September 7, 2018

Siemens Healthcare Diagnostics Products GmbH
Petra Dissmann
Regulatory Affairs Manager
Emil-von-Behring Strasse 76
35041 Marburg, Germany

Re: K181525
Trade/Device Name: INNOVANCE Free PS Ag
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor deficiency test
Regulatory Class: Class II
Product Code: GGP
Dated: June 6, 2018
Received: June 11, 2018

Dear Petra Dissmann:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Leonthena R. Carrington -S

Lea Carrington
Director
Division of Immunology
and Hematology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K181525

Device Name
INNOVANCE® Free PS Ag

Indications for Use *(Describe)*
For the quantitative determination of free protein S antigen in human plasma collected from venous blood samples in 3.2% sodium citrate tubes on the Sysmex® CS-5100 analyzer.

As an aid in the diagnosis of protein S deficiency in patients who are suspected of free protein S deficiency.

The performance of this device has not been established in neonate and pediatric patient populations.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

This summary of 510(k) safety and effectiveness information is submitted in accordance with the requirements of 21 CFR §807.92 and follows the FDA guidance 'The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]', issued July 28, 2014.

1. Submitter

Siemens Healthcare Diagnostics Products GmbH

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Date Prepared:	July 19, 2018

2. Device

Name of Device:	INNOVANCE® Free PS Ag (K181525)
Common or Usual Name:	Test, qualitative and quantitative factor deficiency
Classification Name:	Factor deficiency test (21 CFR 864.7290)
Regulatory Class:	Class II
Product Code:	GGP
510(k) Review Panel	Hematology

3. Predicate Device

Name of Device:	STA®-Liatest® Free Protein S (K010963)
Common or Usual Name:	Test, qualitative and quantitative factor deficiency
Classification Name:	Factor deficiency test (21 CFR 864.7290)
Regulatory Class:	Class II
Product Code:	GGP
510(k) Review Panel	Hematology

Two recalls associated with the predicate reagent were found on the FDA Medical Device Recalls database. However, the recalls were specific to assignment ranges of specific production lots. These lots were not used in the generation of data for this 510(k); they have no bearing on the content of this premarket notification. No reference devices were used in this submission.

4. Device Description / Test Principle

The INNOVANCE® Free PS Ag assay is an immunoturbidimetric assay. The reagent kit consists of two components. One component (Reagent) contains polystyrene particles coated with two different monoclonal antibodies both specific for free protein S. This latex reagent aggregates when mixed with samples containing free protein S. The degree of aggregation is directly proportional to the concentration of free protein S in the test sample and is detected turbidimetrically via the increase in turbidity.

Protein S is a vitamin K-dependent plasma protein that is mainly synthesized by the liver. During blood coagulation, protein S exhibits an essential anticoagulant function by acting as a cofactor of activated protein C (APC). In the presence of calcium, protein S forms a complex with APC that binds to phospholipid surfaces and accelerates the APC-catalyzed proteolytic inactivation of the factors Va and VIIIa. Protein S circulates in human blood with a half-life of about 2 days at a plasma concentration of about 25 mg/L. Approximately 60% of the protein is non-covalently bound to C4b-binding protein (C4BP), a regulator of the classical complement pathway. The remaining approx. 40% of the total protein S fraction, i.e. free protein S, represent the physiologically active form that primarily exhibits APC-cofactor activity. Inherited or acquired deficiency of protein S is associated with an increased risk of venous thromboembolism.

Inherited protein S deficiencies are classified into three types:

- type I is defined by a reduction in both total and free protein S levels (quantitative defect),
- type II is rare and characterized by a decreased protein S activity but normal levels of total and free protein S (qualitative defect),
- type III corresponds to normal levels of total protein S but low levels of free protein S (quantitative defect).

Homozygous and heterozygous deficiencies of protein S are rare and commonly lead to purpura fulminans in neonates.

