units</u>	<u>Gender</u>	<u>Age</u>	<u>Low</u>	<u>High</u>
Chemistries						
Albumin	001081	g/dL	Both	up to 3 yrs	3.4	4.2
			Both	up to 59 yrs	3.5	5.5
			Both	up to 69 yrs	3.6	4.8
			Both	up to 79 yrs	3.5	4.8
			Both	up to 89 yrs	3.5	4.7
			Both	> 90yrs	3.2	4.6
A/G Ratio	012047		Both	All	1.1	2.5
Alkaline Phosphatase	001107	IU/L	Both	1-3 yrs	130	317
			Both	4-6 yrs	133	309
			Both	7-12 yrs	134	349
			Male	13 yrs	143	396
			Female	13 yrs	68	209
			Male	14 yrs	107	340
			Female	14 yrs	62	149
			Male	15 yrs	84	254
			Female	15 yrs	54	121
			Male	16 yrs	71	186
			Female	16 yrs	49	108
			Male	17 yrs	64	146
			Female	17 yrs	45	101
			Male	18 yrs	56	127
			Female	18 yrs	43	101
			Both	>19 Yrs	39	117
ALT (SGPT)	001545	IU/L	Male	All	0	44
			Female	All	0	32
Amylase	001396	U/L	Both	All	31	124
AST (SGOT)	001123	IU/L	Both	up to 6 mons	0	120
			Both	up to 1 yr	0	110
			Both	up to 5 yrs	0	75
			Both	up to 10 yrs	0	60
			Both	Adult	0	40
Bilirubin Direct	001222	mg/dL	Both	All	0.00	0.40



Bilirubin Total	001099	mg/dL	Both	All	0.1	1.2
Bilirubin, Indirect	011247	mg/dL	Both	All	0.10	0.80
Bilirubin, Neonatal	015602	mg/dL	Infant	24 hr Premature	1.0	6.0
				24 hr Full term	2.0	6.0
				48 hr Premature	6.0	8.0
				48 hr Full term	6.0	7.0
				3 - 5 days Premature	10.0	12.0
				3 - 5 days Full term	4.0	6.0
BUN	001040	mg/dL	Both	up to 17 yrs	5	18
				up to 39 yrs	6	20
				up to 59 yrs	6	24
				up to 89 yrs	8	27
				up to 99 yrs	10	36
BUN/Creat ratio	011577		Male	up to 17 yrs	9	25
				up to 39 yrs	8	20
				up to 59 yrs	9	23
				up to 99 yrs	11	26
			Female	up to 17 yrs	9	27
				up to 39 yrs	8	19
				up to 59 yrs	9	20
				up to 99 yrs	10	22
Calcium	001016	mg/dL	Both	0- 10 days	8.6	10.4
				up to 2 yrs	9.2	11.0
				up to 12 yrs	9.1	10.5
				up to 17 yrs	8.9	10.4
				18-59 yrs	8.7	10.2
				>60 yrs	8.6	10.2
Cholesterol	001065	mg/dL	Both	up to 19 yrs	100	169
				20-24 yrs	100	189
				25-99 yrs	100	199
Chol/LDL	012054/ 120295	mg/dL	Both	All	0	99
Chol(VLDL)	011916	mg/dL	Both	All	5	40
Chloride	001206	mmol/L	Both	All	97	108
CK (Creatine Kinase)	001362	U/L	Male	All	24	204
			Female	All	24	173



CKMB	120816	ng/mL	Male	All	0.0	5.0
			Female	All	0.0	2.9
CRP	006627	mg/L	Both	All	0.0	4.9
CO2	001578	mmol/L	Both	All	19	28
Creatinine	001370	mg/dL	Both	up to 2 months	0.44	1.19
			Both	up to 1 year	0.17	1.18
			Both	up to 3 years	0.19	0.42
			Both	up to 5 years	0.26	0.51
			Both	up to 7 years	0.30	0.59
			Both	up to 9 years	0.37	0.62
			Both	up to 11 years	0.39	0.70
			Both	up to 13 years	0.42	0.75
			Both	up to 15 years	0.49	0.90
			Female	15 years and older	0.57	1.00
			Male	15 years and older	0.76	1.27
Folic Acid	002014	ng/mL	Both	All	>5.4	
Glom Filtr Rate, Est		mL/min	Both	All	>59	
Globulin, Total	012039	g/dL	Both	All	1.5	4.5
Glucose	001032	mg/dL	Both	All	65	99
GGT	001958	IU/L	Male	All	0	65
			Female	All	0	60
HDL	001925	mg/dL	Both	All	>39	
Hemoglobin A1c	001453	%	Both	All	4.8	5.6
				Diabetes	>5.4	6.4
				Glycemic control for Adults with diabetes	<7.0	
Iron	001339	ug/dL	Both	up to 4 yrs	11	130
			Both	up to 10 yrs	11	150
			Male	Adult	40	155
			Female	Adult	35	155



