FDA U.S. FOOD & DRUG ADMINISTRATION

EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR INNOVANCE VWF Ac DECISION SUMMARY

I Background Information:

A De Novo Number

DEN200067

B Applicant

Siemens Healthcare Diagnostics Products GmbH

C Proprietary and Established Names

INNOVANCE VWF Ac

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QTY	Von Willebrand factor assay	21 CFR 864.7293	81 – Hematology

II Submission/Device Overview:

A Purpose for Submission:

De Novo request for evaluation of automatic class III designation for INNOVANCE VWF Ac assay

B Measurand:

von Willebrand factor activity

C Type of Test:

Quantitative test of the von Willebrand factor-GPIb-binding activity

III Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

In-vitro diagnostic automated assay for the quantitative determination of the von Willebrand factor-GPIb-binding activity in human plasma collected from venous blood samples in 3.2% sodium citrate tubes on the BCS XP System.
As an aid used in the evaluation of patients with suspected or confirmed von Willebrand factor disorders.
Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other laboratory findings.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

BCS XP System (K013114)

IV Device/System Characteristics:

A Device Description:

The INNOVANCE VWF Ac assay is a particle enhanced turbidimetric assay based on binding of VWF to the recombinant GPIb (two gain-of-function mutations included). The assay provides quantitative VWF activity results on 3.2% citrated human plasma when used with Standard Human Plasma Calibrators (K023141).

The reagent kit consists of three components: Reagent I (containing polystyrene particles coated with anti-GPIb mouse monoclonal antibodies), Reagent II (buffer containing heterophilic blocking reagent) and Reagent III (containing recombinant GPIb).

INNOVANCE VWF Ac assay kit components	Description	Vials provided in the assay kit
INNOVANCE VWF Ac Reagent I	Ready to use liquid containing: • Buffer • Sucrose • Polystyrene particles coated with anti-GPIb mouse monoclonal antibodies (2.2 g/L) • Amphotericin B • Gentamicin sulfate	3 x 2.0 mL
INNOVANCE VWF Ac Reagent II	Ready to use liquid containing: • Buffered saline • Heterophilic blocking reagent • Polyvinylpyrrolidone • Detergent • Sodium azide (< 1 g/L)	3 x 3.5 mL

INNOVANCE VWF Ac Reagent III	Ready to use liquid containing: • Buffered saline • Recombinant GPIb (≤ 80 mg/L) • Amphotericin B • Gentamicin sulfate	1 x 2.5 mL

The assay requires the following components which are not included in the assay kit:

Material	Description	510(k)
Standard Human Plasma	Calibrator	K023141
Control Plasma N	Control (normal range)	K042333
Control Plasma P	Control (pathological range)	K042209
Dade Owren's Veronal Buffer	Buffer	K050928
Washing Solution for Coagulation Analyzers	Washing solution	K924124
BCS XP System	Automated blood coagulation analyzer	K013114

B Principle of Operation

The assay principle makes use of the binding of VWF to its receptor Glycoprotein Ib (GPIb). GPIb is the main VWF receptor on platelets. Polystyrene particles are coated with an antibody against GPIb. Recombinant GPIb (two gain-of-function mutations included) is added and binds to the antibody as well as to the VWF of the sample. Due to the gain-of-function mutations, VWF binding to GPIb does not require ristocetin (VWF:GPIbM). This VWF binding induces a particle agglutination which can be measured as an increase in extinction by turbidimetric measurements.

C Instrument Description Information

1. Instrument Name:

   BCS XP System (K013114)

2. Calibration:

   Calibrator

Item	Calibrator (sold separately from the assay): Standard Human Plasma (K023141)

