510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K253985

B Applicant

Siemens Healthcare Diagnostic Products Gmbh (Siemens Healthineers)

C Proprietary and Established Names

INNOVANCE D-Dimer 2.0

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DAP	Class II	21 CFR 864.7320 Fibrinogen/fibrin degradation products assay	HE - Hematology

II Submission/Device Overview:

A Purpose for Submission:

New assay

B Measurand:

D-Dimer

C Type of Test:

Quantitative Immuno-turbidometry

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

INNOVANCE D Dimer 2.0 is an in vitro diagnostic reagent for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers) for exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) in conjunction with a clinical pretest probability (PTP) assessment model in outpatients suspected of DVT or PE in human sodium citrated plasma collected from venous blood samples in 3.2 % sodium citrate tubes. INNOVANCE D Dimer 2.0 is for use on automated coagulation analyzers.

C Special Conditions for Use Statement(s):

Prescription use only.

The performance of this device has not been established in pediatric patient population less than 10 years. The exclusion of DVT and PE has not been validated in pediatric patient population less than 18 years.

D Special Instrument Requirements:

Sysmex Automated Blood Coagulation Analyzer CS-5100; and
Siemens Healthineers Automated Blood Coagulation Analyzer CS-5100
(K150678)

IV Device/System Characteristics:

A Device Description:

The INNOVANCE D-Dimer 2.0 is an in vitro diagnostic assay kit for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers). Each assay kit contains INNOVANCE D-dimer 2.0 reagent, buffer, sample diluent, and calibrator. D-Dimer 2.0 reagent is a ready to use liquid containing polystyrene particles coated with monoclonal antibody to D-dimer, mouse (0.065 g/L), buffers/stabilizers, and preservatives. The buffer is a ready to use liquid containing heterophilic blocking reagent (0.15 g/L), buffers/stabilizers, and preservatives. The sample diluent is a ready to use liquid containing buffers/stabilizers, and preservatives. The Calibrator is a lyophilized reagent containing human plasma, D-dimer preparation - human (reconstituted: ~8.0 mg/L FEU), buffers/stabilizers, and preservatives. Three level quality controls sold separately.

B Principle of Operation:

Polystyrene particles covalently coated with a monoclonal antibody aggregate when mixed with samples containing D-dimer. The D-dimer cross-linkage region has a stereosymmetrical structure, which means the epitope for the mab occurs twice. Consequently, one antibody suffices in order to trigger an aggregation reaction, which is then detected turbidimetrically via increase in turbidity.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Siemens INNOVANCE D-Dimer

B Predicate 510(k) Number(s):

K093626

C Comparison with Predicate(s):

Device & Predicate Device(s):	Subject Device K253985	Predicate K093626
Device Trade Name	INNOVANCE D-Dimer 2.0	INNOVANCE D-Dimer
General Device Characteristic Similarities	Subject Device K253985	Predicate K093626
Intended Use/Indications For Use	INNOVANCE D Dimer 2.0 is an in vitro diagnostic reagent for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers) for exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) in conjunction with a clinical pretest probability (PTP) assessment model in outpatients suspected of DVT or PE in human sodium citrated plasma collected from venous blood samples in 3.2 % sodium citrate tubes. INNOVANCE D Dimer 2.0 is for use on automated coagulation analyzers.	For the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma on Siemens Healthcare Diagnostics and Sysmex® Coagulation Systems. The INNOVANCE® D-Dimer Assay is intended for use in conjunction with a non-high clinical pretest probability (PTP) assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).
Analyte	D-Dimer	Same
Measurement	Quantitative	Same
Unit	mg/L Fibrinogen Equivalent Units (FEU)	Same
Instrument	Sysmex Automated Blood Coagulation Analyzer CS-5100; and Siemens Healthineers Automated Blood Coagulation Analyzer CS-5100 (K150678)	Same
Clinical cut-off for exclusion of DVT/PE	0.500 mg/L FEU	0.5 mg/L FEU