TIBC	001347	ug/dL	Both	All	250	450
UIBC	001348	ug/dL	Both	All	150	375
Iron Saturation	011362	%	Both	All	15	55
Lactic Acid (LDH)	001115	IU/L	Male	18-99 yrs	0	225
			Female	18-99 yrs	0	214
Lipase	001404	U/L	Both	All	0	59
Magnesium	001537	mg/dL	Both	All	1.6	2.6
Phosphorus	001024	mg/dL	Both	up to 2 yrs	2.5	7.1
			Both	up to 10 yrs	2.8	6.2
			Male	up to 19 yrs	2.5	5.6
			Female	up to 19 yrs	2.5	5.3
			Both	Adult	2.5	4.5
Potassium	001180	mmol/L	Both	All	3.5	5.2
Protein Total	001073	g/dL	Both	up to 6 mons	4.6	7.2
			Both	up to 2 yrs	5.7	8.2
			Both	Adult	6.0	8.5
Sodium	001198	mmol/L	Both	All	134	144
Triglyceride	001172	mg/dL	Both	up to 19 yrs	0	89
				up to 24 yrs	0	114
				up to 99	0	149
Uric Acid	001057	mg/dL	Both	Male	3.7	8.6
				Female	2.5	7.1
Hematology						
WBC	005025	x10E3/uL	Both	0 to 7 days	3.6	12.5
			Both	8 to 30 days	4.5	14.4
			Both	1-3 months	4.4	13.1
			Both	3m-1yr	5.2	14.5
			Both	1-8 yrs	4.3	12.4
			Both	8-12yrs	3.7	10.5
			Both	13-17 yrs	3.4	10.8
			Both	≥ 18 years	3.4	10.8



RBC	005033	x10E6/uL	Both	up to 7 days	3.68	5.77
			Both	up to 30 days	3.29	5.50
			Both	up to 90 days	2.72	4.84
			Both	up to 11 months	3.86	5.16
			Both	up to 7 yrs	3.96	5.30
			Both	up to 12 yrs	3.91	5.45
			Male	≥ 13yrs	4.14	5.80
			Female	≥ 13yrs	3.77	5.28
HGB	005041	g/dL	Both	0-7 days	10.7	20.5
			Both	8-30 days	10.5	18.7
			Both	1-3 months	8.8	14.3
			Both	3m-1yr	10.4	14.1
			Both	1-8 yrs	10.9	14.8
			Both	8-12yrs	11.7	15.7
			Male	≥ 13yrs	12.6	17.7
			Female	≥ 13yrs	11.1	15.9
HCT	005058	%	Both	0-7 days	31.9	57.2
			Both	8-30 days	30.7	53.7
			Both	1-3 months	26.6	41.0
			Both	3m-1yr	31.0	41.0
			Both	1-8 yrs	32.4	43.3
			Both	8-12 yrs	34.8	45.8
			Male	≥ 13yrs	37.5	51.0
			Female	≥ 13yrs	34.0	46.6
MCV	015065	fL	Both	up to 7 days	79	110
			Both	up to 30 days	81	109
			Both	up to 90 days	81	97
			Both	up to 11 months	73	87
			Both	up to 7 yrs	75	89
			Both	up to 12 yrs	77	91
			Both	≥ 13yrs	79	97
MCH	015073	pg	Both	up to 7 days	26.1	38.7
			Both	up to 30 days	27.5	37.6
			Both	up to 90 days	27.1	34.0
			Both	up to 11 months	24.2	30.1
			Both	up to 7 yrs	24.6	30.7
			Both	up to 12 yrs	25.7	31.5
			Both	≥ 13yrs	26.6	33.0
MCHC	015081	g/dL	Both	up to 7 days	31.9	36.8
			Both	up to 30 days	32.0	36.4
			Both	up to 90 days	31.9	36.0



			Both	up to 11 months	31.5	36.0
			Both	up to 12 yrs	31.7	36.0
			Both	≥ 13yrs	31.5	35.7
RDW	105007	%	Both	up to 7 days	12.1	16.9
			Both	up to 30 days	12.3	17.4
			Both	up to 90 days	12.2	16.4
			Both	up to 11 months	12.2	15.8
			Both	up to 7 yrs	12.3	15.8
			Both	up to 12yrs	12.3	15.1
			Both	≥ 13yrs	12.3	15.4
Platelets	015172	x10E3/uL	Both	0-7 days	140	396
			Both	8-30 days	139	531
			Both	1-3 months	152	599
			Both	3m-1yr	191	523
			Both	1-8 yrs	190	459
			Both	8-12yrs	176	407
			Both	13-17yrs	155	379
			Both	≥ 18 years	155	379
Neutrophils	015107	%	Both	0-7 days	20	73
			Both	8-30 days	10	48
			Both	1-3 months	7	39
			Both	3m-1yr	10	37
			Both	1-8 yrs	18	60
			Both	8-12 yrs	32	65
			Both	13-17 yrs	40	74
			Both	≥ 18 years	40	74
Neutrophil Ab	015909	x10E3/uL	Both	0-7 days	1.2	6.1
			Both	8-30 days	1.2	4.8
			Both	1-3 months	0.8	3.8
			Both	3m-1yr	1.0	4.0
			Both	1-8 yrs	0.9	5.4
			Both	8-12 yrs	1.2	6.0
			Both	13-17 yrs	1.4	7.0
			Both	≥ 18 years	1.4	7.0
Lymphocytes	015123	%	Both	0-7 days	16	60
			Both	8-30 days	30	76
			Both	1-3 months	42	81
			Both	3m-1yr	49	81
			Both	1-8 yrs	28	70
			Both	8-12 yrs	24	54
			Both	13-17 yrs	14	46
			Both	≥ 18 years	14	46



