thermo scientific

B·R·A·H·M·S sFlt-1/PIGF KRYPTOR

IVD

Σ 75

Rx only

Federal law restricts this device to sale by or on the order of a licensed Healthcare practitioner (applicable to USA classification only)

Intended Use

The B·R·A·H·M·S™ sFlt-1/ PIGF KRYPTOR™ Test System is comprised of the B·R·A·H·M·S PIGF plus KRYPTOR assay and the B·R·A·H·M·S sFlt-1 KRYPTOR assay.

The B·R·A·H·M·S PIGF plus KRYPTOR is an automated immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE™) technology for the quantitative determination of the concentration of Placental Growth Factor (PlGF) in human serum and plasma (K2 EDTA) on the B·R·A·H·M·S KRYPTOR analyzer.

The B·R·A·H·M·S sFlt-1 KRYPTOR is an automated immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE™) technology for the quantitative determination of the concentration of soluble fms-like tyrosine kinase-1 (sFlt-1), also known as VEGF receptor-1, in human serum and plasma (K2 EDTA) on the B·R·A·H·M·S KRYPTOR analyzer.

The B·R·A·H·M·S PlGF plus KRYPTOR is to be used in conjunction with the B·R·A·H·M·S sFlt-1 KRYPTOR along with other laboratory tests and clinical assessments to aid in the risk assessment of pregnant women (singleton pregnancies between gestational age 23+0 to 34+6/7 weeks) hospitalized for hypertensive disorders of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia, or gestational hypertension) for progression to pre-eclampsia with severe features (as defined by American College of Obstetricians and Gynecologists guidelines) within 2 weeks of presentation.

Warnings and Precautions – Test Interpretation

B·R·A·H·M·S PIGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR are indicated to be used as an aid in the management of the patient and are prognostic assays intended to stratify hospitalized patients in two risk groups (low risk and high risk of progression to pre-eclampsia with severe features within two weeks from presentation). The assay results should only be used in conjunction with information available from clinical evaluations and other standard of care procedures. The test result is not to be used to replace clinical judgement.

B·R·A·H·M·S PIGF plus KRYPTOR must be run in conjunction with B·R·A·H·M·S sFlt-1 KRYPTOR and the same patient sample must be used to run both assays. B·R·A·H·M·S sFlt-1 KRYPTOR and B·R·A·H·M·S PIGF plus KRYPTOR are not intended to be used individually. Use of another manufacturer's assays may result in significantly different results.

B·R·A·H·M·S PIGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR should not be used for a woman with a multiple pregnancy because the safety and effectiveness of the device has not been established in pregnant women with a multiple pregnancy (i.e. pregnancy with more than one fetus).

B·R·A·H·M·S PIGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR should not be used for a woman receiving intravenous heparin within 24 hours of testing because the safety and effectiveness of the device has not been established in pregnant women who received intravenous heparin within 24 hours of testing the device.

B·R·A·H·M·S sFlt-1 KRYPTOR and B·R·A·H·M·S PIGF plus KRYPTOR should not be used for a woman receiving exogenous PlGF-2 or PlGF-3 for therapeutic use at concentration higher than 100 pg/mL because the safety and effectiveness of the device has not been established in pregnant women who received exogenous PlGF-2 or PlGF-3 for therapeutic use at concentration higher than 100 pg/mL. The B·R·A·H·M·S PIGF plus KRYPTOR assay was found in bench studies to be impacted by PlGF-2. With samples at equal levels of PlGF (i.e. PlGF-1) and PlGF-2, the reported concentration is within 1% compared to samples without PlGF-2. The normal endogenous level of PlGF-2 in samples collected from pregnant women has not been established.

The clinical management of each patient should be dependent on the patient's health care provider's recommendations as inferred from their clinical status. Therefore, the test results should not be used as a deciding factor to change management plans, and especially not for decisions of pregnancy delivery or for patient discharge from hospital.

The results of the test are not intended for making a diagnosis of preeclampsia or preeclampsia with severe features.

The results of the test are not a stand-alone test for monitoring of hypertensive disorders of pregnancy.

The results of the test are not intended to inform the healthcare provider whether or not to change treatment, including medication or hospitalization.

Summary and Explanation

Preeclampsia is a serious hypertensive condition occurring at mid-pregnancy (approximately after 20 weeks), that can also affect other organs in the body and can be dangerous for both the mother and her developing fetus. Preeclampsia is a condition unique to pregnancy that affects about 2-8% of pregnancies and is a major cause of perinatal and maternal morbidity and mortality[1]. In the United States, the rate of preeclampsia increased by 25% between 1987 and 2004[2]. Moreover, in comparison with women giving birth in 1980, those giving birth in 2003 were at 6.7-fold increased risk of preeclampsia with severe features[3].

