



PMI RESEARCH & DEVELOPMENT

Study ZRHR-REXC-03-EU **Clinical Study Report Appendix 16.1.9** **Bioanalytical Documentation**

Study Title:	A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement
Study Number:	ZRHR-REXC-03-EU
Product Name:	Tobacco Heating System 2.2 (THS 2.2)
Study Initiated (first subject screened):	29 June 2013
Study Completed (last subject last visit):	26 September 2013
Principal Investigator and Affiliation:	Katarzyna Jarus-Dziedzic, MD, PhD BioVirtus Research Site Sp. z o.o., Mokra 7 05-830 Kajetany, Poland
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 Guillaume de La Bourdonnaye, MEng, MSc, Biostatistician Kausar Aamir, MD, PhD, Medical Safety Officer
Version:	2.0
Date:	08 March 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.



Table of Contents

16.1.9.1 STANDARDIZATION AND LABORATORY REFERENCE RANGES.....	3
16.1.9.2 LABORATORY CERTIFICATES	11
16.1.9.3 BIOANALYTICAL REPORTS	18
16.1.9.4 BIOANALYTICAL REFERENCES.....	20



16.1.9.1 STANDARDIZATION AND LABORATORY REFERENCE RANGES



INSTRUKCJA LABORATORYJNA
Protokół: ZRHR-REXC-03-EU
Zał. Nr: 5 Lista wartości referencyjnych
Strona 35/44

Załącznik Nr. 5 Lista wartości referencyjnych

Laboratorium Medyczne
Synevo Warszawa Ursynów

Date: 2012-06-06
Page 1 of 4

List of Analytical Methods and Reference Intervals, LM Synevo Warszawa Ursynów

Compound	Method	Method reference	Reference interval
B-Hematocrit HCT	The cumulative pulse height detection method Sysmex XT 2000i measuring range: (0 - 100) %	Sysmex XT 2000i Operator's Manual; 2005	years % F 10 - 18 35,0 - 45,0 F >18 37,0 - 47,0 M 10 - 18 36,0 - 48,0 M >18 40,0 - 49,5
B-Haemoglobin HGB	Spectrophotometry SLS-haemoglobin method Sysmex XT 2000i measuring range: 0,00 - 30,0 g/dl	Sysmex XT 2000i Operator's Manual; 2005	years g/dl F 10 - 18 12,0 - 15,0 F >18 12,0 - 16,0 M 10 - 18 12,5 - 16,1 M >18 12,0 - 16,8
B-Erythrocytes RBC	DC Detection Method Sysmex XT 2000i measuring range: (0,00 - 99,99x10 ⁹)/μl	Sysmex XT 2000i Operator's Manual; 2005	years T/l F 10 - 18 4,0 - 5,3 F >18 3,5 - 5,0 M 10 - 18 4,2 - 5,6 M >18 4,5 - 5,7
B-Leukocytes WBC	Flow cytometry Sysmex XT 2000i measuring range: (0 - 999,99x10 ⁹)/μl	Sysmex XT 2000i Operator's Manual; 2005	years G/l >12 3,5 - 10,0
B-Platelets PLT	DC Detection Method Sysmex XT 2000i measuring range: (0 - 999,99x10 ⁹)/μl	Sysmex XT 2000i Operator's Manual; 2005	years G/l >12 125 - 400
B-MCHC Mean cell hemoglobin concentration	Calculated from HCT / HGB Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years g/dl F 10 - 18 31,0 - 35,0 F >18 31,0 - 35,0 M 10 - 18 31,5 - 35,0 M >18 32,0 - 36,0
B-MCH Mean Corpuscular(erythrocyte) Hemoglobin	Calculated from RBC and HGB Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years pg 10 - 18 26,0 - 32,0 >18 28,0 - 34,0
B-MCV Mean Corpuscular(erythrocyte) Volume	Calculated from RBC and HCT Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years fl 10 - 18 78,0 - 95,0 >18 83,0 - 103,0
B-Neutrophils NEUT	Flow cytometry Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years x G/l >10 1,80 - 7,70 % >10 45 - 70
B-Basophils BASO	Flow cytometry Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years x G/l 0 - 100 < 0,20
B-Eosinophils EO	Flow cytometry Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years x G/l >10 < 0,45 % >7 days < 1,0