Measuring Principle	Immuno-turbidometry (660 nm)	Same
Principle of Operation	Polystyrene particles covalently coated with a monoclonal antibody aggregate when mixed with samples containing D-dimer. The D-dimer cross-linkage region has a stereo-symmetrical structure, this means the epitope for the monoclonal antibody occurs twice. Consequently, one antibody suffices in order to trigger an aggregation reaction, which is then detected turbidimetrically via increase in turbidity	Same
Sample Type	Human plasma (3.2% sodium citrate)	Same
General Device Characteristic Differences	Subject Device K253985	Predicate K093626
Analytical Measurement Range	0.190 to 80.000 mg/L FEU	0.19 to 35.20 mg/L FEU
Assay Kit Components	Four Assay Kit Components: • INNOVANCE D-Dimer 2.0 Reagent (liquid) • INNOVANCE D-Dimer 2.0 Buffer (liquid) • INNOVANCE D-Dimer 2.0 Sample Diluent (liquid) • INNOVANCE D-Dimer 2.0 Calibrator (lyophilized)	Five Assay Kit Components: • INNOVANCE D-Dimer Reagent (lyophilized) • INNOVANCE D-Dimer Buffer (liquid) • INNOVANCE D-Dimer Supplement (liquid) • INNOVANCE D-Dimer Sample Diluent (liquid) • INNOVANCE D-Dimer Calibrator (lyophilized)
Reagent (physical status)	Ready to use liquid containing: • polystyrene particles (~1.0 g/L) coated with monoclonal antibody to D-dimer, mouse (0.065 g/L) • buffers/stabilizers, preservatives	Lyophilized reagent containing: • polystyrene particles coated with monoclonal antibody to D-dimer, mouse (reconstituted: 0.1 g/L) • Albumin, human (reconstituted: 0.5 g/L) • Buffers, preservatives
Buffer	Ready to use liquid containing: • heterophilic blocking reagent (0.15 g/L) • buffers/stabilizers, preservatives	Ready to use liquid containing: • buffers/stabilizers, preservatives
Supplement (reagent)	N/A	Ready to use liquid containing: • heterophilic blocking

		reagent (0.63 g/L) • Buffers, preservative
Sample Diluent	Ready to use liquid containing buffers /stabilizers, preservatives	Ready to use liquid containing buffers, preservatives
Calibrators	Lyophilized reagent containing: • human plasma • D-dimer preparation, human* (reconstituted: ~8.0 mg/L FEU) • buffers/stabilizers, preservatives * Nominal value (the analytical value is listed in the lot-specific Table of Analytical Values)	Lyophilized reagent containing: • human plasma • D-dimer preparation, human* (reconstituted: 5.0 mg/L FEU) • buffers/stabilizers, preservatives * Nominal value per vial
Calibration Scheme	7 levels, n = 2 per level	6 levels, n = 2 per level
Quality Control	Three Control Levels (sold separately from the assay kit): • INNOVANCE D-Dimer 2.0 Control 1 (liquid) • INNOVANCE D-Dimer 2.0 Control 2 (liquid) • INNOVANCE D-Dimer 2.0 Control 3 (liquid)	Two Control Levels (sold separately from the assay kit): • INNOVANCE D-Dimer Control 1 (lyophilized) • INNOVANCE D-Dimer Control 2 (lyophilized)

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3 (2014): Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition

CLSI EP06-A2 (2020): Evaluation of the Linearity of Quantitative Measurement Procedures - Second Edition

CLSI EP07 (2018): Interference Testing in Clinical Chemistry - Third Edition

CLSI EP09c (2018): Measurement Procedure Comparison and Bias Estimation Using Patient Samples - Third Edition

CLSI EP12-Ed3 (2023): Evaluation of Qualitative, Binary Output Examination Performance - Third Edition

CLSI EP14-A3 (2014): Evaluation of Commutability of Processed Samples; Approved Guideline - Third Edition

CLSI EP17-A2 (2012): Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second edition

CLSI EP25-A2 (2023): Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline - Second edition