First clinical signs of preeclampsia such as new onset of hypertension and proteinuria can be observed after 20 weeks of gestation. Clinically, preeclampsia may vary from mild to severe forms, requiring delivery before 34 weeks of gestation. The severe form of preeclampsia, HELLP syndrome (Hemolysis, elevated liver enzymes, low platelets), occurs in about 20% of women affected by preeclampsia[4,5]. Currently, the standard diagnostic indicator for both preeclampsia types is the presence of hypertension and proteinuria, but these clinical criteria alone may not adequately predict adverse outcomes. The definition of preeclampsia with severe features is defined by American College of Obstetricians and Gynecologists (ACOG) guidelines:

- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100×10^9/L)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit normal concentration), and severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

While early-onset preeclampsia is the less prevalent subtype, it is associated with an even greater risk of adverse outcomes than late-onset preeclampsia.

Although the cause of preeclampsia remains unclear, the syndrome may be initiated by an imbalance of placental factors that induce endothelial dysfunction. The antiangiogenic factor sFlt-1 (soluble fms-like tyrosine kinase) acts as potent antagonist of proangiogenic factors, such as Placental Growth Factor (PlGF), by adhering to the receptor-binding domains, preventing the interaction with endothelial receptors and thereby inducing endothelial dysfunction[6]. During pregnancy, PlGF levels increase progressively in first and second trimester and decrease towards term. In women with clinical preeclampsia, sFlt-1 levels are significantly increased while concentrations of circulating free PlGF are

significantly decreased. Significantly reduced levels of free PlGF have been shown in pregnant women who subsequently develop preeclampsia[7,8]. Measurement of sFlt-1 levels together with PlGF levels in maternal serum starting in mid-pregnancy can improve the current assessment of patients with suspected preeclampsia, which includes clinical symptoms, proteinuria and Uterine artery Doppler velocimetry.

The tests (B·R·A·H·M·S sFlt-1 KRYPTOR and B·R·A·H·M·S PlGF plus KRYPTOR) help to inform clinicians which patient would be at higher risk for developing the ACOG classification of PE with severe features. Thereafter, women whose test was positive (i.e. high risk) would receive stepped-up care. The elevation in the sFlt-1/PlGF ratio antedates ACOG defined thresholds for delivery (e.g., LFT elevations, thrombocytopenia abnormal umbilical Doppler), and therefore is useful to step-up appropriate care and intensify surveillance before severe features develop.

Principle

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR Instructions for Use (IFU)

Instructions

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Reagents

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Stability and Storage Conditions

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Specimen Collection and Preparation

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Procedure

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Interpretation of Results

The B·R·A·H·M·S PlGF plus KRYPTOR and the B·R·A·H·M·S sFlt-1 KRYPTOR assays measure two different biomarkers associated with preeclampsia. sFlt-1 (soluble fms-like tyrosine kinase 1) and PlGF (placental growth factor) are both associated with placental dysfunction during pregnancy. These are each measured, then a ratio of the two biomarkers is calculated. The ratio is the sFlt-1 concentration divided by the PlGF concentration (both expressed in the same units, pg/mL). The ratio is a unitless number, reported with 4 significant digits when below 1000 and as a whole number above 1000. This calculation can be performed on the B·R·A·H·M·S KRYPTOR analyzer.

The current standard of care is currently defined by the ACOG standard and does not include the usage of a medical devices or IVD.

The intended use of the device (B·R·A·H·M·S sFlt-1 KRYPTOR and B·R·A·H·M·S PlGF plus KRYPTOR that are used to derive a ratio of sFlt-1/PlGF) is to be used as an aid in risk assessment of patients with clinical signs and symptoms consistent with development of preeclampsia with severe features (as defined by ACOG guidelines). The test is indicated for use in pregnant women, with singleton pregnancies (gestational age 23+0 to 34+6/7 weeks) hospitalized for hypertensive disorders of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia, or gestational hypertension), within 2 weeks of presentation.

For the sFlt-1/PlGF ratio, the clinical cut-off was established in the PRAECIS clinical study (NCT03815110). The cut-off of 40 was derived in a derivation cohort of 220 patients. This cut-off was then validated in a validation cohort of 520 patients[9].

If the result of the ratio is higher or equal to 40, the pregnant woman would be at high risk for progression to preeclampsia with severe features within 2 weeks.

If the result of the ratio is lower than 40, the pregnant woman would be at low risk for progression to preeclampsia with severe features within 2 weeks.

Low risk for progression to preeclampsia with severe features within 2 weeks:

The woman at low risk for progression to preeclampsia with severe features within 2 weeks would receive standard of care including expectant management according to the ACOG guidelines. A woman with “false negative” result would continue receive existing standard of care including monitoring of future signs of preeclampsia with severe features.