Lymphocytes Ab	015917	x10E3/uL	Both	0-7 days	0.9	5.0
			Both	8-30 days	0.9	9.1
			Both	1-3 months	1.2	9.2
			Both	3m-1yr	2.9	9.5
			Both	1-8 yrs	1.6	5.9
			Both	8-12 yrs	1.3	3.7
			Both	13-17 yrs	0.7	3.1
			Both	≥ 18 years	0.7	3.1
Monocyte	015131	%	Both	0-7 days	4	13
			Both	8-30 days	4	14
			Both	1-3 months	4	12
			Both	3m-1yr	3	11
			Both	1-8 yrs	3	11
			Both	8-12 yrs	3	11
			Both	13-17 yrs	4	12
			Both	≥ 18 years	4	12
Monocyte Ab	015925	x10E3/uL	Both	0-7 days	0.2	1.3
			Both	8-30 days	0.1	1.6
			Both	1-3 months	0.2	1.2
			Both	3m-1yr	0.2	1.1
			Both	1-8 yrs	0.2	1.0
			Both	8-12 yrs	0.1	0.8
			Both	13-17 yrs	0.1	0.9
			Both	≥ 18 years	0.1	0.9
Eosinophils	015149	%	Both	0-7 days	0	5
			Both	8-30 days	0	6
			Both	1-3 months	0	5
			Both	3m-1yr	0	5
			Both	1-8 yrs	0	5
			Both	8-12 yrs	0	5
			Both	13-17 yrs	0	5
			Both	≥ 18 years	0	5
Eosinophils Ab	015933	x10E3/uL	Both	0-7 days	0.0	0.6
			Both	8-30 days	0.0	0.7
			Both	1-3 months	0.0	0.4
			Both	3m-1yr	0.0	0.4
			Both	1-8 yrs	0.0	0.3
			Both	8-12 yrs	0.0	0.4
			Both	13-17 yrs	0.0	0.4
			Both	≥ 18 years	0.0	0.4
Basophils	015156	%	Both	up to 17 yrs	0	2



			Both	≥18 yrs	0	3
Basophils Ab	015941	x10E3/uI	Both	up to 7 days	0.0	0.6
			Both	up to 11 months	0.0	0.4
			Both	up to 17 yrs	0.0	0.3
			Both	≥18 yrs	0.0	0.2
Immature Granulocytes	015108	%	Both	up to 30 days	Not Established	
			Both	>30 dys to Adult	0	
Immature Grans (Abs)	015911	x10E3/uL	Both	up to 30 days	Not Established	
			Both	>30 dys to Adult	0	
NRBC	015945	x10E3/uL		up to 30 days	Not Established	
				>30 dys to Adult	0	
PT	015289	sec	Both	All	9.1	12.2
Reference interval is for nonmedicated patients						
INR			Both	All	0.8	1.2
Reference interval is for non-anticoagulated patients.						
Suggested INR therapeutic range for Vitamin K antagonist therapy:						
Standard Dose (moderate intensity therapeutic range): 2.0 - 3.0						
Higher intensity therapeutic range 2.5 - 3.5						
PTT	015116	sec	Both	All	24	33
Sedimentation Rate	005215	mm/hr	Male	up to 49 yrs	0	15
			Female	up to 49 yrs	0	32
			Male	> 50 yrs	0	30
			Female	> 50 yrs	0	40
Reticulocyte	005280	%	Both	All	0.5	3.0
Urinalysis						
Specific Gravity	013060		Both	All	1.005	1.030
pH	013078		Both	All	5.0	7.5
Urine Color	013045		Both	All	Yellow	
Urine Appearance	013052		Both	All	Clear	
WBC Esterase	013185		Both	All	Negative	
Protein	013094		Both	All	Negative/Trace	
Glucose	013086		Both	All	Negative	



Ketones	013110		Both	All	Negative	
Occult blood	013102		Both	All	Negative	
Bilirubin	013104		Both	All	Negative	
Urobilinogen	013105	mg/dL	Both	All	0.0	1.9
Nitrite	013106		Both	All	Negative	

Urine Microscopic exam

WBC	013128	/hpf	Both	All	0	5
RBC	013136	/hpf	Both	All	0	3
Casts	013145	/lpf	Both	All	None seen	
Cast type	013147		Both	All	N/A	
Crystals	013146		Both	All	N/A	
Epithelial Cells	013148	/hpf	Both	All	0	10
Renal Cells	013149	/hpf	Both	All	None Seen	
Mucus threads	333351		Both	All	Not Established	
Bacteria	333344		Both	All	None seen/few	
Yeast	333419		Both	All	None seen	
Trichomonas	013151		Both	All	None seen	

hCG

hCG, Beta, serum,qnt	004416	miU/mL	Male		0	3
			Female	Non pregnant	0	5
			Female Postmenopausal		0	8
			Female Preg 3 week		6	71
			(week of gest 4		10	750
			5		217	7138
			6		158	31795
			7		3697	163563
			8		32065	149571
			9		63803	151410
			10		46509	186977
			12		27832	210612
			14		13950	62530
			15		12039	70971
			16		9040	56451
			17		8175	55868
			18		8099	58176

hCG, Beta qual,serum	004556	miU/mL	All	Negative	<6
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hCG, Beta Urine	004036			Negative
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Hepatitis

Hepatitis A Ab, IgM	006734		Both	All	Negative
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Hepatitis A Ab Total	006726		Both	All	Negative	
Hepatitis B Core Ab	006718		Both	All	Negative	
Hepatitis B Core IgM	016881		Both	All	Negative	
Hepatitis B Surface Ag	006510		Both	All	Negative	
Hepatitis B Surface Ab	006395	Index value	Both	All	0.00	0.99
Hepatitis Be Ab	006635		Both	All	Negative	
Hepatitis Be Ag	006619		Both	All	Negative	
Hepatitis C Ab	143991/14365's/co ratio		Both	All	0.0	0.9
HCV (RIBA)	141408		Both	All	Negative	
HIV	083824					
HIV 1/0/2 Index			Both	All	<1.00	
HIV 1/0/2 Abs qual			Both	All	Non Reactive	

Urine Drug Screen**Test Name****Drug screen, urine**

Alcohol	Negative
Amphetamine	Negative
Barbiturates	Negative
Benzodiazepines	Negative
Cannabinoid	Negative
Cocaine	Negative
Methadone	Negative
Methaqualone	Negative
Opiates	Negative
Phencyclidine	Negative
Propoxyphene	Negative

Hormones

LH
Estradiol
Prolactin
Progesterone
FSH



(b) (4)

Office of Scientific Affairs

To: Phase I Operations Management and Study Teams

cc: Quality Assurance and Data Management

Re: Serum ALP Reference Interval change

Date: November 7, 2013

Pursuant to industry guidelines, (b) (4) performs periodic re-evaluation of reference intervals due to changes in methodology, availability of new studies, peer-reviewed publications, or clinical practice guidelines. A re-evaluation was recently performed for adult and pediatric serum ALP based on published and internal studies.