CLSI EP28-A3c (2010): Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition

CLSI EP34 (2018): Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking - First Edition

CLSI EP39 (2021): A Hierarchical Approach to Selecting Surrogate Samples for the Evaluation of In Vitro Medical Laboratory Tests - First Edition

CLSI H21-A5 (2008): Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays - Fifth Edition

CLSI H59-A (2011): Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline - First Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

a) Repeatability

Two short term precision studies were conducted, including evaluation of assay lot variance and analyzer variance. The studies consisted of five sodium citrate pooled plasma samples and three quality controls (QCs) that spanned the analytical measuring range and medical decision levels. Assay lot variance was conducted at three sites with three operators, over the course of 20 days, two runs/day, two replicates, one Siemens Healthineers Automated Blood Coagulation Analyzer CS-5100 analyzer (K150678), and three assay lots, totaling 240 replicates per sample. For single-site analyzer variance, the study was conducted over five days, with two runs/day, four replicates, three analyzers, and one lot, totaling 120 replicates per sample. For the precision evaluations, a three-factorial fully nested ANOVA was conducted. For each reported parameter and for each sample tested, the mean, SD and %CV of the various components of precision were calculated along with the 95% CI of the SD and %CV to determine repeatability. All results met the pre-defined acceptance criteria.

Assay Lot Variance:

Sample ID	N	Mean (mg/L FEU)	SD (mg/L FEU)					
			Repeat-ability	Between-Run	Between-Day	Within-Lot	Between-Lot	Total (combined lots)
Plasma Pool 1	240	0.2436	0.0071	0.0000	0.0018	0.0073	0.0090	0.0116
Quality Control 1	240	0.3519	0.0060	0.0028	0.0016	0.0068	0.0146	0.0161
Plasma Pool 2	240	0.5510	0.0055	0.0032	0.0031	0.0071	0.0181	0.0194
Quality Control 2	240	0.7635	0.0056	0.0061	0.0043	0.0093	0.0216	0.0235
Quality Control 3	240	3.1589	0.0354	0.0239	0.0115	0.0442	0.0522	0.0684
Plasma Pool 3	240	6.2386	0.1037	0.0573	0.0304	0.1223	0.2988	0.3228
Plasma Pool 4	240	25.8271	0.2665	0.0849	0.2049	0.3467	0.3711	0.5079
Plasma Pool 5	240	64.0764	0.9429	0.5263	0.5387	1.2067	1.6859	2.0732

Sample ID	N	Mean (mg/L FEU)	CV (%)					
			Repeat-ability	Between-Run	Between-Day	Within-Lot	Between-Lot	Total (combined lots)
Plasma Pool 1	240	0.2436	2.91	0.00	0.73	3.00	3.69	4.76
Quality Control 1	240	0.3519	1.69	0.79	0.44	1.92	4.15	4.57
Plasma Pool 2	240	0.5510	1.00	0.59	0.56	1.28	3.29	3.53
Quality Control 2	240	0.7635	0.73	0.80	0.56	1.22	2.83	3.08
Quality Control 3	240	3.1589	1.12	0.76	0.36	1.40	1.65	2.17
Plasma Pool 3	240	6.2386	1.66	0.92	0.49	1.96	4.79	5.17
Plasma Pool 4	240	25.8271	1.03	0.33	0.79	1.34	1.44	1.97
Plasma Pool 5	240	64.0764	1.47	0.82	0.84	1.88	2.63	3.24

Analyzer Variance:

Sample ID	N	Mean (mg/L FEU)	SD (mg/L FEU)				
			Repeat-ability	Between-Run	Between-Day	Between-Instrument	Total (combined lots)
Plasma Pool 1	120	0.2378	0.0116	0.0000	0.0032	0.0055	0.0132
Quality Control 1	120	0.3389	0.0079	0.0044	0.0000	0.0058	0.0107
Plasma Pool 2	120	0.5651	0.0092	0.0016	0.0000	0.0038	0.0101
Quality Control 2	120	0.7511	0.0076	0.0000	0.0050	0.0000	0.0091
Quality Control 3	120	3.0501	0.0257	0.0123	0.0000	0.0337	0.0442
Plasma Pool 3	120	6.4254	0.1784	0.0000	0.0520	0.1244	0.2237
Plasma Pool 4	120	25.7976	0.2260	0.0655	0.0931	0.2931	0.3872
Plasma Pool 5	120	62.2069	0.6687	0.2132	0.0183	0.6721	0.9720