High risk for progression to preeclampsia with severe features within 2 weeks:

The woman at high risk for progression to preeclampsia with severe features within 2 weeks would receive stepped up care according to the ACOG guidelines. The elevation in the sFlt-1/PlGF ratio antedates ACOG defined criteria for delivery (e.g., LFT elevations, thrombocytopenia abnormal umbilical Doppler), and therefore is useful to step-up appropriate care and intensify surveillance before severe features develop. A woman with “false positive” result would receive stepped up care and would not be harmed by additional monitoring.

Recommendations for Laboratory Reports

Quantitative results for PlGF, sFlt-1, and sFlt-1/PlGF ratio are individually reported by the analyzer. The results for PlGF and sFlt-1 should only be used by laboratories to assess assay performance as part of a quality control program, and are not intended for interpretation of results.
It is recommended to only provide the sFlt-1/PlGF ratio on the laboratory report for healthcare practitioners. For a guided interpretation of the test result the laboratory report should include a link to the following training program for healthcare practitioners:

www.thermofisher.com/brahms-pe-training

Alternatively, the laboratory report may provide such interpretative criteria directly (as found on the website above) together with the sFlt-1/PlGF ratio result.

Specific Performance Characteristics

Reportable Range

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Reference Range

In a population of 166 healthy pregnant women between week 23+0 up to week 34+6, the sFlt-1/PlGF ratio median was established at 3.16, the 2.5th percentile at 0.84 and the 97.5th percentile at 31.1.

PRAECIS Clinical Study

Based on the data collected during the PRAECIS clinical study (NCT03815110)[9] and subsequent analysis the following conclusions were derived:

The prognostic performance of the sFlt-1/PlGF ratio with a cut-off of 40 established during the derivation study was successfully validated to predict PE with severe features within two weeks during the validation study. The specific data for prognostic performance estimates and 95% CI are summarized in Table 1.

Table 1: Prognostic performance estimates (sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV)) and 95% confidence intervals (CI) of the sFlt-1/PlGF ratio with a cut off at 40 for the development of severe features of PE within 2 weeks (primary endpoint).

	Sensitivity (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)
PE with severe features within 2 weeks[1]	**93.5%** (89.1- 96.3)	**74.9%** (70.2 - 79.0)	**65.2%** (59.3- 70.6)	**95.8%** (92.9 - 97.6)

[1] Severe features of PE: Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time, thrombocytopenia (platelet count less than 100 × 10^9/L), impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for my alternative diagnoses, or both, progressive renal insufficiency (serum creatinine greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease), pulmonary edema, new-onset cerebral or visual disturbances, headache unresponsive to medication and not accounted for by alternative diagnoses. Women with gestational hypertension or chronic hypertension who developed new evidence of thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, visual loss or cerebral disturbances as described above were considered to have preeclampsia with severe features[9].

The prognostic performance of the numeric sFlt-1/PlGF ratio to predict development of PE with severe features within two weeks was statistically significant and substantially higher than the prognostic performance of other commonly used clinical (highest SBP, highest DBP) and laboratory markers (AST, ALT, Creatinine, platelets) considered individually.

Impact of hypertensive disorder at presentation on the prognostic performance of the device:

Hypertensive disorders	**n**	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**PPV** (95% CI)	**NPV** (95% CI)
Preeclampsia	142	**96.3%** (89.7 - 98.7)	**63.9%** (51.4 - 74.8)	**78.0%** (68.9 – 85.0)	**92.9%** (81.0 - 97.5)
Superimposed Preeclampsia	68	**93.8%** (79.9 - 98.3)	**55.6%** (39.6- 70.5)	**65.2%** (50.8 - 77.3)	**90.9%** (72.2 - 97.5)
Chronic Hypertension	232	**91.8%** (80.8 - 96.8)	**80.3%** (74.0 - 85.4)	**55.6%** (44.7 - 65.9)	**97.4%** (93.4 – 99.0)
Gestational Hypertension	114	**87.5%** (69.0 - 95.7)	**78.9%** (69.4- 86.0)	**52.5%** (37.5 - 67.1)	**95.9%** (88.7 - 98.6)

Impact of maternal age at presentation on the prognostic performance of the device:

Maternal age	n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<35 years	370	**93.2%** (87.5 - 96.4)	**79.0%** (73.4 - 83.7)	**71.1%** (63.9 - 77.3)	**95.4%** (91.5 - 97.6)
≥35 years	186	**94.4%** (84.9 - 98.1)	**67.4%** (59.0 - 74.8)	**54.3%** (44.2 – 64.0)	**96.7%** (90.8 - 98.9)

Impact of gestational age at presentation on the prognostic performance of the device:

Gestational age	n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<30 weeks	188	**98.6%** (92.7 – 99.9)	**80.7%** (72.5 - 86.9)	**76.8%** (67.4 – 84.2)	**98.9%** (94.2 - 99.9)
≥30 weeks	368	**90.2%** (83.3 – 94.4)	**72.3%** (66.5 – 77.4)	**58.7%** (51.3 – 65.8)	**94.4%** (90.2 - 96.8)

From the data collected during the PRAECIS clinical study (NCT03815110), the sFlt-1/PlGF ratio were found to be between 0.38 and 7,367.