Effective **November 4, 2013**, the reference intervals for ALP, Serum (test code 001107 and CT lookalike test codes 309678, 001106 and 353406) will be adjusted to maintain consistency with the distribution of serum ALP values in the reference population as well as the manufacturer's expected values. This change will affect Phase I studies that are conducted within the LCLS system only.

New serum ALP Reference Intervals{ 4 Nov 13}			Current serum ALP Reference Intervals		
Age Range	Male (IU/L)	Female (IU/L)	Age Range	Male (IU/L)	Female (IU/L)
0-1 day	45-111	45-111	0-1 day	45-111	45-111
2-5 days	46-119	46-119	2-5 days	46-119	46-119
6-10 days	48-229	48-229	6-10 days	48-229	48-229
11-30 days	59-414	59-414	11-30 days	59-414	59-414
1-6 months	91-445	91-445	1-6 months	91-445	91-445
7-12 months	124-341	124-341	7-12 months	124-341	124-341
1-3 years	130-317	130-317	1-3 years	130-317	130-317
4-6 years	133-309	133-309	4-6 years	133-309	133-309
7-12 years	134-349	134-349	7-12 years	134-349	134-349
13 years	143-396	68-209	13 years	143-396	68-209
14 years	107-340	62-149	14 years	107-340	62-149
15 years	84-254	54-121	15 years	84-254	54-121
16 years	71-186	49-108	16 years	71-186	49-108
17 years	61-146	45-101	17 years	61-146	45-101
18 years	56-127	43-101	18 years	56-127	43-101
>19 years	39 - 117	39 - 117	19-60 years	44-102	42-107
			61-70 years	44-103	47-112
			>70 years	44-105	45-108

If you have any questions about this reference interval change please contact your study Project Manager.



(b) (4)

Office of Scientific Affairs

To: Phase I Operations Management and Study Teams

cc: Quality Assurance and Data Management

Re: CBC, Platelet, Differential Reference Interval change

Date: September 27, 2013

Pursuant to industry guidelines, (b) (4) performs periodic re-evaluation of reference intervals due to changes in methodology, availability of new studies, peer-reviewed publications, or clinical practice guidelines. A re-evaluation was recently performed for adult and pediatric CBC, Platelet and Differential parameters based on published and internal studies.

Effective **Sept 9, 2013**, the reference intervals for CBC, Platelet and Differential parameters (test code 005009) were adjusted to maintain consistency with the distribution of CBC, Platelet and Differential parameters in the reference population as well as the manufacturer's expected values. This change will affect Phase I studies that are conducted within the LCLS system only.

New CBC Reference Intervals (Sept 9, 2013)			
Parameter	Age Range	Units	Male/Female
WBC	0-7 days	$10^3 / \mu\text{L}$	3.6 - 12.5
	8-30 days	$10^3 / \mu\text{L}$	4.5 - 14.4
	1-3 months	$10^3 / \mu\text{L}$	4.4 - 13.1
	3m-1yr	$10^3 / \mu\text{L}$	5.2 - 14.5
	1-8 yrs	$10^3 / \mu\text{L}$	4.3 - 12.4
	8-12yrs	$10^3 / \mu\text{L}$	3.7 - 10.5
	13-17yrs	$10^3 / \mu\text{L}$	3.4 - 10.8
	≥ 18 yrs	$10^3 / \mu\text{L}$	3.4 - 10.8
HGB	0-7 days	g/dL	10.7 - 17.1
	8-30 days	g/dL	10.5 - 16.3
	1-3 months	g/dL	8.8 - 13.9
	3m-1yr	g/dL	10.4 - 13.2
	1-8 yrs	g/dL	10.9 - 13.5
	8-12yrs	g/dL	11.7 - 15.7
	≥ 13 yrs	g/dL	M 12.6 - 17.7
	≥ 13 yrs	g/dL	F 11.1 - 15.9

Current CBC Reference Intervals			
Parameter	Age Range	Units	Male/Female
WBC	up to 7 days	$10^3 / \mu\text{L}$	4.1 - 11.9
	up to 30 days	$10^3 / \mu\text{L}$	4.7 - 14.4
	up to 90 days	$10^3 / \mu\text{L}$	5.0 - 12.4
	up to 11 months	$10^3 / \mu\text{L}$	5.9 - 13.5
	up to 7 yrs	$10^3 / \mu\text{L}$	4.8 - 11.4
	up to 17 yrs	$10^3 / \mu\text{L}$	4.0 - 9.1
	>18 yrs	$10^3 / \mu\text{L}$	4.0 - 10.5
HGB	up to 7 days	g/dL	10.7 - 20.5
	up to 30 days	g/dL	10.5 - 18.7
	up to 90 days	g/dL	8.8 - 14.3
	up to 11 months	g/dL	10.4 - 14.1
	up to 7 yrs	g/dL	10.9 - 14.8
	up to 12 yrs	g/dL	11.7 - 15.7
	≥ 13 yrs	g/dL	M 12.6 - 17.7
	≥ 13 yrs	g/dL	F 11.1 - 15.9