Prepared by: Anna Fanyj



INSTRUKCJA LABORATORYJNA

Protokół: ZRHR-REXC-03-EU

Zał. Nr: 5 Lista wartości referencyjnych

Strona 36/44

Laboratorium Medyczne
Synevo Warszawa UrsynówDate: 2012-06-06
Page 2 of 4

List of Analytical Methods and Reference Intervals, LM Synevo Warszawa Ursynów

B-Lymphocytes LYMPH	Flow cytometry Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years >10 >10	x G/l 1,00 – 5,00 %
B-Monocytes MONO	Flow cytometry Sysmex XT 2000i	Sysmex XT 2000i Operator's Manual; 2005	years >1 >6	x G/l < 0,80 %
S-ALP Alkaline Phosphatase	p-Nitrophenyl phosphate, AMP buffer 2 gen.(IFCC comparable AMP methods); VIS photometry; Cobas Integra 400 Plus measuring range: 3-1200 U/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 1, 220, 69	years F 13 – 18 F > 18 M 13 – 18 M > 18	U/l < 187 35 – 104 < 390 40 – 129
S-ALT Alanine Aminotransferase	IFCC recommendation, without P-5-P; UV photometry; 2 gen. Cobas Integra 400 Plus measuring range: 2-700 U/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 139, 220	years F > 17 M > 17	U/l < 31 < 41
S-AST Aspartate Aminotransferase	IFCC recommendation, without P-5-P; UV photometry; Cobas Integra 400 Plus measuring range: 2-700 U/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 139, 69, 220	years F > 17 M > 17	U/l < 32 < 38
S-ALB Albumine	Colometric assay with bromocresol green(BCG) 2 gen. Cobas Integra 400 Plus measuring range: 2-60 g/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 220, 239, 303	years 1 – 14 14 – 18 > 18	g/l 38 – 54 32 – 45 35 – 52
S-Bilirubin, total	DPD / Detergent; VIS photometry; 2 gen. Cobas Integra 400 Plus measuring range: 0,1-38 mg/dL	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008:267, 288	years > 1	mg/dl < 1,0
S-Bilirubin, direct	Diazotized sulfanilic acid; VIS photometry; 2 gen. Cobas Integra 400 Plus measuring range: 0,1-25 mg/dL	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Considerations 2008: 302, 249		< 0,3 mg/dl

Prepared by: Anna Faryj

h



INSTRUKCJA LABORATORYJNA

Protokół: ZRHR-REXC-03-EU

Zał. Nr: 5 Lista wartości referencyjnych

Strona 37/44

Laboratorium Medyczne
Synevo Warszawa UrsynówDate: 2012-06-06
Page 3 of 4

List of Analytical Methods and Reference Intervals, LM Synevo Warszawa Ursynów

S-BUN	Calculation test: S-Urea= BUN / 2,14	Roche Operator's Manual	years 1 – 65	mg/dl 5,0 – 23,0
B-Carboxyhaemoglobin, COHb	Spectrophotometry System Cobas b 221	System Cobas b 221 Operator's Manual	Smokers No Smokers	8,0 – 9,0% 0,5 – 1,5%
S-Cholesterol, total	Cholesterol esterase / cholesterol oxidase / H ₂ O ₂ / peroxidase / chromogen; VIS photometry; Cobas Integra 400 Plus measuring range: 3,87-800 mg/dL	acc. III raportu NCEP I ATP III 2002	< 200 mg/dl	
S-Creatinine	Alkaline picrate (Jaffe) without deproteinization, kinetic; 2 gen. VIS photometry; Cobas Integra 400 Plus measuring range: 0,2-15 mg/dl	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 220, 235, 173	years F > 14 M > 14	mg/dl 0,5 – 0,9 0,7 – 1,2
S-Glucose	Enzymatic, Colorimetric assay UV photometry; 3 gen Cobas Integra 400 Plus measuring range: 2-720 mg/dl	1.C.A.Burtis, E.R. Ashwood, Tietz Textbook of Clinical Chemistry 3-d edition 1999: 1815 2. recommendation PTD 2007	years 15 – 60 60 – 70 > 70	mg/dl fasting 70 – 105 80 – 115 83 – 110
S-Gamma- glutamyltransferase γGT	Enzymatic Colorimetric assay by Szasz, 2 gen. Cobas Integra 400 Plus measuring range: 3-1200 U/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 69, 1, 220	Female: 5 – 36 U/l Male: 8 – 61 U/l	
S – LDH Lactate dehydrogenase	Spectrophotometry recommended by DGKC Cobas Integra 400 Plus measuring range: 40-1200 U/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 69, 220, 292	240 – 480 U/l	
S-Potassium	ISE indirect Cobas Integra 400 Plus measuring range: 0,2-30 mmol/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 220	3,5 – 5,1 mmol/l	
S-Protein, total	Biuret method; VIS photometry;	W.Heil, V.Ehrhardt, Roche Diagnostics.	years >15	g/l 64 – 83