Intended Use	Standard Human Plasma is used for the calibration of the following coagulation and fibrinolysis tests: • Prothrombin time (PT) • Fibrinogen (Clauss method) • Coagulation factors II, V, VII, VIII, IX, X, XI, XII and VWF • Inhibitors: Antithrombin III, protein C, protein S, α2-antiplasmin • 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).
Matrix	Normal human plasma (lyophilized)
Directly traceable to WHO Standard	Yes
Traceability	INNOVANCE VWF Ac results are traceable to the WHO 6th International Standard (IS) Factor VIII / Von Willebrand Factor (NIBSC code 07/316) as confirmed by the *De Novo* request data. The observed bias for the recovery of the WHO IS was + 2.3% (relative).
Calibration Curve	A standard curve is generated by automatic determination of different dilutions of Standard Human Plasma with Dade Owren's Veronal Buffer. The respective levels are defined by the actual VWF:GPIbM activity in the Standard Human Plasma lot as provided in the Table of Analytical Values, and by the system-specific dilution settings for calibration. Calibration scheme for the BCS XP System: 5 level (low setting) 6 level (standard setting), each n = 2 /level.
Stability / Shelf-Life	12 months, according to the current *De Novo* request study data
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.
Stability after Reconstitution	4 hours when stored at 15 to 25°C 4 weeks when stored at -20°C 2 hours stored at 15 to 25°C once frozen and thawed

V Standards/Guidance Documents Referenced:

- CLSI EP07: *Interference Testing in Clinical Chemistry*, Third Edition

- CLSI EP06, 2nd Ed: *Evaluation of the Linearity of Quantitative Measurement Procedures*; Approved Guideline. Second Edition
- CLSI EP05-A3: *Evaluation of Precision of Quantitative Measurement Procedures*; Approved Guideline. Third Edition
- CLSI EP09c-A3: *Measurement Procedure Comparison and Bias Estimation Using Patient Samples*. Third Edition
- CLSI EP17-A2: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures*; Approved Guideline – Second Edition
- CLSI EP25-A: *Evaluation of Stability of In Vitro Diagnostic Reagents*; Approved Guideline
- CLSI EP28-A3c: *Defining, Establishing, and Verifying Reference Intervals in Clinical Laboratory*; Approved Guideline – Third Edition
- CLSI EP37, *Supplemental Tables for Interference Testing in Clinical Chemistry*. First Edition
- CLSI H21-A5, *Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays*; Approved Guideline – Fifth Edition

VI Performance Characteristics:

A Analytical Performance:

1. Precision/Reproducibility:

Precision (single site) studies and a reproducibility (multi-site) study were performed in accordance with the CLSI document EP05-A3 'Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline' – Third Edition.

a. Study 1: Repeatability (single site)

An internal precision study was carried out on 20 days, with two runs per day and two replicates of each sample per run (20 x 2 x 2) on one BCS XP System. The study investigated three different reagent lots in combination with one calibrator lot. In addition, three calibrator lots were investigated in combination with one reagent lot for a total of 240 determinations (i.e., 80 determinations per reagent or calibrator lot).

Five plasma pools (PP1–5) 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 VWF Ac (4 to 300% of norm) and the medical decision levels (30% of norm, 50% of norm). The results for within-run, between-lot and total imprecision are provided in the summary table below.

Table 1. Evaluation of 3 x 20 x 2 x 2 Precision Study at Single Site (Germany), investigation of reagent variability.

Sample	N	Mean (% of norm)	SD (% of norm), CV (%) *									
			Within-Run		Between-Run		Between-Day		Between-Reagent Lot		Total (combined reagent lots)	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
PP1	240	10.22	0.14	1.34	0.12	1.20	0.03	0.25	0.23	2.26	0.30	2.90
PP2	240	22.50	0.34	1.49	0.70	3.12	0.05	0.23	0.36	1.61	0.86	3.82
CPP	240	28.32	0.77	2.71	0.44	1.54	0.00	0.00	0.39	1.37	0.96	3.40
PP3	240	50.69	0.66	1.30	0.85	1.68	0.34	0.66	1.76	3.47	2.09	4.12
CPN	240	85.16	1.11	1.30	0.52	0.62	0.59	0.70	1.32	1.55	1.90	2.23
PP4	240	129.91	4.28	3.30	3.69	2.84	2.41	1.85	0.00	0.00	6.15	4.73
PP5	240	264.57	8.86	3.35	7.66	2.89	5.50	2.08	9.28	3.51	15.92	6.02

* SD: Standard Deviation; CV: Coefficient of Variation

Table 2. Evaluation of 3 x 20 x 2 x 2 Precision Study at Single Site (Germany), investigation of calibrator variability.

