Elecsys PIGF

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REF		Σ	SYSTEM
			cobas e 411
05144671190	05144671500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 820
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 083

Intended use

Immunoassay for the in vitro quantitative determination of placental growth factor (PlGF) in human serum.

The Elecsys PlGF assay is used in combination with the Elecsys sFlt-1 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.

This assay is intended for the use as one component, in combination with other parameters, to evaluate the risk of early-onset preeclampsia during the first trimester of pregnancy.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "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 induces endothelial dysfunction. Serum levels of PlGF (placental growth factor) and sFlt-1 (soluble fms-like tyrosine kinase-1, also known as soluble 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]

In the first trimester of pregnancy, different screening models using PlGF as one of the components have been proposed for predicting the risk of early onset preeclampsia.[26,27,28,29,30,31]

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.[5,6,13,15,16,32,33,34]

PlGF in cardiovascular diseases: PlGF can be detected in normal non-pregnant subjects at lower levels. Increased levels of PlGF can be found in patients with cardiovascular diseases as an indicator of micro- and macrovascular atherosclerosis and as a sign of pathological angiogenesis. In addition PlGF has been shown to be an independent predictor of cardiovascular morbidity and mortality in patients with type 1 und type 2 diabetes.[35,36,37,38]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 50 µL of sample, a biotinylated monoclonal PlGF-specific antibody and a monoclonal PlGF-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 or e-barcode.

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

Reagents - working solutions

The reagent rackpack is labeled as PLGF.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-PlGF-Ab~biotin (gray cap), 1 bottle, 8 mL:
Biotinylated monoclonal anti-PlGF antibody (mouse) 0.6 mg/L; phosphate buffer 50 mmol/L, pH 6.0; preservative.

R2 Anti-PlGF-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 8 mL:
Monoclonal anti-PlGF antibody (mouse) labeled with ruthenium complex 4.0 mg/L; phosphate buffer 50 mmol/L, pH 6.0; 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.

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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

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 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 the analyzers	12 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, 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 05144701190, PlGF 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 the **cobas e** 411 analyzer:

- 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, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Additional materials for **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, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Additional materials 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.

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 PlGF 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).

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

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.

If necessary, repeat the measurement of the samples concerned.

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 ≤ 428 µmol/L or ≤ 25 mg/dL), hemolysis (Hb ≤ 0.311 mmol/L or ≤ 0.5 g/dL), lipemia (Intralipid ≤ 1500 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 PlGF concentrations up to 100000 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

3-10000 pg/mL (defined by the Limit of Detection and the maximum of the master curve). Values below 3 pg/mL are reported as < 3 pg/mL. Values above the measuring range are reported as > 10000 pg/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 2 pg/mL

Limit of Detection = 3 pg/mL

Limit of Quantitation = 10 pg/mL

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 ≥ 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 PlGF samples.

Dilution

Not necessary due to the broad measuring range.

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 syndrome, 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

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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
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 duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	112	1.12	1.0	4.55	4.1
Human serum 2	595	5.11	0.9	23.9	4.0
Human serum 3	4510	38.2	0.8	181	4.0
Human serum 4	9542	66.4	0.7	342	3.6
PreciControl MM[b)]1	104	0.954	0.9	2.79	2.7
PreciControl MM2	1010	9.33	0.9	27.1	2.7

b) MM = Multimarker

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	107	1.21	1.1	2.93	2.7
Human serum 2	563	6.81	1.2	14.9	2.6
Human serum 3	4255	46.2	1.1	104	2.4
Human serum 4	9150	83.7	0.9	253	2.8
PreciControl MM1	97.4	2.90	3.0	4.48	4.6
PreciControl MM2	978	29.6	3.0	39.9	4.1

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]

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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]

Risk assessment for early-onset preeclampsia in 1st trimester:
The following results were obtained in a study by Tsiakkas et al.[26] evaluating 40212 women with singleton pregnancies screened at 11-13 gestational weeks using maternal characteristics and PlGF.

	False positive rate (%)	Estimated detection rate of preeclampsia with delivery (%)	
		< 32 weeks	32+0 – 36+6 weeks
Maternal characteristics and PlGF at 11-13 weeks	5	68	44
	10	79	57

The following results were obtained in another study by Akolekar et al.[27], evaluating 58884 women with singleton pregnancies screened at 11-13 gestational weeks using maternal characteristics plus uterine artery pulsatility index (PI), mean arterial pressure (MAP) and PlGF.

	False positive rate (%)	Estimated detection rate of preeclampsia with delivery (%)
		< 34 weeks
Maternal characteristics, Uterine artery PI, MAP, PlGF at 11-13 weeks	5	87.4
	10	95.8

Similar results were also obtained in other studies using PlGF as one of the parameters to evaluate the risk of preeclampsia.[28,29,30,31]

Method comparison

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

Number of samples measured: 119

Passing/Bablok[39]	Linear regression
y = 1.07x + 0.144	y = 1.06x - 1.03
τ = 0.930	r = 0.994

The sample concentrations were between approximately 9 and 850 pg/mL.

Analytical specificity

The monoclonal antibodies used are highly specific against human PlGF. The following cross-reactivities were found:

Substance	Maximum concentration tested pg/mL	Cross-reactivity %
VEGF 165	10000	0.001
VEGF/PlGF-1 heterodimer	10000	0.8
Glycosylated recombinant human PlGF-2	5000	16.8

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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.

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

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