Sample ID	N	Mean (mg/L FEU)	CV (%)				
			Repeat-ability	Between-Run	Between-Day	Between-Instrument	Total (combined lots)
Plasma Pool 1	120	0.2378	4.86	0.00	1.33	2.32	5.55
Quality Control 1	120	0.3389	2.32	1.30	0.00	1.70	3.16
Plasma Pool 2	120	0.5651	1.62	0.29	0.00	0.67	1.78
Quality Control 2	120	0.7511	1.01	0.00	0.66	0.00	1.21
Quality Control 3	120	3.0501	0.84	0.40	0.00	1.11	1.45
Plasma Pool 3	120	6.4254	2.78	0.00	0.81	1.94	3.48
Plasma Pool 4	120	25.7976	0.88	0.25	0.36	1.14	1.50
Plasma Pool 5	120	62.2069	1.07	0.34	0.03	1.08	1.56

b) Reproducibility

The study was conducted at three clinical laboratory sites, over five days with two runs per day and three replicates per run using a 3-level control set comprising low, normal and high levels of measurands. Throughout the study, one Siemens Healthineers Automated Blood Coagulation Analyzer CS-5100 analyzer (K150678) and one lot of the assay / calibrators were utilized by a total of seven operators. The data generated from this assessment was used to calculate, repeatability, between-run, between-day, between-site, and reproducibility (total precision), using a nested ANOVA model for statistical analysis. For each reported parameter and for each level of control tested, the mean, SD and %CV of the various components of precision were calculated along with the 99% CI of the SD and %CV to determine reproducibility. The results were analyzed in accordance with the CLSI EP05-A3 approved guideline and met the pre-acceptance defined criteria.

Sample ID	N	Mean (mg/L FEU)	SD (mg/L FEU)				
			Repeat-ability	Between-Run	Between-Day	Between-Site	Total Reproducibility
Plasma Pool 1	90	0.2539	0.007	0.004	0.005	0.007	0.011
Quality Control 1	90	0.3413	0.007	0.000	0.007	0.008	0.012
Plasma Pool 2	90	0.5665	0.009	0.005	0.011	0.005	0.016
Quality Control 2	90	0.7366	0.007	0.007	0.015	0.015	0.024
Quality Control 3	90	3.0235	0.039	0.031	0.066	0.040	0.092
Plasma Pool 3	90	6.4584	0.107	0.105	0.189	0.136	0.277
Plasma Pool 4	90	25.8025	0.247	0.236	0.551	0.793	1.024
Plasma Pool 5	90	61.8035	0.627	0.645	1.311	1.979	2.538

Sample ID	N	Mean (mg/L FEU)	CV (%)				
			Repeat-ability	Between-Run	Between-Day	Between-Site	Total Reproducibility
Plasma Pool 1	90	0.2539	2.54	1.49	1.91	2.63	4.39
Quality Control 1	90	0.3413	2.01	0.00	1.93	2.32	3.62
Plasma Pool 2	90	0.5665	1.58	0.87	1.84	0.92	2.74
Quality Control 2	90	0.7366	0.92	0.93	2.09	2.03	3.19
Quality Control 3	90	3.0235	1.27	1.02	2.19	1.31	3.03
Plasma Pool 3	90	6.4584	1.65	1.63	2.93	2.11	4.30
Plasma Pool 4	90	25.8025	0.96	0.92	2.14	3.07	3.97
Plasma Pool 5	90	61.8035	1.02	1.04	2.12	3.20	4.11

2. Linearity:

The linearity interval of D-dimer was evaluated using sodium citrate plasma samples supplementally spiked with d-dimer antigen. A 20-level sample curve was prepared, and each sample was tested in four replicates with three lots on the Siemens Healthineers Automated Blood Coagulation Analyzer CS-5100 (K150678). Linear Regression was performed for data analysis, and all parameters met the predefined acceptance criteria for the established linear range of 0.190 to 80.000 mg/L FEU.