New CBC Reference Intervals (Sept 9, 2013)				Current CBC Reference Intervals			
Parameter	Age Range	Units	Male/Female	Parameter	Age Range	Units	Male/Female
HCT	0-7 days	%	31.9 - 57.2	HCT	up to 7 days	%	31.9 - 57.2
	8-30 days	%	30.7 - 53.7		up to 30 days	%	30.7 - 53.7
	1-3 months	%	26.6 - 41.0		up to 90 days	%	26.6 - 41.0
	3m-1yr	%	31.0 - 41.0		up to 11 months	%	31.0 - 41.0
	1-8 yrs	%	32.4 - 43.3		up to 7 yrs	%	32.4 - 43.3
	8-12yrs	%	34.8 - 45.8		up to 12 yrs	%	34.8 - 45.8
	≥13 yrs	%	M 37.5 - 51.0		≥ 13yrs	%	M 37.5 - 51.0
	≥13 yrs	%	F 34.0 - 46.6		≥ 13yrs	%	F 34.0 - 46.6
PLT	0-7 days	10 ³ / uL	140 - 396	PLT	up to 7 days	10 ³ / uL	150 - 381
	8-30 days	10 ³ / uL	139 - 531		up to 30 days	10 ³ / uL	150 - 477
	1-3 months	10 ³ / uL	152 - 599		up to 90 days	10 ³ / uL	150 - 579
	3m-1yr	10 ³ / uL	191 - 523		up to 11 months	10 ³ / uL	150 - 496
	1-8 yrs	10 ³ / uL	190 - 459		up to 7 yrs	10 ³ / uL	150 - 440
	8-12yrs	10 ³ / uL	176 - 407		up to 17yrs	10 ³ / uL	150 - 349
	13-17yrs	10 ³ / uL	155 - 379		≥18 yrs	10 ³ / uL	140 - 415
	≥18 yrs	10 ³ / uL	155 - 379				
Neut %	0-7 days	%	20 - 73	Neut %	up to 7 days	%	24 - 73
	8-30 days	%	10 - 48		up to 30 days	%	14 - 50
	1-3 months	%	7 - 39		up to 90 days	%	10 - 42
	3m-1yr	%	10 - 37		up to 11 months	%	13 - 41
	1-8 yrs	%	18 - 60		up to 7 yrs	%	22 - 60
	8-12yrs	%	32 - 65		up to 17 yrs	%	40 - 70
	13-17yrs	%	40 - 74		≥18 yrs	%	40 - 74
	≥18 yrs	%	40 - 74				
Neut Abs	0-7 days	10 ³ / uL	1.2 - 6.1	Neut Abs	up to 7 days	10 ³ / uL	1.4 - 6.0
	8-30 days	10 ³ / uL	1.2 - 4.8		up to 30 days	10 ³ / uL	1.1 - 5.4
	1-3 months	10 ³ / uL	0.8 - 3.8		up to 90 days	10 ³ / uL	0.6 - 4.4
	3m-1yr	10 ³ / uL	1.0 - 4.0		up to 11 months	10 ³ / uL	0.9 - 4.4
	1-8 yrs	10 ³ / uL	0.9 - 5.4		up to 7 yrs	10 ³ / uL	1.2 - 5.2
	8-12yrs	10 ³ / uL	1.2 - 6.0		up to 17 yrs	10 ³ / uL	1.5 - 5.6
	13-17yrs	10 ³ / uL	1.4 - 7.0		≥18 yrs	10 ³ / uL	1.8 - 7.8
	≥18 yrs	10 ³ / uL	1.4 - 7.0				



New CBC Reference Intervals (Sept 9, 2013)				Current CBC Reference Intervals			
Parameter	Age Range	Units	Male/Female	Parameter	Age Range	Units	Male/Female
Lymph %	0-7 days	%	16 - 60	Lymph %	up to 7 days	%	19 - 55
	8-30 days	%	30 - 76		up to 30 days	%	32 - 72
	1-3 months	%	42 - 81		up to 90 days	%	41 - 78
	3m-1yr	%	49 - 81		up to 11 months	%	43 - 78
	1-8 yrs	%	28 - 70		up to 7 yrs	%	28 - 66
	8-12yrs	%	24 - 54		up to 17 yrs	%	20 - 47
	13-17yrs	%	14 - 46		≥18 yrs	%	14 - 46
	≥18 yrs	%	14 - 46				
Lymph Abs	0-7 days	10 ³ / uL	0.9 - 5.0	Lymph Abs	up to 7 days	10 ³ / uL	1.1 - 7.8
	8-30 days	10 ³ / uL	0.9 - 9.1		up to 30 days	10 ³ / uL	1.2 - 8.9
	1-3 months	10 ³ / uL	1.2 - 9.2		up to 90 days	10 ³ / uL	1.4 - 8.6
	3m-1yr	10 ³ / uL	2.9 - 9.5		up to 11 months	10 ³ / uL	2.9 - 8.7
	1-8 yrs	10 ³ / uL	1.6 - 5.9		up to 7 yrs	10 ³ / uL	1.6 - 5.6
	8-12yrs	10 ³ / uL	1.3 - 3.7		up to 17 yrs	10 ³ / uL	1.1 - 3.1
	13-17yrs	10 ³ / uL	0.7 - 3.1		≥18 yrs	10 ³ / uL	0.7 - 4.5
	≥18 yrs	10 ³ / uL	0.7 - 3.1				
Mono %	0-7 days	%	4 - 13	Mono %	up to 7 days	%	3 - 11
	8-30 days	%	4 - 14		up to 30 days	%	3 - 12
	1-3 months	%	4 - 12		up to 90 days	%	3 - 11
	3m-1yr	%	3 - 11		up to 17 yrs	%	3 - 10
	1-8 yrs	%	3 - 11		≥18 yrs	%	4 - 13
	8-12yrs	%	3 - 11	Mono Abs	up to 7 days	10 ³ / uL	0.2 - 1.6
	13-17yrs	%	4 - 12		up to 30 days	10 ³ / uL	0.1 - 1.5
	≥18 yrs	%	4 - 12		up to 90 days	10 ³ / uL	0.2 - 1.1
Mono Abs	0-7 days	10 ³ / uL	0.2 - 1.3		up to 11 months	10 ³ / uL	1.2 - 1.0
	8-30 days	10 ³ / uL	0.1 - 1.6		up to 7 yrs	10 ³ / uL	0.2 - 0.8
	1-3 months	10 ³ / uL	0.2 - 1.2		up to 17 yrs	10 ³ / uL	0.1 - 0.7
	3m-1yr	10 ³ / uL	0.2 - 1.1		≥18 yrs	10 ³ / uL	0.1 - 1.0
	1-8 yrs	10 ³ / uL	0.2 - 1.0				
	8-12yrs	10 ³ / uL	0.1 - 0.8				
	13-17yrs	10 ³ / uL	0.1 - 0.9				
	≥18 yrs	10 ³ / uL	0.1 - 0.9				