Sample	N	Mean (% of norm)	SD (% of norm), CV (%)									
			Within-Run		Between-Run		Between-Day		Between-Calibrator Lot		Total (combined calibrator lots)	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
PP1	240	10.22	0.14	1.39	0.14	1.40	0.00	0.00	0.23	2.20	0.30	2.95
PP2	240	22.50	0.42	1.80	0.78	3.34	0.20	0.84	0.96	4.13	1.32	5.67
CPP	240	28.32	0.39	1.37	0.32	1.10	0.00	0.00	0.82	2.84	0.96	3.34
PP3	240	50.69	0.81	1.57	1.03	1.99	0.00	0.00	0.94	1.82	1.62	3.12
CPN	240	85.16	1.10	1.31	0.61	0.72	0.47	0.55	1.33	1.57	1.89	2.24
PP4	240	129.91	2.39	1.81	3.07	2.32	2.31	1.75	5.30	4.02	6.97	5.28
PP5	240	264.57	8.86	3.35	7.66	2.89	5.50	2.08	9.28	3.51	15.92	6.02

b. Study 2: Reproducibility (multi-site)

The external reproducibility study was carried out at three external sites, on five days, with two runs per day and three replicates of each sample per run (3 x 5 x 2 x 3) for a total of 90 determinations (i.e., 30 determinations per site). All external sites performed the reproducibility study with the same reagent/calibrator lot combination.

Five plasma pools 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 VWF Ac (4 to 300% of norm) and the medical decision levels (30% of norm, 50% of norm). The results for within-run, between-laboratory and total imprecision are provided in the summary table below.

Table 3. Evaluation of 3x5x2x3 Reproducibility study for INNOVANCE VWF Ac on the BCS XP System; all sites combined.

Sample	N	Mean (% of norm)	SD (% of norm), CV (%)											
			Within-Run		Between-Run		Between-Day		Within-Site		Between-Site		Total (combined sites)	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
PP1	90	9.14	0.19	2.10	0.17	1.84	0.00	0.00	0.25	2.79	0.19	2.08	0.32	3.48
PP2	90	22.81	0.48	2.12	0.23	1.02	0.22	0.96	0.58	2.54	1.27	5.58	1.40	6.14
CPP	90	28.97	0.36	1.25	0.32	1.12	0.18	0.63	0.52	1.79	1.44	4.98	1.53	5.30
PP3	90	49.26	0.83	1.68	0.34	0.70	0.21	0.43	0.92	1.87	1.05	2.13	1.39	2.83
CPN	90	87.75	1.73	1.97	0.93	1.05	0.00	0.00	1.96	2.24	1.69	1.92	2.59	2.95
PP4	90	128.29	3.47	2.71	2.93	2.29	0.00	0.00	4.54	3.54	6.67	5.20	8.07	6.29
PP5	89	251.63	8.37	3.33	2.96	1.18	0.00	0.00	8.88	3.53	9.07	3.61	12.69	5.04

c. Study 3:

This study was conducted to evaluate instrument/operator variability at one internal site. This study was conducted on five days, with two runs per day and four replicates of each sample per run (5 x 2 x 4) on three BCS XP Systems for a total of 120 determinations (i.e., 40 determinations per instrument/operator combination). The study investigated one reagent/calibrator lot combination on all three BCS XP Systems.

Five plasma pools 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 VWF Ac (4 to 300% of norm) and the medical

decision levels (30% of norm, 50% of norm). The results for within-run, between-instrument/operator and total imprecision are provided in the summary table below.

Table 4. Evaluation of 3 x 5x 2 x 4 precision study for INNOVANCE VWF Ac on the BCS XP System; instrument/operator combined.