3. Analytical Specificity/Interference:

A study was conducted to determine the interference level for the following interfering substances: lipemia (intralipid; 400 mg/dl), conjugated bilirubin (40 mg/dl), unconjugated

bilirubin (60 mg/dl), hemoglobin (1000 mg/dl), albumin (5.8 g/dl), creatinine (75 mg/dl), IgG (3.3 g/dl), urea (500 mg/dl), uric acid (31 mg/dl), in addition to the follow exogenous interferences.

Drug	Concentration Tested	Drug	Concentration Tested	Drug	Concentration Tested
Acetaminophen	20 mg/dl	Dextran 40	1200 mg/dl	Lithium chloride	2.3 mg/dl
Acetylsalicylic acid	60 mg/dl	Diazepam	3 mg/dl	Losartan	0.09 mg/ml
Amikacin	15 mg/dl	Digoxin	39 ng/ml	Metformin	1.2 mg/dl
Ampicillin	7.5 mg/dL	Edoxaban	1560 ng/mL	Nicotine	0.1 mg/dl
Apixaban	990 ng/mL	Enoxaparin	15 IU/mL	Penicillin G	25 U/mL
Ascorbic acid	5.25 mg/dL	Eplerenone	0.03 mg/dl	Phenobarbital	69 mg/dl
Atorvastatin	0.76 mg/L	Erythromycin	13.8 mg/dl	Phenytoin	6.0 mg/dl
Caffeine	10.8 mg/dL	Ethanol	600 mg/dl	Primidone	5.7 mg/dl
Captopril	20 mg/dl	Ethosuximide	30 mg/dl	Propranolol	0.5 mg/dl
Carbamazepine	4.5 mg/dl	Furosemide	6.0 mg/dl	Rivaroxaban	1250 ng/mL
Chloramphenicol	7.8 mg/dl	Gentamycin	12 mg/dl	Theophylline	6.0 mg/dl
Cimetidine	3.0 mg/dl	Heparin, sodium	3.3 IU/ml	Valproic acid	19 mg/dl
Cyclosporin A	35 mg/dl	Ibuprofen	50 mg/dl	Verapamil	0.288 mg/ml
Dabigatran	900 ng/mL	Lidocaine	1.5 mg/dl	Warfarin	11 mg/dl

The interference levels were evaluated by testing sodium citrated plasma spiked with the interferent at study concentration levels. For each interferent, blood samples were spiked with the interferent, and four or five replicate tests were performed with both control group (no spiking) and test group (with spiking) for comparison. A total of four blood samples were tested for each interferent (normal, cut-off level, and pathological pools 1 & 2). The non-significant %Interferences were defined as %Interferences within the pre-defined acceptance criteria. Dose response studies were conducted for interferents that failed initial specificity testing. The results of the interference study demonstrated that there was no significant interference up to the levels evaluated.

Additionally, to evaluate interference from rheumatoid factor, samples which had RF concentrations up to 1246 IU/mL and samples with no detectable RF concentration were used to prepare samples for the study. To evaluate interference from HAMA, samples which had HAMA concentrations up to 896.44 ng/mL and samples with no detectable HAMA concentration were used to prepare samples for the study. Samples were compared in the presence and absence of Heterophilic Blocking Tubes. For fibrinogen, to evaluate interference, samples of various D-Dimer concentrations, which contained high concentrations of fibrinogen (up to 9.32 g/L) were compared to samples of various D-Dimer concentrations, containing normal levels of fibrinogen (control). A cross-reactivity study to evaluate fibrinogen degradations products (FDP; up to 20 mg/L) was also conducted. The results of the additional interference / cross-reactivity studies demonstrated that there was no significant interference up to the levels evaluated.