New CBC Reference Intervals (Sept 9, 2013)				Current CBC Reference Intervals			
Parameter	Age Range	Units	Male/Female	Parameter	Age Range	Units	Male/Female
Eos %	0-7 days	%	0 - 5	Eos %	up to 7 days	%	0 - 5
	8-30 days	%	0 - 6		up to 30 days	%	0 - 6
	1-3 months	%	0 - 5		up to 90 days	%	0 - 5
	3m-1yr	%	0 - 5		up to 17 yrs	%	0 - 4
	1-8 yrs	%	0 - 5		≥18 yrs	%	0 - 7
	8-12yrs	%	0 - 5				
	13-17yrs	%	0 - 5				
	≥18 yrs	%	0 - 5				
Eos Abs	0-7 days	$10^3 / \text{uL}$	0.0 - 0.6	Eos Abs	up to 7 days	$10^3 / \text{uL}$	0.0 - 0.8
	8-30 days	$10^3 / \text{uL}$	0.0 - 0.7		up to 30 days	$10^3 / \text{uL}$	0.0 - 0.7
	1-3 months	$10^3 / \text{uL}$	0.0 - 0.4		up to 11 months	$10^3 / \text{uL}$	0.0 - 0.4
	3m-1yr	$10^3 / \text{uL}$	0.0 - 0.4		up to 7 yrs	$10^3 / \text{uL}$	0.0 - 0.3
	1-8 yrs	$10^3 / \text{uL}$	0.0 - 0.3		≥18 yrs	$10^3 / \text{uL}$	0.0 - 0.4
	8-12yrs	$10^3 / \text{uL}$	0.0 - 0.4				
	13-17yrs	$10^3 / \text{uL}$	0.0 - 0.4				
	≥18 yrs	$10^3 / \text{uL}$	0.0 - 0.4				
Baso Abs	8-30 days	$10^3 / \text{uL}$	0.0 - 0.4	Baso Abs	up to 7 days	$10^3 / \text{uL}$	0.0 - 0.6
					up to 11 months	$10^3 / \text{uL}$	0.0 - 0.4

If you have any questions about this reference interval change please contact your study Project Manager.



16.1.9.2 LABORATORY CERTIFICATES



The Swiss GLP Monitoring Authorities

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Federal Department of Home Affairs DHA
Federal Office of Public Health FOPHFederal Department of the Environment,
Transport, Energy and Communications DETEC
Federal Office for the Environment FOENSWISSmedic

Swiss Agency for Therapeutic Products

Statement of GLP Compliance

According to Article 14 paragraph 3 Ordinance on Good Laboratory Practice [OGLP, SR 813.112.1]

The notification authority for chemicals confirms that the following test facility was inspected with respect to the compliance with the Swiss Ordinance on Good Laboratory Practice, adopted on 18th May 2005 [OGLP, SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted on 26th November 1997 by decision of the OECD Council [C(97)186/Final].

Unequivocal name and address
of the test facility:Area of expertise according to
article 3 paragraph 1 letter d OGLP:Celerion Switzerland Ltd
Allmendstrasse 32
8320 Fehraltorf, Switzerland

8. analytic and clinical chemistry testing.

Inspection authority: Swiss Agency for Therapeutic Products (Swissmedic)

Date of inspection: 13 to 14 May 2013

Date of decision: 27 June 2013

Based on the above mentioned decision it can be confirmed that the above mentioned test facility is able to conduct studies according to the aforementioned area of expertise in compliance with the principles of GLP. The above mentioned test facility is listed in the register and GLP list according to the Article 14 OGLP and is inspected on a regular basis according to Article 6 paragraph 2 OGLP.

Swiss Federal Office of Public Health
Consumer protection directorate
Notification authority for chemicals
CH-3003 Bern

Bern, 14 August 2013, The Head, Dr. Dag Kappes.

The notification authority for chemicals is the coordination and decision authority for the good laboratory practice (GLP) for the FOEN, the FOPH and Swissmedic.

Swiss Federal Office of Public Health, Consumer protection directorate, Notification authority for chemicals, CH-3003 Bern.

www.glp.admin.ch, Phone: +41 (0)31 322 73 05, Fax: +41 (0)31 323 54 86



LAP #: 2542201
AU ID: 1188932
November 7, 2014

Gregory R. Post, PhD
Celerion Inc
Clinical Laboratory
PO Box 80837
Lincoln, NE 68501-0837

Dear Dr. Post:

Celerion Inc Clinical Laboratory, in Lincoln, Nebraska under the direction of Gregory R. Post, PhD is accredited by the College of American Pathologists' CAP Accreditation Program.

Accreditation is a continual process. A laboratory remains accredited until otherwise notified. Accreditation does not necessarily terminate on the expiration date of the Accreditation certificate.

If you have any questions regarding this matter, please call 800-323-4040.