Prepared by: Anna Faryj



INSTRUKCJA LABORATORYJNA

Protokół: ZRHR-REXC-03-EU

Zał. Nr: 5 Lista wartości referencyjnych

Strona 38/44

Laboratorium Medyczne
Synevo Warszawa UrsynówDate: 2012-06-06
Page 4 of 4

List of Analytical Methods and Reference Intervals, LM Synevo Warszawa Ursynów

	Cobas Integra 400 Plus measuring range: 2-120 g/l	Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 220, 302	
S-Sodium	ISE Idirect Cobas Integra 400 Plus measuring range: 20-250 mmol/l	W.Heil, V.Ehrhardt, Roche Diagnostics. Reference Ranges for Adults and Children, Pre-Analytical Considerations 2008: 249, 302	136 – 146 mmol/l
S-Triglycerides	Lipase / GK / G-3-P-oxidase / H ₂ O ₂ / peroxidase / chromogen; VIS photometry; Cobas Integra 400 Plus measuring range: 4-1000 mg/dl	Acc. III reportu NCEP i ATP III 2002	50 – 200 mg/dl
U- Urine analysis	Urine test strip Combur 10 Roche; measurement of bacteria (nitrite), erythrocytes, protein, glucose, ketone, pH, relative density, bilirubin, urobilinogen; reading with Miditron Junior II	Miditron Junior II Operator's Manual; ver 1.1	First morning urine: U-Density 1010 – 1030 g/l U-pH 5,0 – 8,0 U-Protein negative U-Glucose negative U-Nitrite negative U-Bilirubin negative U- Red blood cell negative
S-HBs Ag Hepatitis B virus	Electrochemiluminescence Immunoassay ECLIA Cobas E 411	Roche Operators's Manual	Negative
S-HCV Ab Hepatitis C antibodies (anti-HCV)	Electrochemiluminescence Immunoassay ECLIA Cobas E 411	Roche Operators's Manual	Negative
S-HIV antigen and total antibodies to HIV-1 and HIV-2 (anti-HIV1/2)	Electrochemiluminescence Immunoassay ECLIA Cobas E 411	Roche Operators's Manual	Negative

Authorized by: Anna Faryj
Manager of Laboratory

Prepared by: Anna Faryj



INSTRUKCJA LABORATORYJNA

Protokół: ZRHR-REXC-03-EU

Zal. Nr: 6 Ocena wyników badań

laboratoryjnych wg skali CTCAE

Strona 39/44

Załącznik Nr. 6 Ocena wyników badań laboratoryjnych wg skali CTCAE**CTCAE ABNORMAL LABORATORY VALUES RATING: SERUM CHEMISTRY PARAMETERS**

