

sFlt-1

Soluble fms-like tyrosine kinase-1

cobas®

REF	Σ	SYSTEM
05109523 190	100	Elecsys 2010 MODULAR ANALYTICS E170 cobas e 411 cobas e 601 cobas e 602

English

Intended use

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

The sFlt-1 assay is used in combination with the Elecsys PIGF assay to determine the sFlt-1/PIGF ratio. The sFlt-1/PIGF 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/PIGF 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 electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and **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 induce endothelial dysfunction. Serum levels of PIGF (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 PIGF and sFlt-1 can discriminate normal pregnancy from preeclampsia even before clinical symptoms occur. In normal pregnancy, the pro-angiogenic factor PIGF 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 PIGF levels have been found to be lower than in normal pregnancy.^{7,8,9,10}

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

The level of anti-angiogenic factor sFlt-1 seems correlated with sub-clinical cardiac dysfunction and elevated in women with peri-partum cardiomyopathy. 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.^{16,17}

In summary, PIGF 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.^{5,6,13,15,18,19,20,21}

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 20 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/ProCell 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 reagent barcode.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Reagents - working solutions

The reagent rackpack is labeled as SFLT-1.

- M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-sFlt-1-Ab-biotin (gray cap), 1 bottle, 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)₃²⁺ (black cap), 1 bottle, 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.

Exercise the normal precautions required for handling all laboratory reagents.

Disposal of all waste material should be in accordance with local guidelines. Safety data sheet available for professional user on request.

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 read in from the respective reagent barcodes.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **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
after opening at 2-8 °C	12 weeks
on all analyzers	6 weeks

Specimen collection and preparation

Only the specimens listed below were tested in a sufficient number 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 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, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls 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, sFit-1 CalSet, for 4 x 1 mL
- [REF] 05341787190, PreciControl Multimarker, for 3 x 2 mL each of PreciControl Multimarker 1 and 2
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- [REF] 11662988122, ProCell, 6 x 380 mL system buffer
- [REF] 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- [REF] 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- [REF] 11933159001, Adapter for SysClean
- [REF] 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- [REF] 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers:

- [REF] 04880340190, ProCell M, 2 x 2 L system buffer
- [REF] 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- [REF] 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- [REF] 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- [REF] 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- [REF] 12102137001, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- [REF] 03023150001, WasteLiner, waste bags
- [REF] 03027651001, SysClean Adapter M

Accessories for all analyzers:

- [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. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Calibration

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

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. 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 reagent kit was registered on the analyzer). Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit 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 reagent kit, 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.

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

Note: The controls are not barcode-labeled and therefore have to be run like external controls. All values and ranges have to be entered manually. Please refer to the section "QC" in the operator's manual or to the online help of the instrument software.

Calculation

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

Limitations - interference

The assay is unaffected by icterus (bilirubin < 427 µmol/L or < 25 mg/dL), hemolysis (Hb < 0.311 mmol/L or < 0.5 g/dL), lipemia (Intralipid < 1400 mg/dL) and biotin (< 123 nmol/L or < 30 ng/mL).

Criterion: Recovery within ± 15 % of initial value.

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.

No interference was observed from rheumatoid factors up to a concentration of 600 IU/mL.

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

In vitro tests were performed on 18 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 10 pg/mL are reported as < 10 pg/mL. Values above the measuring range are reported as > 85000 pg/mL.

Lower limits of measurement

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)

Limit of Blank = 6 pg/mL

Limit of Detection = 10 pg/mL

Limit of Quantitation = 15 pg/mL

sFlt-1

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

The Limit of Quantitation was determined using the result of functional sensitivity testing.

The Limit of Blank is the 95th percentile value from $n \geq 60$ 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 (functional sensitivity) 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 PIGF assay (Roche study No. CIM RD000556/X06P006).^{5,21}

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 PE/HELLP, no intrauterine growth restriction). For each sample the levels of sFlt-1 and PIGF were determined in parallel and the sFlt-1/PIGF ratio was calculated.

Weeks of gestation: 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 PIGF 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/PIGF 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 (EP5-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days ($n = 84$). The following results were obtained:

Elecsys 2010 and cobas e 411 analyzers					
		Repeatability		Intermediate precision	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	63.1	0.984	1.6	2.71	4.3
Human serum 2	589	4.79	0.8	13.8	2.3
Human serum 3	34516	359	1.0	1017	2.9
Human serum 4	79101	915	1.2	2933	3.7
PreciControl MM ^b 1	107	1.59	1.5	4.05	3.8
PreciControl MM2	1080	15.2	1.4	42.4	3.9

b) MM = Multimarker

MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers					
		Repeatability		Intermediate precision	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	65.5	0.849	1.3	2.12	3.2
Human serum 2	617	11.5	1.9	15.7	2.5
Human serum 3	34243	527	1.5	1148	3.4
Human serum 4	78677	1213	1.5	3054	3.9
PreciControl MM1	100	3.94	3.9	5.58	5.6
PreciControl MM2	988	26.3	2.7	35.0	3.5

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 PIGF assay (Roche study No. CIM RD000556/X06P006).^{5,21}

In this case-control study, the Elecsys sFlt-1 and Elecsys PIGF assays were tested in parallel on samples from 468 pregnant women with normal pregnancy outcome (no PE/HELLP, no intrauterine growth restriction) and 234 patients with PE/HELLP. All pregnancies were singleton pregnancies. PE 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 $\geq 1+$ 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/PIGF 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/PIGF 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).

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. One single cutoff of 38 for sFlt-1/PIGF ratio was identified in the PROGNOSIS Study:

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

Short-term prediction of preeclampsia – RULE-OUT	
sFlt-1/PIGF ratio	< 38
NPV ^{c)} (95 % CI) ^{d)}	99.1 % (98.2-99.6)
Sensitivity (95 % CI)	85.7 % (72.8-94.1)
Specificity (95 % CI)	79.1 % (76.5-81.6)

c) NPV = negative predictive value

d) CI = confidence interval

Short-term prediction of preeclampsia – RULE-IN	
sFlt-1/PIGF ratio	> 38
PPV ^{e)} (95 % CI)	38.6 % (32.6-45.0)
Sensitivity (95 % CI)	70.3 % (61.9-77.8)
Specificity (95 % CI)	83.1 % (80.5-85.5)

e) PPV = positive predictive value

Method comparison

A comparison of the Elecsys sFlt-1 assay (y) with a commercially available sFlt-1 assay (x) using clinical samples gave the following correlations (pg/mL):

Number of samples measured: 112

Passing/Bablok²² Linear regression

$$y = 1.11x - 47.3$$

$$y = 1.05x - 23.7$$

$$\tau = 0.827$$

$$r = 0.952$$

The sample concentrations were between approximately 42 and 1860 pg/mL.

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sFlt-1

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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).

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.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume after reconstitution or mixing
	Global Trade Item Number

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Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

