Elecsys sFlt-1

cobas®

REF		Σ	SYSTEM
07027818190	07027818500	100	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
SFLT1	10046

Intended use

Immunoassay for the in vitro quantitative determination of soluble fms-like tyrosine kinase-1 (sFlt-1) in human serum.

The Elecsys sFlt-1 assay is used in combination with the Elecsys PlGF assay to determine the sFlt-1/PlGF ratio. The sFlt-1/PlGF ratio is intended for use as an aid in the diagnosis of preeclampsia in conjunction with other diagnostic and clinical information.

In addition the sFlt-1/PlGF ratio is intended for use as an aid in short-term prediction of preeclampsia (rule-out and rule-in) in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Preeclampsia (PE) is a serious complication of pregnancy characterized by hypertension and proteinuria after 20 weeks of gestation. Preeclampsia occurs in 3-5 % of pregnancies and results in substantial maternal and fetal or neonatal mortality and morbidity. Clinical manifestations can vary from mild to severe forms; preeclampsia is still one of the leading causes of fetal and maternal morbidity and mortality.[1,2,3,4,5,6]

Preeclampsia appears to be due to the release of angiogenic factors from the placenta that induces endothelial dysfunction. Serum levels of PlGF (placental growth factor) and sFlt-1 (soluble fms-like tyrosine kinase-1, also known as VEGF receptor-1) are altered in women with preeclampsia. Moreover, circulating levels of PlGF and sFlt-1 can discriminate normal pregnancy from preeclampsia even before clinical symptoms occur. In normal pregnancy, the pro-angiogenic factor PlGF increases during the first two trimesters and decreases as pregnancy progresses to term. In contrast, levels of the anti-angiogenic factor sFlt-1 remain stable during the early and middle stages of gestation and increase steadily until term. In women who develop preeclampsia, sFlt-1 levels have been found to be higher and PlGF levels have been found to be lower than in normal pregnancy.[7,8,9,10]

The ratio of sFlt-1 to PlGF has been shown to be a better predictor of preeclampsia than either measure alone. The sFlt-1/PlGF ratio seems a reliable tool for discriminating between different types of pregnancy-related hypertensive disorders. In addition, sFlt-1/PlGF has potential relevance as a prognostic parameter in PE and may be useful in prediction of preeclampsia and related maternal and fetal adverse outcomes, risk stratification and management.[5,11,12,13,14,15,16,17,18,19]

In patients with signs and symptoms of preeclampsia, the sFlt-1/PlGF ratio was proven helpful in the short-term prediction of the disease.[17,18] The sFlt-1/PlGF ratio can also improve the prediction of early-onset preeclampsia for women with risk factors (including: history of intrauterine growth restriction (IUGR); preeclampsia; eclampsia; hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome; pre-gestational diabetes; abnormal uterine artery Doppler ultrasound).[20] In unselected nulliparous women with a singleton pregnancy, screening with the sFlt-1/PlGF ratio at ≈ 20, ≈ 28, and ≈ 36 gestational weeks was proven to provide clinically useful prediction of the risk of the most important manifestations of preeclampsia (at 36 gestational weeks, an sFlt-1/PlGF ratio ≤ 38 had a negative predictive value for severe preeclampsia of more than 99 %).[21]

A high sFlt 1/PlGF ratio is associated with a shorter remaining pregnancy duration and a higher risk of preterm delivery.[22] The use of the sFlt-1/PlGF ratio was demonstrated to influence clinical decision making towards appropriate hospitalization in a considerable proportion of women with suspected preeclampsia.[23] An health economic study demonstrated that introducing the sFlt-1/PlGF ratio test into clinical practice in the UK can be cost-saving by reducing unnecessary hospitalization of women at low risk of developing preeclampsia.[24] The Elecsys sFlt-1/PlGF ratio, used with standard clinical assessment and subsequent clinical follow-up, is recommended by the UK National Institute for Health and Care Excellence (NICE) to help rule-out preeclampsia in women presenting with suspected preeclampsia between 20 weeks and 34+6 weeks of gestation.[25]

The level of anti angiogenic factor sFlt-1 seems correlated with sub-clinical cardiac dysfunction and elevated in women with peripartum cardiomyopathy.[26] Removal of sFlt-1 may benefit women with very preterm PE: in a pilot study, apheresis with dextran sulfate cellulose (DSC) columns reduced circulating sFlt-1 levels and allowed prolonged pregnancy without maternal/fetal adverse outcomes.[27,28]

In summary, PlGF and sFlt-1 concentrations measured by immunoassay in maternal blood improve the diagnostic possibilities in preeclampsia which comprise clinical symptoms, proteinuria and uterine artery Doppler velocimetry.[5,6,13,15,16,28,29,30]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, a biotinylated monoclonal sFlt-1-specific antibody, and a monoclonal sFlt-1-specific antibody labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The **cobas e** pack is labeled as SFLT1.