4. Detection Limit and Assay Reportable Range:

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) were determined according to CLSI EP17-A2. Three lots of INNOVANCE D-Dimer 2.0 were used in this evaluation. The following human citrated plasma samples were utilized: five

blank samples (individual plasma samples stripped of D-Dimer by affinity chromatography), five LOD samples (patient plasma pools with an analyte concentration ranging from 1-5x times the LoB), and five LOQ samples (plasma pools, below or near target lower limit of 0.190 mg/L FEU). With each lot, the blank and low-concentration samples were tested in four replicates in a single run per day for three days. The LoB was determined to be 0.0277 mg/L FEU, LoD was determined to be 0.0416 mg/L FEU, and LoQ was determined to be 0.135 mg/L FEU. Based on the Linearity and the LoQ study results, the Assay Measuring Range for D-Dimer was determined to be 0.190–80.000 mg/L FEU.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

The calibrator is traceable to an internal reference preparation (Master Standard). A new calibration is required for each new lot of INNOVANCE D-Dimer 2.0, after major maintenance or service, as indicated by quality control results, as indicated in laboratory quality control procedures, when required by local regulations. The INNOVANCE D-Dimer 2.0 Controls 1, 2, and 3 are single analyte, liquid, human plasma-based products containing D-dimer. The control is traceable to an in-house reference preparation (Master Standard. INNOVANCE D-Dimer 2.0 Controls must be tested at least once each day of use, following each calibration, and for each vial of reagent for the respective measurement range to ensure that the system is functioning correctly.

Reagent Stability
Real-time stability studies were conducted to establish shelf-life, in use, and on-board stability for the INNOVANCE D-Dimer 2.0 assay reagents and quality controls materials (QCs), when stored at the recommended storage conditions. Three lots were tested. Each lot was stored at 2-8°C and tested at defined time points and then evaluated using either five plasma pools covering AMR (including MDL) and QCs (reagents) or QCs only (QC evaluation). Based on the results of this study, the INNOVANCE D-Dimer 2.0 shelf-life stability is 18 months at 2-8°C, 31 days opened at 2-8°C, and 120 hours on board at 2-8°C. Additionally, the QC shelf-life stability is 6 months at 2-8°C, 31 days opened at 2-8°C, and 24 hours on board at 2-8°C.

Sample Stability
The evaluation of sample stability was conducted at two sites using 38 sodium citrate plasma samples spanning the AMR including samples near the cutoff. Samples were evaluated (n=4) initially after collection to determine the T0 value, and then sub-aliquoted and stored at various temperatures for future stability evaluation. Once a timepoint was established, samples were tested in quadruplicate, and results were compared to the baseline T0. The individual deviation limit, mean deviation limit, and regression analysis were evaluated for each timepoint. The data support the following sample stability:

- 4 hours stability at 15-25 °C in primary tube (plasma stored on cells) or in secondary cup (plasma siphoned from cells),
- 24 hours stability at 2-8 °C in primary tube (plasma stored on cells) or in secondary cup (plasma siphoned from cells),
- 3 months stability at ≤ -18 °C in secondary cup (plasma siphoned from cells),
- 6 months stability at ≤ -74 °C in secondary cup (plasma siphoned from cells),
- 4 hours ‘once frozen’ stability (sample measured after one freeze-thaw cycle in a secondary cup (plasma siphoned from cells)) stored at 15-25 °C.

6. Assay Cut-Off:

See clinical sensitivity/specificity.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison study was performed with 13 operators in total, across three external US sites and one external OUS sites (with 33 additional samples measured internally at Siemens), to evaluate the performance of the INNOVANCE D-Dimer 2.0 assay compared to the predicate, INNOVANCE D-Dimer assay (K093626). A total of 377 subjects were evaluated in the study (59.4% fresh sodium citrate plasma samples; 40.6% frozen sodium citrate plasma samples), of which there were 54% female and 46% male. Eight percent of the patients evaluated were pediatric (10-18 years old). The study included patients with suspicion for PE, DVT, and DIC. Statistical analyses for the method comparison were performed based on correlation plots with Passing-Bablok regression and difference plots for bias. The slope, intercept, and correlation coefficient from the Passing-Bablok fittings, as well as the bias at the medical decision level were acceptable, as shown in the table below.