Acquired protein S deficiencies, indicated by decreased free protein S levels, may be caused by:

- hepatic disorders
- nephrotic syndrome
- oral anticoagulation with vitamin K antagonists
- L-asparaginase treatment
- pregnancy
- oral contraceptives
- estrogen therapy
- viral infections
- disseminated intravascular coagulation
- elevated plasma levels of C4BP in an acute-phase reaction.

Newborns may also have decreased levels of free protein S.

5. Intended Use / Indications for Use

For the quantitative determination of free protein S antigen in human plasma collected from venous blood samples in 3.2% sodium citrate tubes on the Sysmex® CS‑5100 analyzer.

As an aid in the diagnosis of protein S deficiency in patients who are suspected of free protein S deficiency.

The performance of this device has not been established in neonate and pediatric patient populations.

6. Comparison of Technological Characteristics with the Predicate Device

A) Assay

Similarities between INNOVANCE® Free PS Ag and STA®-Liatest® Free Protein S		
Item	**Proposed Device** INNOVANCE® Free PS Ag	**Predicate Device (K010963)** STA®-Liatest® Free Protein S
Intended Use	For the quantitative determination of free protein S antigen in human plasma collected from venous blood samples in 3.2% sodium citrate tubes on the SYSMEX CS ‑5100 analyzer.	The STA®-Liatest® Free Protein S kits are intended for use on STA-R® and STA Compact® for the antigenic assay of free protein S in plasma by the immune-turbidimetric method.
Indications for Use	As an aid in the diagnosis of protein S deficiency in patients who are suspected of free protein S deficiency. The performance of this device has not been established in neonate and pediatric patient populations.	Not specified in package insert
Test Principle	Immuno-turbidimetry	Same
Protein S type detected (specificity)	Free protein S	Same
Sample Type	Human plasma, 3.2% sodium citrate	Same

Similarities between INNOVANCE® Free PS Ag and STA®-Liatest® Free Protein S		
Item	**Proposed Device** INNOVANCE® Free PS Ag	**Predicate Device (K010963)** STA®-Liatest® Free Protein S
Control Level	2 Control levels (sold separately from the assay): Control Plasma N (K042333, normal range) Control Plasma P (K042209, pathological range)	2 Control levels (sold separately from the assay): STA®-Liatest® Control N (normal range) STA®-Liatest® Control P (pathological range)
Units	% of norm	Same
Storage	Until expiration date printed on each vial and carton at 2 – 8°C	Until expiration date indicated on the box label, when stored at 2 – 8°C
Measuring Interval	10 - 150% of norm	Same
Composition	Liquid [polystyrene particles (latex) coated with two different monoclonal antibodies both specific for free protein S]	Liquid (latex microparticles coated by covalent bonding with monoclonal antibodies specific for free protein S)
Stability / Shelf Life	12 months according to 510(k) data	Not specified in package insert
Stability Once Opened	8 weeks at 2 – 8°C	Not specified in package insert

Differences between INNOVANCE® Free PS Ag and STA®-Liatest® Free Protein S		
Item	**Proposed Device** INNOVANCE® Free PS Ag	**Predicate Device (K010963)** STA®-Liatest® Free Protein S
Buffer	Buffered saline solution containing heterophilic blocking reagent for minimizing interferences by heterophilic antibodies and rheumatoid factors.	HEPES buffer
On Board Stability	96 hours	32 hours (in original vials) 5 days (with STA® - mini Reducer and the perforated cap)
High Dose Hook Effect	The INNOVANCE® Free PS Ag assay on the SYSMEX® CS-5100 system shows no high dose hook effect up to 588% of norm free protein S.	No dose-hook effect has been observed with free protein S levels up to 200%.