M Streptavidin-coated microparticles, 1 bottle, 5.8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-sFlt-1-Ab~biotin, 1 bottle, 9.9 mL:
Biotinylated monoclonal anti-sFlt-1 antibody (mouse) 0.5 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

R2 Anti-sFlt-1-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 9.9 mL:
Monoclonal anti-sFlt-1 antibody (mouse) labeled with ruthenium complex 1.0 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

Elecsys sFlt-1

cobas®

H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

After centrifugation, the separated serum sample should be stored at 2-8 °C for a maximum of 48 hours inclusive of shipment of the sample at 2-8 °C. Measure samples immediately or freeze them at -20 °C (± 5 °C) or lower for up to 6 months. Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 05109531190, sFlt-1 CalSet, for 4 x 1.0 mL
- REF 05341787190, PreciControl Multimarker, for 6 x 2.0 mL
- General laboratory equipment
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibration

Traceability: This method has been standardized against a commercially available sFlt-1 assay.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl Multimarker.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in pg/mL.

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 427 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.311 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 123 nmol/L or ≤ 30 ng/mL
Rheumatoid factors	≤ 600 IU/mL

Criterion: For concentrations of 10-25 pg/mL the deviation is ≤ ± 5 pg/mL. For concentrations > 25 pg/mL the deviation is ≤ ± 15 %.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

There is no high-dose hook effect at sFlt-1 concentrations up to 200000 pg/mL.

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

10-85000 pg/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 10 pg/mL. Values above the measuring range are reported as > 85000 pg/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 6 pg/mL

Limit of Detection = 10 pg/mL

Limit of Quantitation = 15 pg/mL

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

It has been determined using low concentration sFlt-1 samples.

Dilution

Not necessary due to the broad measuring range.

Please note

For linearity studies within the measuring range, samples may be diluted with human serum. The final concentration of the diluted sample must be > 5000 pg/mL.

The analyte sFlt-1 is known to be heterogeneous and this may give rise to non-linear dilution phenomena for certain individual samples.

Expected values

The following results were obtained in the Prospective Multicenter Study: Diagnosis of Preeclampsia by means of the Elecsys sFlt-1 assay and the Elecsys PlGF assay (Roche study No. CIM RD000556/X06P006).[16]

To define the reference ranges for normal pregnancies, 877 normotensive pregnant women from 9 sites in Europe (Germany, Spain, Austria, Czech Republic, Switzerland) provided samples at 1685 visits. All women had a singleton pregnancy with normal pregnancy outcome (i.e. no preeclampsia/HELLP, no IUGR). For each sample the levels of sFlt-1 and PlGF were determined in parallel and the sFlt-1/PlGF ratio was calculated.

Gestational week: defined as completed weeks of pregnancy beginning with the start of the last menstruation cycle.

The following results were obtained:

Percentile Elecsys sFlt-1 assay (pg/mL)

	Gestational week						
	10+0-14+6	15+0-19+6	20+0-23+6	24+0-28+6	29+0-33+6	34+0-36+6	37+0-delivery
5th percentile	652	708	572	618	773	992	1533
50th percentile	1328	1355	1299	1355	1742	2552	3485
95th percentile	2501	2807	2997	3205	5165	7363	9184
N (visits)	246	157	217	346	319	224	176

Percentile Elecsys PlGF assay (pg/mL)

	Gestational week						
	10+0-14+6	15+0-19+6	20+0-23+6	24+0-28+6	29+0-33+6	34+0-36+6	37+0-delivery
5th percentile	28.8	66.2	119	169	114	78.0	54.4
50th percentile	52.6	135	264	465	471	284	191
95th percentile	122	289	605	1117	1297	984	862
N (visits)	246	157	217	346	319	224	176