Sample	N	Mean (% of norm)	SD (% of norm), CV (%)									
			Within-Run		Between-Run		Between-Day		Between-Instrument/ operator		Total (combined instrument/operator)	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
PP1	120	9.50	0.44	4.60	0.15	1.57	0.00	0.00	0.34	3.53	0.57	6.01
PP2	120	22.92	0.41	1.77	0.43	1.89	0.00	0.00	0.46	2.01	0.75	3.28
CPP	120	28.78	0.33	1.16	0.22	0.77	0.13	0.46	0.71	2.46	0.82	2.86
PP3	120	49.20	0.78	1.59	0.91	1.85	0.50	1.03	1.40	2.85	1.91	3.89
CPN	120	83.58	1.00	1.20	0.82	0.98	0.23	0.28	2.99	3.58	3.27	3.91
PP4	120	125.25	1.98	1.58	2.96	2.37	0.00	0.00	5.09	4.06	6.21	4.96
PP5	120	226.09	3.54	1.57	2.13	0.94	2.22	0.98	7.25	3.21	8.64	3.82

2. Linearity:

Linearity studies were performed following the CLSI EP06 2nd Ed. guideline using three BCS XP Systems (each day with a different BCS XP system) with three lots of reagent (one lot per analyzer) on three days (one lot per day), one run per day, and four replicates of each sample (dilution). The dilution series was prepared by mixing a high concentration sample pool (high pool) with a low concentration sample pool (low pool). The high pool was prepared by spiking a normal plasma pool with a VWF concentrate. The low pool was prepared by dilution of the high pool with VWF deficient plasma. The VWF deficient plasma was internally produced by immunoaffinity chromatography.

Samples with 10 different concentrations were evaluated in the linearity study. Based on the results of the linearity studies, the claimed assay reportable range is 4 to 300% of norm on the BCS XP System.

Native sample linearity study:

An additional linearity study was performed using native samples following the CLSI EP06 2nd Ed. guideline using three BCS XP Systems (each day with a different BCS XP system) with three lots of reagent (one lot per analyzer) on three days (one lot per day), one run per day, and four replicates of each sample (dilution). The dilution series was prepared by mixing

a high concentration sample pool (high pool) with a low concentration sample pool (low pool). The high pool was prepared by using frozen aliquots from three native samples (from contract blood plasma provider) with high VWF levels. The low pool was prepared by dilution of the high pool with VWF deficient plasma. The VWF deficient plasma was internally produced by immunoaffinity chromatography.

Samples with 12 different concentrations were evaluated to establish the extended analytical measuring interval in addition to the analytical measuring interval (4 to 300 % of norm).

The native sample linearity study shows linearity of the assay is 4 to 300% of norm on the BCS XP System.

3. Analytical Specificity/Interference:

Interference studies were conducted based on the CLSI EP07 3rd edition guideline.

Endogenous Interference Study:

Dose-response experiments were carried out to determine the degree of interference as a function of the interferent concentration for following substances: Hemoglobin, unconjugated bilirubin, conjugated bilirubin, triglycerides (lipids), human anti-mouse antibodies and rheumatoid factors.

The interferent test concentrations were investigated regarding four different von Willebrand factor (VWF) activity levels: Low level (10 to 20% of norm), medical decision levels (30% of norm, 50% of norm), and high level (160 to 200% of norm). Each sample was prepared with native plasma and dilution with VWF deficient plasma or spiking with VWF concentrate, respectively. Control specimen (un-spiked with interference) and test specimen (spiked with interferent) were measured with INNOVANCE VWF Ac on the BCS XP System. The interference study was carried out with one BCS XP System and one INNOVANCE VWF Ac lot. Each VWF activity level was investigated with five test samples (1 to 5) with different interference levels. Each sample was tested in four replicates on one day with one lot of Standard Human Plasma as calibrator. This protocol results in 20 measurements per sample type and 80 measurements overall (all test sample types: Low, MDP 1, MDP 2 and High).

None of the substances in the following table (endogenous substances) were found to lead to clinically significant interference.

Interferent	**No interference up to:**
Hemoglobin	1000 mg/dL
Bilirubin (unconjugated)	60 mg/dL
Bilirubin (conjugated)	40 mg/dL
Triglycerides*	726 mg/dL
Rheumatoid Factors	438 IU/mL

* Evaluated with native lipemic samples.