Measurand	N	Range	R	Slope (95% CI)	Intercept	Bias at MDL (0.500mg/L FEU)
D-Dimer	377	0.195-79.76	0.995	1.036 (1.024-1.052)	-0.017 mg/L FEU	0.0010 mg/L FEU

2. Matrix Comparison:

Not applicable.

C Clinical Studies:

1. Clinical Sensitivity/Specificity:

The INNOVANCE D-Dimer 2.0 assay was evaluated on the CS-5100 System in a multi-center study to validate the exclusion of DVT and PE using frozen specimens collected previously from 1246 patients (≥ 18 years of age) presenting to the emergency department with suspected PE and 1263 patients (≥ 18 years of age) presenting in the emergency department with suspected DVT. All patients were evaluated using the Wells' rules to estimate a likely or unlikely pre-test probability (PTP) of DVT and of PE. Patient specimens were tested with the INNOVANCE D-Dimer 2.0 assay and results were compared to a cutoff value of 0.500 mg/L (FEU). A D-dimer result <0.500 mg/L (FEU) was considered negative and a D-dimer result ≥0.500 mg/L (FEU) was considered positive.

Patients with a positive D-dimer result were evaluated by imaging methods, e.g. compression ultrasound and/or venography. Patients with a negative D-dimer, as well as those with

negative imaging results, were followed for three months to evaluate potential development of DVT. All patients were subject to imaging at the physician's discretion. The overall prevalence of DVT in those adult patients available for final analysis was 6.2 % (78/1263). The overall prevalence of PE in those adult patients available for final analysis was 7.8 % (97/1246). The following instrument-specific sensitivity, specificity and negative predictive value (NPV) with upper and lower 95 % confidence limits (CL) were obtained with the INNOVANCE D-Dimer 2.0 clinical cutoff of 0.500 mg/L (FEU). All studies demonstrated acceptable performance.

DVT - Combined Sites (< 0.500 mg/L FEU= negative)	**Imaging and 3-month follow-up**			**Predictive Value (Lower confidence limit)**	
INNOVANCE D-dimer 2.0 on CS-5100	Positive	Negative	Total	NPV	99.7 (LCL: 99.0)
Positive	76	611	687	PPV	11.1 (LCL: 9.2)
Negative	2	574	576	Sensitivity	97.4 (LCL: 92.1)
Total	78	1185	1263	Specificity	48.4 (LCL: 46.0)

PE - Combined Sites (< 0.500 mg/L FEU= negative)	**Imaging and 3-month follow-up**			**Predictive Value (Lower confidence limit)**	
INNOVANCE D-dimer 2.0 on CS-5100	Positive	Negative	Total	NPV	99.8 (LCL: 99.3)
Positive	96	489	585	PPV	16.4 (LCL: 14.1)
Negative	1	660	661	Sensitivity	99.0 (LCL: 95.2)
Total	97	1149	1246	Specificity	57.4 (LCL: 55.0)

2. Clinical Cut-Off:

   0.500 mg/L FEU

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   N/A

D Expected Values/Reference Range:

A reference interval study was performed to determine the reference intervals of adults and pediatrics for the INNOVANCE D-Dimer 2.0 Assay. Healthy subjects were enrolled at three sites for the adult study (one site for pediatrics), including 153 adults 18 years old and over (70 male, 83 female) and 24 pediatric subjects (< 18 years old). Sodium citrate plasma samples were collected from each subject and tested. For the adult group (≥18 years old), reference intervals

were established to be <0.190 to 0.942 mg/L FEU, by non-parametric method following CLSI EP28-A3c. The 90th percentile was determined to be 0.468 mg/L FEU. For the pediatric group, the reference intervals were verified against the pediatric reference range determined from literature.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.