Percentile Elecsys sFlt-1/PlGF ratio

	Gestational week						
	10+0-14+6	15+0-19+6	20+0-23+6	24+0-28+6	29+0-33+6	34+0-36+6	37+0-delivery
5th percentile	9.27	3.51	1.82	0.945	0.941	1.23	2.18
50th percentile	24.8	10.5	4.92	3.06	3.75	9.03	19.6
95th percentile	54.6	25.7	14.6	10.0	33.9	66.4	112
N (visits)	246	157	217	346	319	224	176

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

Elecsys sFlt-1

cobas®

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	15.8	1.47	9.3	1.62	10.2
Human serum 2	53.2	2.03	3.8	2.14	4.0
Human serum 3	614	11.9	1.9	19.0	3.1
Human serum 4	38858	953	2.5	1687	4.3
Human serum 5	70552	2979	4.2	4279	6.1
PC[b)] Multimarker 1	133	3.24	2.4	4.62	3.5
PC Multimarker 2	1062	21.3	2.0	38.2	3.6

b) PC = PreciControl

Clinical sensitivity and specificity

Aid in diagnosis of preeclampsia:

The following results were obtained in the Prospective Multicenter Study: Diagnosis of Preeclampsia by means of the Elecsys sFlt-1 assay and the Elecsys PlGF assay (Roche study No. CIM RD000556/X06P006).[16]

In this case-control study, the Elecsys sFlt-1 and Elecsys PlGF assays were tested in parallel on samples from 468 pregnant women with normal pregnancy outcome (no preeclampsia/HELLP syndrome, no IUGR) and 234 patients with preeclampsia/HELLP syndrome. All pregnancies were singleton pregnancies. Preeclampsia was defined as new onset of both hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and proteinuria (> 0.3 g/24 h or dipstick ≥ 1+ if a 24 h urine collection could not be obtained) after week 20 of gestation. A PE-pregnancy was defined as early-onset PE if clinical signs of PE appeared before week 34 of gestation. Different sets of cutoffs are suggested for early-onset and late-onset preeclampsia.

Early gestational phase (week 20+0 - week 33+6)

Aid in diagnosis of preeclampsia			
	sFlt-1/PlGF ratio	Sensitivity	Specificity
Rule-out cutoff	33	95.0 %	94.0 %
Rule-in cutoff	85	88.0 %	99.5 %

Late gestational phase (week 34+0 - delivery)

Aid in diagnosis of preeclampsia			
	sFlt-1/PlGF ratio	Sensitivity	Specificity
Rule-out cutoff	33	89.6 %	73.1 %
Rule-in cutoff	110	58.2 %	95.5 %

Aid in short-term prediction of preeclampsia:

The following results were obtained in the Prospective Multicenter Study: PROGNOSIS - a multicenter, prospective, double-blind, non-interventional study evaluating the short-term prediction of preeclampsia/eclampsia/HELLP in pregnant women with suspected preeclampsia (Roche Study No. CIM RD000817).[17]

Sample and clinical data collection was completed at 30 sites globally from December 2010 to January 2014. 1273 pregnant women with clinical suspicion of preeclampsia between gestational weeks 24+0 days - 36+6 days were enrolled in the study and 1050 subjects were considered for the primary study objectives (500 in the development cohort and 550 in the validation cohort). One single cutoff of 38 for sFlt-1/PlGF ratio was identified in the PROGNOSIS Study:

- sFlt-1/PlGF ratio ≤ 38: rule-out preeclampsia for 1 week
- sFlt-1/PlGF ratio > 38: rule-in preeclampsia within 4 weeks

The results in the following tables were obtained in the validation cohort:

Short-term prediction of preeclampsia – RULE-OUT	
sFlt-1/PlGF ratio	≤ 38
NPV[c)] (95 % CI[d)])	99.3 % (97.9-99.9)
Sensitivity (95 % CI)	80.0 % (51.9-95.7)
Specificity (95 % CI)	78.3 % (74.6-81.7)

c) NPV = negative predictive value

d) CI = confidence interval

Short-term prediction of preeclampsia – RULE-IN	
sFlt-1/PlGF ratio	> 38
PPV[e)] (95 % CI)	36.7 % (28.4-45.7)
Sensitivity (95 % CI)	66.2 % (54.0-77.0)
Specificity (95 % CI)	83.1 % (79.4-86.3)

e) PPV = positive predictive value

The negative predictive value was also calculated for ruling-out preeclampsia for 2, 3 and 4 weeks after testing as a secondary outcome of the PROGNOSIS Study.[18]