Sensitivity

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Linearity

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

High Dose Hook Effect

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Recovery

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Precision

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Interfering Substances

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Metrological Traceability

Refer to the B·R·A·H·M·S PlGF plus KRYPTOR and B·R·A·H·M·S sFlt-1 KRYPTOR IFUs

Bibliography

1. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222.Obstet Gynecol, 2020; 135(6): p. e237-e260
2. Wallis, A.B. et al., Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. Am J Hypertens, 2008; 21(5): p. 521-6
3. Ananth, C.V. et al., Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ, 2013; 347: p. f6564
4. Ghulmiyyah L et al., Maternal Mortality from Preeclampsia/Eclampsia. Seminars in Perinatology, 2012; 36:56-59
5. Powe C et al., Preeclampsia, a Disease of the Maternal Endothelium: The Role of Antiangiogenic Factors. Circulation, 2011; 123: 2856-2869
6. Levine et al., Circulating Angiogenic Factors and the Risk of Preeclampsia. N Engl J Med, 2004; 350:672-683
7. Lam C et al., Circulating Angiogenic Factors in the Pathogenesis and Prediction of Preeclampsia. Hypertension, 2005; 46: 1077-1085
8. De Vivo et al., Endoglin, PlGF and sFlt-1 as markers for predicting pre-eclampsia. Acta Obstet et Gynecol, 2008; 87: 837-842
9. Thadhani et al., Circulating Angiogenic Factor Levels In Hypertensive Disorders of Pregnancy. NEJM, 2022;1 (12), EVIDoa2200161

Revision History

Date: [2023-09]
(This version supersedes all earlier instruction manuals.)

Date of Revision	Version	Description of Changes
[2023-05]	Version 1.0	Initial release
[2023-09]	Version 2.0	Update of the ratio unit number

Manufactured by:
B·R·A·H·M·S GmbH
Neuendorfstrasse 25
16761 Hennigsdorf, GERMANY

Customer Service and Orders:
Fisher Scientific Company L.L.C
8365 Valley Pike
Middletown
Virginia 22645
USA

Tel.: 800.232.3342
Fax: 540.869.8126
e-Mail: techservice.mgc@thermofisher.com
www.thermoscientific.com/brahms

Symbols

Symbols used in Instruction for Use and Product Labelling of B·R·A·H·M·S KRYPTOR compact PLUS products.

Symbol	Usage	Symbol	Usage	Symbol	Usage
	Manufacturer	CE 0197	CE Conformity Marking According to Regulation (EU) 2017/746 on In Vitro Diagnostics Medical Devices, with Reg. Number of Notified Body	Σ 50	Contains sufficient for (Number of) tests, e.g. 50
	Use by		Temperature Limitation	REF	Article Number/ Catalogue Number
	Green Dot according to German Law	BUF	Buffer	SOLN 1	B·R·A·H·M·S KRYPTOR compact SOLUTION 1
	Consult Instructions for use	LOT	Batch code	SOLN 2	B·R·A·H·M·S KRYPTOR compact SOLUTION 2
LYOPH	Lyophilized, freeze dried	**Intended Use**	Reference to the intended use of the Medical Device	IVD	In Vitro Diagnostic Medical Device
CONT	Contents	CAL	Calibrator	CONTROL	Control
SOLN 3	B·R·A·H·M·S KRYPTOR compact SOLUTION 3	SOLN 4	B·R·A·H·M·S KRYPTOR compact SOLUTION 4	CONT BAGS	Bags contained
BAGS	Bags	CONT PLATES	Plates contained	PLATES	Plates
CONT VIALS	Vials contained	VIALS	Vials	VIAL	Vial
H_2O	Use given volume of distilled water (conductivity of less than 50 µS/cm is recommended) for reconstitution, e.g. 0.75 mL	RCNS	Reconstitute	®	Registered Trade Mark
	Biohazard		Wear Protective Gloves		Wear Safety Glasses
	Wash hands		General Regulatory Sign		General Prohibitive Sign
	Do not smoke		Do not Eat and Drink		GHS07 Harmful

Symbol	Usage	Symbol	Usage	Symbol	Usage
	GHS05 Corrosive	**TRACE**	Trade Mark for TRACE-technology		Do not Reuse
	Caution, consult accompanying documents		Accidental Release Measures		Waste
	For IVD Performance Evaluation only	**Rx only**	Federal law restricts this device to sale by or on the order of a licensed Healthcare practitioner (applicable to USA classification only)		Barcode that provides UDI information according to FDA regulations