B) Calibrator

Comparison between Calibrators		
Item	**Proposed Device** INNOVANCE® Free PS Ag	**Predicate Device (K010963)** STA®-Liatest® Free Protein S
Intended Use	Standard Human Plasma is used for the calibration of the following coagulation and fibrinolysis tests: 1. Prothrombin time (PT) 2. Fibrinogen (Clauss method) 3. Coagulation factors II, V, VII, VIII, IX, X, XI, XII and VWF 4. Inhibitors: Antithrombin III, protein C, protein S, α2-antiplasmin 5. Plasminogen The percentage values given in the enclosed table of values relate to a pool of fresh citrated human plasma, which by definition, exhibits 100 % of norm for all the factors. Coagulation factors and inhibitors for which a WHO Standard is available are referenced to this standard and the values are given in International Units (IU).	Unknown
Matrix	Normal human plasma (lyophilized)	Unknown
Directly traceable to WHO Standard	Yes	Information given in the instructions for use of the predicate: Kit reagents are pre-calibrated against a secondary standard of the 03/228 International Standard for free protein S established in 2006.
Calibration Curve	Standard Human Plasma (K023141, calibrator sold separately from the assay) is diluted automatically by the instrument used. The respective levels are defined by the actual concentration of free protein S in the Standard Human Plasma lot as provided in the enclosed Table of Analytical Values, and by the system-specific dilution settings for calibration (6-point-calibration curve on the Sysmex® CS-5100).	Information given in the instructions for use of the predicate: To enter the calibration curve on the analyzer, the barcode printed on the Assay Value insert has to be scanned with the instrument barcode reader. The calibration curve is validated subsequently after the two control levels are determined on the analyzer.

Comparison between Calibrators		
Item	**Proposed Device** INNOVANCE® Free PS Ag	**Predicate Device (K010963)** STA®-Liatest® Free Protein S
Stability / Shelf Life	12 month according to 510(k) data	Unknown
On Board Stability	Because calibrators are intended to be used immediately, Siemens does not claim the on-board stability of Standard Human Plasma in the labeling.	Unknown
Stability after Reconstitution	4 hours stored at 15 to 25 °C and 4 weeks stored at –20 °C	Unknown

The above described differences do not raise new questions as to safety and effectiveness of the new device.

7. Performance Data

The following performance data were provided in support of the substantial equivalence determination.

7.1. Non-Clinical Studies

7.1.1. Measuring Interval (Limit of Quantitation and Linearity)

The measuring interval of the application was established with respect to the results of the limit of quantitation (LoQ) and the linearity study.

The LoQ study was carried out in accordance with the CLSI document EP17-A2 '*Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition*', chapter 6. The verification of the LoQ was performed with five independent low-analyte plasma pools. Normal plasma pools were diluted with commercial protein S deficient plasma. The free protein S concentrations of these plasma pools were determined with INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer to be between 7.68 to 7.91% of norm.
The LoQ candidate (≤ 10% of norm) was successfully verified allowing a maximum Total Error of ≤ 4.0% of norm. The study result confirms that the lower limit of the measuring interval (10% of norm) can be accurately measured with the proposed device.

The linearity study was performed in accordance with the CLSI document EP06-A '*Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*'. The linearity of the application was evaluated across the measuring range (10 to 150% of norm). A dilution series was prepared using a sample beyond the intended measuring interval (high pool) and a

sample below the expected LoQ (low pool) to equal 11 different dilutions spanning a free protein S concentration of 7 to 183% of norm. To estimate the deviation from the theoretical ideal linearity, the deviation between the linear regression model and the best fitting polynomial regression model was calculated for each sample concentration. The respective acceptance criteria 'maximal deviation' was predefined with a maximal deviation of ± 3.2% of norm for dilution levels < 40% of norm and ± 8.0% relative for dilution levels ≥ 40 to 150% of norm. Based on the results of the LoQ and linearity study, the measuring interval for the INNOVANCE® Free PS Ag assay was established as 10 to 150% of norm.

7.1.2. Specificity

The effects of potentially interfering substances were investigated in interference studies according to CLSI document EP07-A2 '*Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition*'.

Dose-response experiments were carried out to determine the degree of interference as a function of the interferent concentration for endogenous interferents (hemoglobin, not conjugated bilirubin, conjugated bilirubin, platelets, cholesterol and fibrinogen) and for known exogenous interferents (Dalteparin sodium, Danaparoid sodium, Enoxaparin sodium, Unfractionated heparin). The interferent test concentrations were investigated in the low level of the free protein S concentration (10 to 30% of norm), in the medical decision range (approximately 60 to 70% of norm) and in the high range (100 to 130% of norm). Each sample was prepared with native plasma. The evaluation regarding the endogenous interferents triglycerides (lipids), human anti-mouse antibodies and rheumatoid factors was carried out with single native plamas.