The following statement will be included in the instructions for use (labeling) of the INNOVANCE VWF Ac assay kit:
"*Patient samples may contain heterophile antibodies [e.g. human anti-mouse antibodies (HAMA) or rheumatoid factors] that could react in antibody using assays to give a falsely elevated (observed more often) or depressed result. This assay has been designed to minimize interference from heterophile antibodies by addition of a blocking reagent. Nevertheless, complete elimination of such an interference from all patient specimens cannot be guaranteed. The diagnosis or exclusion of any type of VWD should therefore never be based solely on the INNOVANCE VWF Ac result.*"

Exogenous Interference Study

The studies regarding interfering substances (drug panel) were conducted to evaluate the potential interference of over-the-counter drugs and prescription drugs with the INNOVANCE VWF Ac assay on the BCS XP System. The interference study (drug panel) was carried out with one BCS XP System and one INNOVANCE VWF Ac lot. The interferent test concentrations were investigated with the following four von Willebrand factor (VWF) activity levels: low level (10 to 20% of norm), medical decision levels (MDP, 30% of norm, 50% of norm), and high level (160 to 200% of norm). Each sample was prepared with native plasma and dilution with VWF deficient plasma or spiking with VWF concentrate, respectively. Each VWF concentration (Low, MDP 1, MDP 2 and High) was investigated either as a test pool with spiked interferent or as a control pool without interferent added. With each of these samples, single determinations of four individual aliquots were performed on one day and with one calibrator. This protocol results in 32 measurements per interferent investigated.

None of the substances in the following table (exogenous substances/ drug panel) were found to lead to clinically significant interference.

Interferent	**No interference up to:**
Acetaminophen (Paracetamol)	156 µg/mL
Acetyl salicylic acid	30 µg/mL
Amitriptyline hydrochloride	550 ng/ml
Atorvastatin calcium salt trihydrate	812 ng/mL
Budesonide	6.3 ng/mL
Carbimazol	3.6 µg/ml
Ciprofloxacin	12 µg/mL
Cisplatin	33 µg/mL
Citalopram hydrobromide	6.8 µg/mL
Clopidogrel hydrogensulfate	24 ng/mL
Diclofenac sodium salt	26 µg/mL
Emicizumab	300 µg/mL
Estradiol	7.5 ng/mL
Ibuprofen sodium salt	240 µg/mL
Lenalidomide	2.13 µg/mL
Lisinopril dihydrate	268 ng/mL
L-Thyroxin	180 ng/mL
Metformin Hydrochloride	15.4 µg/mL

Pantoprazole sodium sesquihydrate	34 µg/mL
Progesterone	540 ng/mL
Ramipril	156 ng/mL
RFVIIa: NovoSeven® (Eptacog alfa activated)	4.5 µg/mL
RFVIII: ELOCTA® (Efmoroctocog alfa)	1.87 IU/mL
RFVIII: NovoEight® (Turoctocog alfa)	1.87 IU/mL
Tetracyclin	24 µg/mL
Theophylline	60 µg/mL
Thiouracil (2-Thiouracil)	15.9 µg/mL
Ticagrelor	108 µg/mL
Tranexamic Acid	162.9 µg/mL
Valproic Acid	318 µg/mL
Valsartan	11.7 µg/mL

4. High Dose Hook

The high dose hook study was performed on one BCS XP System with three lots of reagent and one lot of calibrator. Ten different dilution samples were prepared by diluting a high VWF Ac activity plasma pool (high pool) with VWF deficient plasma. The high pool was prepared by spiking a normal plasma pool with a VWF concentrate. The maximum VWF Ac activity investigated was ≥ 1000% of norm VWF activity. The high pool and the dilution series representing 10 different VWF Ac activities were measured randomized in six replicates.

Based on the results of the study, no high dose hook effect is observed up to a VWF activity of 656% of norm.

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

a. Traceability

The traceability study was performed on one BCS XP System with three lots of INNOVANCE VWF Ac reagent and three Standard Human Plasma (calibrator) lots. Three vials of the WHO 6th International Standard for Factor VIII / von Willebrand Factor were measured as samples in single determination on one day with one trained operator. With each INNOVANCE VWF Ac reagent lot, three calibration curves were established with the three Standard Human Plasma lots. The result shows that INNOVANCE VWF Ac results are traceable to the WHO 6th International Standard (IS) Factor VIII / Von Willebrand Factor (NIBSC code 07/316)