Sincerely,

CAP Accreditation Programs
College of American Pathologists

STILACCRED



Advancing Excellence

Accredited
Laboratory



The College of American Pathologists

certifies that the laboratory named below

***Celerion Inc
Clinical Laboratory
Lincoln, Nebraska
Gregory R. Post, PhD***

LAP Number: 2542201
AU-ID: 1188932
CLIA Number: 28D0652627

*has met all applicable standards for accreditation and
is hereby accredited by the College of American Pathologists'
Laboratory Accreditation Program. Reinspection should occur prior
to November 4, 2014 to maintain accreditation.*

Accreditation does not automatically survive a change in director, ownership,
or location and assumes that all interim requirements are met.

Frank R Rudy

Chair, Commission on Laboratory Accreditation

Stanley H. Hobbins

President, College of American Pathologists



CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS
CERTIFICATE OF ACCREDITATION

LABORATORY NAME AND ADDRESS

CELERION, INC
621 ROSE STREET
LINCOLN, NE 68502

CLIA ID NUMBER

28D0652627

EFFECTIVE DATE

02/09/2013

LABORATORY DIRECTOR

GREGORY R POST PHD

EXPIRATION DATE

02/08/2015

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.



Judith A. Yost
Judith A. Yost, Director
Division of Laboratory Services
Survey and Certification Group
Center for Medicaid and State Operations

728 Certs2_011213

If you currently hold a Certificate of Compliance or Certificate of Accreditation, below is a list of the laboratory specialties/subspecialties you are certified to perform and their effective date:

LAB CERTIFICATION (CODE)	EFFECTIVE DATE	LAB CERTIFICATION (CODE)	EFFECTIVE DATE
GENERAL IMMUNOLOGY (220)	03/29/2003		
ROUTINE CHEMISTRY (310)	10/13/1995		
URINALYSIS (320)	10/13/1995		
ENDOCRINOLOGY (330)	07/19/2000		
TOXICOLOGY (340)	03/29/2003		
HEMATOLOGY (400)	10/13/1995		



FOR MORE INFORMATION ABOUT CLIA, VISIT OUR WEBSITE AT WWW.CMS.HHS.GOV/CLIA
OR CONTACT YOUR LOCAL STATE AGENCY. PLEASE SEE THE REVERSE FOR
YOUR STATE AGENCY'S ADDRESS AND PHONE NUMBER.
PLEASE CONTACT YOUR STATE AGENCY FOR ANY CHANGES TO YOUR CURRENT CERTIFICATE.



Advancing Excellence

Accredited
Laboratory



The College of American Pathologists

certifies that the laboratory named below

Covance Central Lab Svcs Inc

Main Laboratory

Indianapolis, Indiana

William E. Tarr, Jr., MD

LAP Number: 2926401

AU-ID: 1189428

CLIA Number: 15D0647217

*has met all applicable standards for accreditation and
is hereby accredited by the College of American Pathologists'
Laboratory Accreditation Program. Reinspection should occur prior
to December 19, 2015 to maintain accreditation.*

Accreditation does not automatically survive a change in director, ownership,
or location and assumes that all interim requirements are met.

Chair, Commission on Laboratory Accreditation

President, College of American Pathologists



CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS
CERTIFICATE OF ACCREDITATION

LABORATORY NAME AND ADDRESS

COVANCE CENTRAL LABORATORY SERVICES IN
8211 SCICOR DR
INDIANAPOLIS, IN 46214-2985

CLIA ID NUMBER

15D0647217

EFFECTIVE DATE

04/28/2013

LABORATORY DIRECTOR

WILLIAM E TARR JR M.D.

EXPIRATION DATE

04/27/2015

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.



Judith A. Yost, Director
Division of Laboratory Services
Survey and Certification Group
Center for Medicaid and State Operations

201 Certs2_033013

If you currently hold a Certificate of Compliance or Certificate of Accreditation, below is a list of the laboratory specialties/subspecialties you are certified to perform and their effective date:

LAB CERTIFICATION (CODE)	EFFECTIVE DATE	LAB CERTIFICATION (CODE)	EFFECTIVE DATE
HISTOCOMPATIBILITY (010)	07/17/2007	CYTOGENETICS (900)	06/29/2009
BACTERIOLOGY (110)	09/14/1995		
MYCOBACTERIOLOGY (115)	09/14/1995		
MYCOLOGY (120)	09/14/1995		
PARASITOLOGY (130)	09/14/1995		
VIROLOGY (140)	09/14/1995		
SYPHILIS SEROLOGY (210)	09/04/2003		
GENERAL IMMUNOLOGY (220)	09/14/1995		
ROUTINE CHEMISTRY (310)	09/14/1995		
URINALYSIS (320)	09/14/1995		
ENDOCRINOLOGY (330)	09/04/2003		
TOXICOLOGY (340)	03/29/2003		
HEMATOLOGY (400)	09/14/1995		

FOR MORE INFORMATION ABOUT CLIA, VISIT OUR WEBSITE AT WWW.CMS.HHS.GOV/CLIA
OR CONTACT YOUR LOCAL STATE AGENCY. PLEASE SEE THE REVERSE FOR
YOUR STATE AGENCY'S ADDRESS AND PHONE NUMBER.
PLEASE CONTACT YOUR STATE AGENCY FOR ANY CHANGES TO YOUR CURRENT CERTIFICATE.