Serum Chemistry*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Sodium - Hyponatremia (mmol/l) ** ⁽¹⁾	<LLN - 130	-	<130 - 120
Sodium - Hypernatremia (mmol/l) ** ⁽¹⁾	>ULN - 150	>150 - 155	>155 - 160; hospitalization indicated
Potassium - Hyperkalemia (mmol/l) ** ⁽¹⁾	>ULN - 5.5	>5.5 - 6.0	>6.0 - 7.0; hospitalization indicated
Potassium - Hypokalemia (mmol/l) ** ⁽¹⁾	<LLN - 3.0	<LLN - 3.0; symptomatic; intervention indicated	<3.0 - 2.5; hospitalization indicated
Glucose - Hypoglycemia ** ⁽¹⁾ (mg/dl) (mmol/l)	<LLN - 55; <LLN - 3.0	<55 - 40; <3.0 - 2.2	<40 - 30; <2.2 - 1.7
Glucose - Hyperglycemia: ** ⁽¹⁾ Fasting (mg/dl) (mmol/l)	>ULN-160; >ULN-8.9	>160-250; >8.9-13.9	- - >250-500; >13.9-27.8; hospitalization indicated
Non-fasting (mg/dl) (mmol/l)	- -	- -	- -
Blood Urea Nitrogen (BUN) (mg/dl) ⁽²⁾	23 - 26	27 - 31	> 31
Creatinine increased ** ⁽¹⁾	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN
Albumin - Hypoalbuminemia ** ⁽¹⁾ (g/dl) (g/l)	<LLN - 3; <LLN - 30	<3 - 2; <30 - 20	<2; <20
Total Protein - Hypoproteinemia ⁽²⁾ (g/dl)	5.5 - 6.0	5.0 - 5.4	< 5.0
Alkaline phosphatase increased ** ⁽¹⁾	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN
ALT / AST increased ** ⁽¹⁾	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN
Gamma-glutamyl transferase (GGT) increased ⁽¹⁾	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN
Blood bilirubin increased ** ⁽¹⁾	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 ULN
Cholesterol high ** ⁽¹⁾			



INSTRUKCJA LABORATORYJNA

Protokół: ZRHR-REXC-03-EU

Załącznik Nr 6 Ocena wyników badań

laboratoryjnych wg skali CTCAE

Strona 40/44

(mg/dl)	>ULN - 300; >ULN - 7.75	>300-400; >7.75-10.34	>400-500; >10.34-12.92
(mmol/l)			
Triglycerides - Hypertriglyceridemia ⁽¹⁾			
(mg/dl)	150 - 300;	>300 - 500;	>500 - 1000;
(mmol/l)	1.71 - 3.42	>3.42 - 5.70	>5.70 - 11.40

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; LLN = lower limit of the normal range; ULN = upper limit of the normal range.

Data Sources:

(1) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

(2) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

* Those parameters that are not listed do not have grading categories in either the CTCAE or the FDA guidance documents and will therefore be reviewed by the Investigator and only reported as an AE if considered to be clinically relevant.

** Where parameters in this table are listed in both the CTCAE and the FDA guidance documents, and each document has different values within each grading category, the grading in CTCAE guidance document predominates.

CTCAE ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS

Hematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (Female) - (g/dl) ⁽¹⁾	11.0 - 12.0	9.5 - 10.9	8.0 - 9.4
change from baseline value - (g/dl) ⁽¹⁾	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0
Hemoglobin (Male) - (g/dl) ⁽¹⁾	12.5 - 13.5	10.5 - 12.4	8.5 - 10.4
change from baseline value - (g/dl) ⁽¹⁾	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0
Hemoglobin increase - (g/dl) ⁽²⁾	Increase in >0 - 2 above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 above ULN or above baseline if baseline is above ULN	Increase in >4 above ULN or above baseline if baseline is above ULN
WBC Increase - (cell/mm ³) ⁽¹⁾	10,800 - 15,000	15,001 - 20,000	20,001 - 25,000
WBC Decrease - (cell/mm ³) ^{(2)**}	<LLN - 3000; <LLN - 3.0 x 10 ⁹ /l	<3000 - 2000; <3.0 - 2.0 x 10 ⁹ /l	<2000 - 1000; <2.0 - 1.0 x 10 ⁹ /l
Lymphocytes Increase - (cell/mm ³) ⁽²⁾	-	>4,000 - 20,000	>20,000
Lymphocytes Decrease - (cell/mm ³) ^{(2)**}	<LLN - 800; <LLN - 0.8 x 10 ⁹ /l	<800 - 500; <0.8 - 0.5 x 10 ⁹ /l	<500 - 200; <0.5 - 0.2 x 10 ⁹ /l
Neutrophils Decrease - (cell/mm ³) ^{(2)**}	<LLN - 1500; <LLN - 1.5 x 10 ⁹ /l	<1500 - 1000; <1.5 - 1.0 x 10 ⁹ /l	<1000 - 500; <1.0 - 0.5 x 10 ⁹ /l
Eosinophils - (cell/mm ³) ⁽¹⁾	650 - 1500	1501 - 5000	>5000
Platelets Decrease - (cell/mm ³) ^{(2)**}	<LLN - 75,000;	<75,000 - 50,000;	<50,000 - 25,000;