% (95% CI)	**Rule out within 1 week**	**Rule out within 2 weeks**	**Rule out within 3 weeks**	**Rule out within 4 weeks**
NPV	99.3 97.9-99.9	97.9 96.0-99.0	95.7 93.3-97.5	94.3 91.7-96.3
Sensitivity	80.0 51.9-95.7	78.0 62.4-89.4	70.0 56.8-81.2	66.2 54.0-77.0
Specificity	78.3 74.6-81.7	81.1 77.5-84.4	82.4 78.8-85.7	83.1 79.4-86.3

sFlt-1/PlGF ratio and maternal and fetal adverse outcomes:
The results of post hoc analysis of the PROGNOSIS study data demonstrated the ability of the sFlt-1/PlGF ratio cutoff of 38 to predict a combined end point of preeclampsia, eclampsia, or HELLP syndrome or maternal or fetal adverse outcomes.[17]

The results in the following tables were obtained in the validation cohort:

Prediction of combined end point within 1 week	
NPV (95 % CI)	98.5 % (96.9-99.5)
PPV (95 % CI)	18.5 % (12.0-26.6)
Sensitivity (95 % CI)	78.6 % (59.0-91.7)
Specificity (95 % CI)	80.8 % (77.0-84.1)

Prediction of combined end point within 4 weeks	
NPV (95 % CI)	90.1 % (86.8-92.8)
PPV (95 % CI)	65.5 % (56.3-74.0)
Sensitivity (95 % CI)	65.5 % (56.3-74.0)
Specificity (95 % CI)	90.1 % (86.8-92.8)

sFlt-1/PlGF ratio and time to delivery:
A secondary analysis of the PROGNOSIS study demonstrated that a sFlt-1/PlGF ratio greater than 38 is associated with a shorter remaining pregnancy duration and a higher risk of preterm delivery, in early and late gestational phases and regardless of preeclampsia status.[22]
Women with an sFlt-1/PlGF ratio greater than 38 (n = 250) had a 2.9-fold greater likelihood of imminent delivery (i.e., delivery on the day of the test) and shorter remaining time to delivery than women with an sFlt-1/PlGF ratio of 38 or less, whether or not they developed preeclampsia.[22]

Remaining pregnancy duration from the day of the test was 17 days (median; interquartile range (IQR): 10-26 days) for women with sFlt-1/PlGF ratio > 38 versus 51 days (median; IQR: 30-75 days) for women with sFlt-1/PlGF ratio ≤ 38.[22]

The preterm birth rate in the group of women with sFlt-1/PlGF ratio > 38 was 71.2 % (131/184 women) versus 17.8 % in the group with sFlt-1/PlGF ratio ≤ 38 (118/664 women).[22]

Method comparison

a) A comparison of the Elecsys sFlt-1 assay, REF 07027818190 (**cobas e** 801 analyzer; y), with the Elecsys sFlt-1 assay, REF 05109523190 (**cobas e** 601 analyzer; x), gave the following correlations (pg/mL):

Number of samples measured: 160

Passing/Bablok[31]	Linear regression
y = 0.964x + 10.5	y = 0.977x - 33.8
τ = 0.992	r = 1.000

The sample concentrations were between 10.5 and 79907 pg/mL.

b) A comparison of the Elecsys sFlt-1 assay, REF 07027818190 (**cobas e** 402 analyzer; y), with the Elecsys sFlt-1 assay, REF 07027818190 (**cobas e** 801 analyzer; x), gave the following correlations (pg/mL):

Number of samples measured: 153

Passing/Bablok[31]	Linear regression
y = 1.01x + 4.60	y = 0.991x + 74.1
τ = 0.988	r = 1.00

The sample concentrations were between 19.7 and 83013 pg/mL.

References

1 Brown MA, Lindheimer MD, de Swiet M, et al. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20(1):IX-XIV.

2 Uzan J, Carbonnel M, Piconne O, et al. Pre-eclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag 2011;7:467-474.

3 Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet 2001;357:53-56.

4 Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365:785-799.

5 Verlohren S, Galindo A, Schlembach D, et al. An automated method for the determination of the sFlt-1/PlGF ratio in the assessment of preeclampsia. Am J Obstet Gynecol 2010;202:(161).e1-11.

6 Verlohren S, Stepan H, Dechend R. Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia. Clin Sci 2012;122(2):43-52.

7 Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649-658.