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CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS
CERTIFICATE OF ACCREDITATION

LABORATORY NAME AND ADDRESS CLIA ID NUMBER

(b) (4)

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

 *Judith A. Yost*
Judith A. Yost, Director
Division of Laboratory Services
Survey and Certification Group
Center for Medicaid and State Operations

164 Cert2_051513

If you currently hold a Certificate of Compliance or Certificate of Accreditation, below is a list of the laboratory specialties/subspecialties you are certified to perform and their effective dates:

LAB CERTIFICATION (CODE)	EFFECTIVE DATE	LAB CERTIFICATION (CODE)	EFFECTIVE DATE
BACTERIOLOGY (110)	06/14/1995	ANTIBODY TRANSFUSION (520)	06/14/1995
MYCOBACTERIOLOGY (115)	06/14/1995	ANTIBODY NON-TRANSFUSION (530)	06/14/1995
MYCOLOGY (120)	06/14/1995	ANTIBODY IDENTIFICATION (540)	06/14/1995
PARASITOLOGY (130)	06/14/1995		
VIROLOGY (140)	06/14/1995		
SYPHILIS SEROLOGY (210)	06/14/1995		
GENERAL IMMUNOLOGY (220)	06/14/1995		
ROUTINE CHEMISTRY (310)	06/14/1995		
URINALYSIS (320)	06/14/1995		
ENDOCRINOLOGY (330)	06/14/1995		
TOXICOLOGY (340)	06/14/1995		
HEMATOLOGY (400)	06/14/1995		
ABO & RH GROUP (510)	06/14/1995		

FOR MORE INFORMATION ABOUT CLIA, VISIT OUR WEBSITE AT WWW.CMS.HHS.GOV/CLIA
OR CONTACT YOUR LOCAL STATE AGENCY. PLEASE SEE THE REVERSE FOR
YOUR STATE AGENCY'S ADDRESS AND PHONE NUMBER.
PLEASE CONTACT YOUR STATE AGENCY FOR ANY CHANGES TO YOUR CURRENT CERTIFICATE.



16.1.9.3 BIOANALYTICAL REPORTS

Determination of Nicotine and Cotinine in Human Plasma (K₂EDTA) Samples by LC MS/MS (Study AA99128-01)

A Randomized, Controlled, Open-label, 3-Arm Parallel Group, Multi-Center Study (Study AA99128-02)

A Randomized, Controlled, Open-label, 3-Arm Parallel Group, Multi-Center Study (Study AA99128-03)

Determination of Total NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) and NNN (*N*-Nitrosonornicotine) in Human Urine Samples by LC-MS/MS (Study AA99128-04)

Determination of HEMA (Hydroxyethyl Mercapturic Acid) in Human Urine Samples by LC-MS/MS (Study AA99128-05)

Determination of Nicotine, Cotinine, *trans*-3'-Hydroxycotinine, Nicotine-*N*-Glucuronide, Cotinine-*N*-Glucuronide, *trans*-3'-Hydroxycotinine-*O*-Glucuronide in Human Urine Samples by LC-MS/MS (Study AA99128-06)

Determination of Total 3-Hydroxybenzo[a]pyrene in Human Urine Samples by LC-MS/MS (Study AA99128-07)

Determination of Caffeine and Paraxanthine in Human Plasma (Heparin) Samples by LC-MS/MS (Study AA99128-08)

Determination of Total 4-Aminobiphenyl, *o*-Toluidine, 2-Aminonaphthalene, and 1-Aminonaphthalene in Human Urine Samples by LC-MS/MS (Study AA99128-09)

Determination of Cotinine and *trans*-3'-Hydroxycotinine in Human Plasma (K₂EDTA) Samples by LC-MS/MS (Study AA99128-10)

Determination of 11-Dehydrothromboxane B₂ in Human Urine Samples by LC-MS/MS (Study AA99128-11)

Determination of 8-Iso-Prostaglandin-F_{2α} (Type III) in Human Urine Samples by LC-MS/MS (Study AA99128-12)

Determination of Nicotine, Cotinine, *trans*-3'-Hydroxycotinine, Nicotine-*N*-Glucuronide, Cotinine-*N*-Glucuronide, *trans*-3'-Hydroxycotinine-*O*-Glucuronide in Human Urine Samples by LC-MS/MS (Study AA99128-13)

Determination of Creatinine in Human Urine Samples by Spectrophotometry (Study AA99128-14)



Determination of Urine Mutagenicity (Study AA99128-15)

Determination of Carboxyhemoglobin in Human Whole Blood Samples by Spectrophotometry (Study AA99128-16)

Determination of S-Benzyl Mercapturic Acid (SBMA) and S-Phenyl Mercapturic Acid (SPMA) in Human Urine Samples by LC-MS/MS (Study AAA99598-01)

Determination of Monohydroxy-3-butenyl-mercapturic Acid (MHBMA) in Human Urine Samples by LC-MS/MS (Study AAA99598-02)

Determination of Total 1-Hydroxypyrene (1-OHP) in Human Urine Samples by LC-MS/MS (Study AAA99598-03)

Quantitative Determination of Apolipoprotein A1 (Apo A1) in Human Serum

Quantitative Determination of Apolipoprotein B (Apo B) in Human Serum

Quantitative Determination of Fibrinogen (FIB) in Human Sodium Citrate Plasma

Quantitative Determination of Hemoglobin A1c (HbA1c) in Human EDTA Whole Blood

Quantitative Determination of Homocysteine (HCY) in EDTA Human Plasma

Quantitative Determination of High Density Lipoprotein Cholesterol (HDL-c) in Human Serum

Quantitative Determination of High Sensitivity C-Reactive Protein (hsCRP) in Human Serum

Quantitative Determination of Low Density Lipoprotein Cholesterol (LDL-c) in Human Serum

Quantitative Determination of Soluble Intercellular Adhesion Molecule-1 (sICAM-1) in Human Serum

Study ZRHM-REXA-08-US Sample Reconciliation Report



16.1.9.4 BIOANALYTICAL REFERENCES

Please refer to Section 14 of the CSR for all publications referenced in the report. Copies of these publications are available upon request.