Paired-difference experiments were carried out to evaluate the amount of interferent up to which no interference is to be expected. Individual native samples with and without interferent were compared within the studies. Such interference testing was performed with a panel of exogenous substances including Over-the-Counter and Prescription Drugs.

Following concentrations of listed endogenous substances were found to cause no interference up to the indicated concentrations:

Interferent	No interference up to
Hemoglobin	1 000 mg/dL
Bilirubin (not conjugated)	80 mg/dL
Bilirubin (conjugated)	80 mg/dL
Triglycerides*	961.5 mg/dL
Cholesterol	788.8 mg/dL
Fibrinogen	13 g/dL
Platelets (fresh or frozen plasma)	19.9 x 10^7/ mL
Rheumatoid Factors	2 500 IU/mL

*Evaluated with native lipemic samples.

Patient samples may contain heterophile antibodies (e. g. human anti-mouse antibodies (HAMA) or rheumatoid factors) that could react in immunoassays to give a falsely elevated or depressed

result. INNOVANCE® Free PS Ag has been designed to minimize interference from heterophile antibodies by addition of a blocking reagent. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed.

In addition, no interferences up to the indicated concentrations of following exogenous substances were observed:

Interferent	No interference up to
Acarbose	150 mg/L
Acetyl salicylic acid	300 mg/L
Amiodarone hydrochloride	7.5 µg/mL
Amitriptyline	600 µg/mL
Amoxicillin	45 µg/mL
Apixaban	1050 ng/mL
Argatroban	1350 ng/mL
Atorvastatin calcium salt trihydrate	75 ng/mL
Bisoprolol fumarate	0.35 mg/mL
Bivalidrudin trifluoro acetate salt	1050 ng/mL
Carbamazepin	30 µg/mL
Carbapanem (Imipenem monohydrat)	150 mg/L
Ciprofloxacin	24 mg/L
Citalopram x HBr	330 µg/mL
Clarithromycin	30 mg/L
Clopidogrel hydrogensulfate	9.0 mg/L
Dabigatran	1500 ng/mL
Dalteparin sodium	15 IU/mL
Danaparoid sodium	15 IU/mL
Diclofenac sodium salt	60 mg/L
Digoxin	6.0 µg/mL
Enoxaparin sodium	15 IU/mL
Estrogene	510 pg/mL
Etilefrine hydrochloride	30 µg/mL
Folic acid	24 U/mL
Fondaparinux sodium salt	3.0 mg/L
Furosemide solution	30 ng/mL
Ibuprofen sodium salt	560 mg/L
Ketoconazole	4.5 mg/L
L-Asparaginase	0.009 mg/mL
Lisinopril Dihydrat	24 mg/L
Metformin hydrochloride	3.9 mg/L
N-Acetyl-4-aminophenol	300 mg/L
Pantoprazole sodium sesquihydrate	15 mg/L
Phenobarbital	90 µg/mL
Prasugrel	2400 ng/mL

Interferent	No interference up to
Progesteron	3.0 ng/mL
Ramipril	0.12 mg/mL
Rivaroxaban	1200 ng/mL
Ticagrelor	0.108 mg/mL
Torasemid	9.0 ng/mL
Unfractionated heparin, sodium salt	15 IU/mL
Valproic acid	300 µg/mL
Valsartan	450 ng/mL
Verapamil hydrochloride	1050 ng/mL
Warfarin	15 µg/mL

The following drugs were investigated regarding their potential interference: Harvoni® (ledipasvir and sofosbuvir), Zepatier® (elbasvir and grazoprevir), Epivir-HBV® (lamivudine), Edurant® (rilpivirine), Aptivus® (tipranavir) and Isentress® (raltegravir). No interference could be observed when evaluating plasma samples spiked with the respective drug at a quantity based on the daily prescribed dosage.