INSTRUKCJA LABORATORYJNA

Protokół: ZRHR-REXC-03-EU

Załącznik Nr: 6 Ocena wyników badań

laboratoryjnych wg skali CTCAE

Strona 41/44

	<LLN - 75.0 x 10 ⁹ /l	<75.0 - 50.0 x 10 ⁹ /l	<50.0 - 25.0 x 10 ⁹ /l
--	----------------------------------	-----------------------------------	-----------------------------------

Abbreviations: LLN = lower limit of the normal range; ULN = upper limit of the normal range; WBC = white blood cell.

Data Source: (1) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

(2) Common Terminology Criteria for Adverse Event and Common Toxicity Criteria (CTCAE) version 4.03.

* Those parameters that are not listed do not have grading categories in either the CTCAE or the FDA guidance documents and will therefore be reviewed by the Investigator and only reported as an AE if considered to be clinically relevant.

** Where parameters in this table are listed in both the CTCAE and the FDA guidance documents, and each document has different values within each grading category, the grading in CTCAE guidance document predominates.

CTCAE ABNORMAL LABORATORY VALUES RATING: URINALYSIS PARAMETERS

Urine*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Protein** ⁽¹⁾	1+ proteinuria; urinary protein <1.0 g/24-hours	2+ proteinuria; urinary protein 1.0-3.4 g/24-hours	Urinary protein ≥3.5 g/24-hours
Glucose ⁽²⁾	Trace	1+	2+
Blood - Hematuria ** ⁽¹⁾	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self-care ADL

Abbreviations: ADL = activities of daily living; IV = intravenous.

Data Source: (1) Common Terminology Criteria for Adverse Event and Common Toxicity Criteria (CTCAE) version 4.03.

(2) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

* Those parameters that are not listed do not have grading categories in either the CTCAE or the FDA guidance documents and will therefore be reviewed by the Investigator and only reported as an AE if considered to be clinically relevant.

** Where parameters in this table are listed in both the CTCAE and the FDA guidance documents, and each document has different values within each grading category, the grading in CTCAE guidance document predominates.



16.1.9.2 LABORATORY CERTIFICATES



Advancing Excellence

Accredited
Laboratory



The College of American Pathologists

certifies that the laboratory named below

***Covance Central Laboratory Services SA
Meyrin-Geneva, Switzerland
Jean-Paul Lewest, MD***

LAP Number: 4658701
AU-ID: 1190700

*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 March 3, 2015 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 A. Rothman

President, College of American Pathologists

REPUBLIC AND CANTON OF GENEVA
Folio 12003-2002

DECISION

dated September 11th, 2002

relative to the authorization to operate a laboratory
intended to analyze human material, located at
rue Moïse-Marcinhes 7, 1217 Meyrin
issued to the public company
COVANCE CENTRAL LABORATORY SERVICES

by the

COUNCIL OF STATE

Whereas its decree dated August 23rd, 1999, authorizing the public company COVANCE CENTRAL LABORATORY SERVICES to operate a laboratory intended to analyze human material exclusively taken as part of the multi-centre (programme) of clinical tests of drugs, located at rue Moïse-Marcinhes 7, 1217 Meyrin, under the management and scientific responsibility of Mrs Véronique MICHEL TREIL, Doctor of Pharmacy, on temporary basis;

Whereas the letter dated December 20th, 2001 by which the public company COVANCE CENTRAL LABORATORY SERVICES applies to obtain the authorization to entrust the general management of its laboratory with Mr Jean-Marc LEROUX, Doctor of Pharmacy, and the scientific responsibility with Mrs Véronique MICHEL TREIL, maiden name MICHEL, Doctor of Pharmacy;

Whereas the decrees dated April 17th, 1996 and August 23rd, 1999 according to which Mrs Véronique MICHEL TREIL, maiden name MICHEL, has already been authorized to assume the scientific responsibility and the management of the aforesaid laboratory;

Whereas the law dated May 11th, 2001 relative to the practice of the professions related to the (public) health, the medical institutions and the various companies in the medical field and its regulations;

Whereas the favorable advance notice of service of the cantonal physician dated April 26th, 2002;

Whereas the regulations on the emoluments of the cantonal administration dated September 15th, 1975;

The Council of States decides as follows:

The public company COVANCE CENTRAL LABORATORY SERVICES is authorized to operate a laboratory intended to analyze human material exclusively taken as part of the multi-centre (programme) of clinical tests of drugs, located at rue Moïse-Marcinhes 7, 1217 Meyrin.