8 Levine RJ, Thadhani R, Qian C, et al. Urinary Placental Growth Factor and Risk of Preeclampsia. JAMA 2005;293:77-85.

9 Molvarec A, Szarka A, Walentin S, et al. Circulating angiogenic factors determined by electrochemiluminescence immunoassay in relation to the clinical features and laboratory parameters in women with pre-eclampsia. Hypertens Res 2010;33:892-898.

10 Schiettecatte J, Russcher H, Anckaert E, et al. Multicenter evaluation of the first automated Elecsys sFlt-1 and PlGF assays in normal pregnancies and preeclampsia. Clin Biochem 2010;43(9):768-770.

11 Verlohren S, Herraiz I, Lapaire O, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol 2012;206:58.e1-8.

12 Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation 2012;125(7):911-919.

13 Moore AG, Young H, Keller JM, et al. Angiogenic biomarkers for prediction of maternal and neonatal complications in suspected preeclampsia. J Matern Fetal Neonatal Med 2012;25(12):2651-2657.

14 Chaiworapongsa T, Romero R, Korzeniewski SJ, et al. Maternal plasma concentrations of angiogenic/antiangiogenic factors in the third trimester of pregnancy to identify the patient at risk for stillbirth at or near term and severe late preeclampsia. Am J Obstet Gynecol 2013;208:287.e1-15.

15 Rana S, Schnettler WT, Powe C, et al. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. Hypertens Pregnancy 2013;32(2):189-201.

16 Verlohren S, Herraiz I, Lapaire O, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. Hypertension 2014;63(2):346-352.

17 Zeisler H, Llurba E, Chantraine F, et al. Predictive Value of the sFlt-1: PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med 2016;374:13-22.

18 Verlohren S, Llurba E, Chantraine F, et al. The sFlt-1/PLGF ratio can rule out preeclampsia for up to four weeks in women with suspected preeclampsia. Pregnancy Hypertension 2016;6(3):140-141.

19 Stepan H, Herraiz I, Schlembach D, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. Ultrasound Obstet Gynecol 2015;45(3):241-246.

20 Perales A, Delgado JL, de La Calle M, et al. sFlt-1/PlGF for early-onset pre-eclampsia prediction: STEPS (Study of Early Pre-eclampsia in Spain). Ultrasound Obstet Gynecol 2017;50(3):373-382.

21 Sovio U, Gaccioli F, Cook E, et al. Prediction of Preeclampsia Using the Soluble fms-Like Tyrosine Kinase 1 to Placental Growth Factor Ratio: A Prospective Cohort Study of Unselected Nulliparous Women. Hypertension 2017;69(4):731-738.

22 Zeisler H, Llurba E, Chantraine F, et al. Soluble fms-Like Tyrosine Kinase-1-to-Placental Growth Factor Ratio and Time to Delivery in Women With Suspected Preeclampsia. Obstet Gynecol 2016;128(2):261-269.

23 Klein E, Schlembach D, Ramoni A, et al. Influence of the sFlt-1/PlGF Ratio on Clinical Decision-Making in Women with Suspected Preeclampsia. PLoS One 2016;31:11(5):e0156013.

24 Vatish M, Strunz-McKendry T, Hund M, et al. sFlt-1/PlGF ratio test for pre-eclampsia: an economic assessment for the UK. Ultrasound Obstet Gynecol 2016;48(6):765-771.

25 Diagnostics guidance [DG23] PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). May 2016

26 Patten IS, Rana S, Shahul S, et al. Cardiac angiogenic imbalance leads to peri-partum cardiomyopathy. Nature 2012;485(7398):333-338.

27 Thadhani R, Kisner T, Hagmann H, et al. Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation 2011;124(8):940-950.

28 Hagmann H, Thadhani R, Benzing T, et al. The promise of angiogenic markers for the early diagnosis and prediction of preeclampsia. Clin Chem 2012;58(5):837-845.

29 Cerdeira AS, Karumanchi SA. Angiogenic factors in preeclampsia and related disorders. Cold Spring Harb Perspect Med 2012;2(11),pii:a006585.

30 Goel A, Rana S. Angiogenic factors in preeclampsia: potential for diagnosis and treatment. Curr Opin Nephrol Hypertens 2013;22:643-650.

31 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

US patents pending.

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

Elecsys sFlt-1

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

CE 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com
+800 5505 6606