7.2. Clinical Studies

7.2.1. Reference Interval

Reference interval studies were conducted at three clinical study sites in the United States with ostensibly healthy subjects aged ≥ 18 years of age following the guidance of CLSI document EP28-A3c *'Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition*'. The summary is provided below. The study population did not include neonate and pediatric sample populations.

Reference Interval Study for INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer		
Gender	**N**	**2.5^{th} - 97.5^{th} percentile (% of norm)**
Males	149	72.8 – 138.8
Females without oral contraception, hormone replacement therapy or pregnancy	151	65.8 – 146.7

7.2.2. Frozen versus Fresh Samples (Bridging Study)

To demonstrate that test results of INNOVANCE® Free PS Ag are not affected by freezing and thawing of the specimens, a bridging study was performed for the comparison between test results obtained with frozen or fresh plasma samples.

The study was performed at one external site in Germany. A minimum of 60 fresh individual plasma samples covering at least 80% of the measuring interval of INNOVANCE® Free PS Ag

(10 to 150% of norm) were measured on the Sysmex® CS-5100 analyzer within four (4) hours after blood collection. One aliquot of each sample was stored for at least seven (7) days at ≤ -74 °C. The aliquots were thawed and measured. To ensure that the study did not introduce bias, one reagent lot was used to exclude reagent lot-to-lot variability.

Results were analyzed by both Passing-Bablok regression analysis and Bland Altman analysis. The predetermined acceptance criteria for Passing-Bablok regression and predicated bias from medical decision points (MDPs) were fulfilled.

The study results of the frozen *versus* fresh samples bridging study is presented in the following table:

Results of the Frozen versus Fresh Samples Bridging Study for INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer							
N	**Slope**	**Intercept (% of norm)**	**r**	**r^2**	**Gender**	**MPDs (% of norm)**	**Bias (% relative)**
66	0.98	1.50	0.999	0.998	Combined	67.9	0.65
					Female	65.8	0.72
					Male	72.8	0.51

7.2.3. Precision / Reproducibility

A precision (single site) and reproducibility (multi-site) study was performed in accordance with the CLSI document EP05-A3 '*Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition'* to investigate the precision performance characteristics of INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer. The reproducibility investigation was performed in a multi-center study, including two study sites in the U.S. (Site 1 and Site 2) and one study site in Germany (Site 3). The precision investigation was performed internally at the Siemens company site in Germany (Site 4). Three plasma pools (Low, MDL, High) as well as two control materials (Control Plasma N, Control Plasma P) were investigated as test samples. The samples were chosen to cover the respective measuring interval of INNOVANCE® Free PS Ag (10 to 150% of norm) and the medical decision level. The plasma pools were prepared at the Siemens company site and sent frozen to the external study sites for testing with the two control materials following routine operation and calibration. The order of samples and control materials for each run and day varied to avoid an inherent bias to the study.

The external reproducibility study was carried out on twenty (20) days, with two (2) runs per day and two (2) replicates of each sample per run (20x2x2) on the Sysmex® CS-5100 analyzer. Site 1 performed the reproducibility study with three (3) different reagent/calibrator lots; the other two (2) external sites (Site 2 and Site 3) used one (1) reagent/calibrator lot.
The results are presented in the following tables:

INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer: Evaluation of 20x2x2 Precision Study at Single Sites.				
Study Site	**CV (%)**			
	Within-Run	**Between-Run**	**Between-Day**	**Total (Within-Site)**
Site 1	0.47 – 2.78	0.00 – 2.09	0.00 – 0.76	**0.76 – 2.79**
Site 2	0.52 – 2.54	0.00 – 0.65	0.00 – 0.34	**0.58 – 2.56**
Site 3	1.01 – 5.29	0.00 – 1.87	0.09 – 1.40	**1.14 – 5.48**

INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer: Evaluation of 20x2x2 Precision Study with three Lots at one Single Site.				
CV (%)				
Within-Run	**Between-Run**	**Between-Day**	**Between-Lot**	**Total (Combined Lots)**
0.54 - 2.63	0.00 - 1.47	0.00 - 0.50	0.62 - 1.36	**1.05 - 2.82**

INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer: Evaluation of 20x2x2 Reproducibility Study with one Lot at three Sites combined.				
CV (%)				
Within-Run	**Between-Run**	**Between-Day**	**Between-Site**	**Total (Combined Sites)**
0.72 - 3.74	0.00 - 1.18	0.00 - 0.89	1.24 - 1.89	**2.10 - 4.08**

The internal precision study was carried out on five (5) days, with two (2) runs per day and four (4) replicates of each sample per run (5x2x4) on the Sysmex® CS-5100 analyzer.
The internal site performed the precision study with three (3) different Sysmex® CS-5100 analyzers, three (3) different operators and one (1) reagent/calibrator lot.
The results are presented in the following table:

INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer: Evaluation of 5x2x4 Precision Study with one Lot and three Analyzer/Operator combinations at Internal Site.				
CV (%)				
Within-Run	**Between-Run**	**Between-Day**	**Between-instrument**	**Total (Combined Instruments)**
0.79 - 1.69	0.39 - 1.92	0.00 - 0.36	0.00 - 4.13	**1.15 - 4.86**

7.2.4. Method comparison

Method comparison studies designed according to EP09-A3 CLSI Guideline '*Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition*' were conducted at three external sites in the United States, all sites using the same protocol.

Samples were measured on both the predicate device (STA® Liatest® Free Protein S on the STA-R Evolution® Expert Series Hemostasis System) as well as on the proposed device (INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer), in random order to eliminate any inherent bias. The samples tested ensured the intended use population was tested, including representative patient samples from various demographics like race, gender, and ages. The study was performed with fresh and frozen samples from patients ≥ 18 years of age.

<table>
<tr><th colspan="4">Distribution of Intended Use Population (Total N = 350)</th></tr>
<tr><td colspan="3">Samples with clinical demand for protein S testing (suspected protein S deficiency or suspected thrombophilia)</td><td>Samples from patients with congenital Protein S deficiency as assessed by commercial vendor</td><td>Samples from patients without clinical demand for Protein S testing</td></tr>
<tr><td colspan="3">304</td><td rowspan="3">31</td><td rowspan="3">15</td></tr>
<tr><td>Suspected thrombophilia</td><td>Congenital protein S deficiency</td><td>Other reasons</td></tr>
<tr><td>137</td><td>1</td><td>166</td></tr>
</table>

Results were compared by Passing-Bablok regression analysis as well as Bland-Altman plots. Results from each application met the predetermined acceptance criteria. The following summary of Passing-Bablok regression shows that the proposed and predicate devices provide equivalent results when used in a clinical setting.

Method Comparison Results (Passing-Bablok Regression); proposed device = INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer and **predicate device** = STA® Liatest® Free Protein S on the STA-R Evolution® Expert Series Hemostasis System			
1st Site	**2nd Site**	**3rd Site**	**Sites Combined**
N = 119 y = 0.85 x – 6.34 r = 0.941 (r^2 = 0.886)	N = 119 y = 0.95 x – 5.70 r = 0.962 (r^2 = 0.926)	N = 112 y = 1.00 x + 3.31 r = 0.949 (r^2 = 0.900)	N = 350 y =0.95 x + 4.92 r = 0.940 (r^2 = 0.883)

8. Conclusions

The predicate device was cleared based in part on the results of clinical studies; therefore clinical testing was required to support substantial equivalence.

The non-clinical and clinical data support the safety of the device.

The clinical data demonstrate that the INNOVANCE® Free PS Ag on the Sysmex® CS-5100 analyzer performs comparably to the predicate device (STA® Liatest® Free Protein S on the STA R Evolution® Expert Series Hemostasis System) that is currently marketed for the same intended use.

The data submitted for this premarket notification demonstrates that the device raises no new concerns as to safety and effectiveness when compared to the predicate device, and is substantially equivalent to the predicate device.