It is noted that Mr Jean-Marc LEROUX, Doctor of Pharmacy and Mrs Véronique MICHEL TREIL, maiden name MICHEL, Doctor of Pharmacy, are respectively the general manager and the technical manager of the aforementioned laboratory.

Any change concerning the persons responsible for the laboratory or the ones responsible for various analyses, as well as any modification of the premises, the activity or the structure of the laboratory have to be immediately communicated to the service of the cantonal physician.

An emolument of 350 francs (three hundred and fifty francs) has been collected for this present decree, which cancels and replaces the decree dated August 23rd, 1999.

Communicated to:

DASS	4 copies
OCP	1 copy
Interested party	1 copy

Certified true copy
The State Chancellor
(Signature)

(The seal of the Council of State of the Republic and Canton of Geneva)

CERTIFIED TRUE TRANSLATION FROM FRENCH

A. SIMSAR
SWORN TRANSLATOR
58, rue de la Terrassière
CH-1207 Geneva
Tel. / Fax: 022 700 36 85
E-mail: asimsar@worldcom.ch



Geneva, March 16th, 2005



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	CLIA ID NUMBER
CELERION, INC 621 ROSE STREET LINCOLN, NE 68502	28D0652627
LABORATORY DIRECTOR	EFFECTIVE DATE
GREGORY R POST PHD	02/09/2013
	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, 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.



16.1.9.3 BIOANALYTICAL REPORTS

Determination of Nicotine and Cotinine in Human Plasma (K₂EDTA) Samples by LC-MS/MS (Study AA99071-01)

Determination of Nicotine and Cotinine in Human Plasma (K₂EDTA) Samples by LC-MS/MS (Study AA99071-02)

Determination of 3-HPMA, HBMA, and CEMA in Human Urine Samples by LC-MS/MS (Study AA99071-03)

Determination of Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and N'-Nitrososornicotine (NNN) in Human Urine Samples by LC-MS/MS (Study AA99071-04)

Determination of HEMA in Human Urine Samples by LC-MS/MS (Study AA99071-05)

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 AA99071-06)

Determination of Total 3-Hydroxybenzo[*a*]pyrene in Human Urine Samples by LC-MS/MS (Study AA99071-07)

Determination of Caffeine and Paraxanthine in Human Plasma (Lithium Heparin) Samples by LC-MS/MS (Study AA99071-08)

Determination of Total 4-Aminobiphenyl, *o*-Toluidine, 2-Aminonaphthalene, and 1-Aminonaphthalene in Human Urine Samples by LC-MS/MS (Study AA99071-09)

Determination of Cotinine and *trans*-3'-Hydroxycotinine in Human Plasma (K₂EDTA) Samples by LC-MS/MS (Study AA99071-10)

Determination of 11-Dehydrothromboxane B₂ in Human Urine Samples by LC-MS/MS (Study AA99071-11)

Determination of 8-Iso-Prostaglandin-F_{2α} (Type III) in Human Urine Samples by LC-MS/MS (Study AA99071-12)

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 AA99071-13)



Determination of Creatinine in Human Urine by Spectrophotometry (Study AA99071-14)

Determination of S-Benzyl Mercapturic Acid (SBMA) and S-Phenyl Mercapturic Acid (SPMA) in Human Urine Samples by LC-MS/MS (Study AA99602-01)

Determination of Monohydroxy-3-butenyl-mercapturic acid (MHBMA) in Human Urine Samples by LC-MS/MS (Study AA99602-02)

Determination of Total 1-Hydroxypyrene (1-OHP) in Human Urine Samples by LC-MS/MS (Study AA99602-03)

Determination of Carboxyhemoglobin (COHb) in Human Plasma (Lithium Heparin) by Spectrophotometry

Determination of Urine Mutagenicity (Study AA99071-15)

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.