b. Value assignment

The study was conducted to describe the calibration concept / value assignment process of Standard Human Plasma (SHP) for use as the calibrator for the INNOVANCE VWF Ac assay. For the primary calibration, the testing is performed on three BCS XP Systems with three lots of INNOVANCE VWF Ac. With each reagent lot, a calibration curve

using the WHO 6th International Standard (WHO IS) is established [three curves per analyzer, nine curves in total]. For the secondary calibration, the testing is performed on three BCS XP Systems with three lots of INNOVANCE VWF Ac. With each reagent lot a calibration curve using the SHP in-house standard is established [three curves per analyzer, nine curves in total]. On each of the three analyzers, four aliquots (prepared by using two vials) of the SHP commercial lot to be calibrated are measured in single determination. The value of VWF (% of norm) for INNOVANCE VWF Ac is calculated as mean value of a total of 36 measurements.

The result shows that the calibration curve is stable to the reference value of WHO IS for VWF:GPIbM (87% of norm) when using Standard Human Plasma (SHP) for the in vitro quantitative determination of VWF-activity.

c. Expected Values – Controls

Control Plasma N (CPN) and Control Plasma P (CPP) are used as normal and pathologic control, respectively

d. Shelf-Life Stability

i. Shelf-Life Stability (Reagent)

The reagent shelf-life stability was evaluated in accordance with the CLSI document EP25-A '*Evaluation of Stability of In Vitro Diagnostic Calibrators; Approved Guideline*'. The study was conducted using three lots of INNOVANCE VWF Ac at the following time points: 0 (baseline), 3, 6, 9, 12 and 15 months. The study was performed with five plasma pools as well as three control materials covering the measuring interval (4 to 300% of norm) and medical decision points (MDP1 = 30% of norm, MDP2 = 50% of norm) of INNOVANCE VWF Ac assay. The INNOVANCE VWF Ac reagent were stored at 2–8°C at the start of the study and then withdrawn for testing at different time points throughout the study duration. Six to twelve replicates per sample were measured at each time point. The INNOVANCE VWF Ac assay is determined to be stable for a shelf-life of 12 months when stored at 2–8°C.

ii. Shelf-Life Stability (Calibrator)

The shelf-life stability of the Standard Human Plasma (SHP) was evaluated in accordance with the CLSI document EP25-A. The study was conducted by testing three lots of SHP at the following time points: 0 (baseline), 3, 6, 9, 12 and 15 months. The SHP is placed under the test storage conditions (2 to 8°C) at the start of the study and then withdrawn for testing at different time points throughout the study duration. Six to twelve replicates per sample were measured at each time point. The SHP is stable for a shelf-life of 12 months when stored at 2–8°C.

e. In-Use Stability

i. On-Board Stability (Reagent)

Classical on-board stability: Three lots of INNOVANCE VWF Ac reagents were used to evaluate classical on-board stability (18 to 32°C) at the following time points and covering the expected on-board stability duration: 0 (T0), 10, 24, 34 and 48 hours. Five plasma pools and three control materials covering the measuring interval (4 to 300% of norm) and medical decision points (MDP1 = 30% of norm, MDP2 = 50% of norm) of INNOVANCE VWF Ac assay were tested with six replicates at each time point.

Accumulated on-board stability: The accumulated on-board stability study is to investigate the reagent stability during use on the BCS XP System while being stored closed at 2°C to 8°C in a refrigerator. Three lots of INNOVANCE VWF Ac reagents and six plasma pools covering the measuring interval (4 to 300% of norm) and medical decision points (MDP1 = 30% of norm, MDP2 = 50% of norm) of INNOVANCE VWF Ac assay were used. The following time test points for reagents I and II were distributed over the expected accumulated on-board stability duration: 0 (T0), 6, 18, 36 and 42 hours, and for reagent III: 0 (T0), 3, 15, 30 and 42 hours. Six replicates were tested for each sample at each time point.

Result show that the INNOVANCE VWF Ac reagent is stable up to 36 hours when opened and maintained on-board at 18 to 32 °C. If the reagents are removed and stored closed at 2 to 8°C in between the measurement periods, the maximum accumulated on board stability is 24 hours for INNOVANCE VWF Ac reagents I and II and 36 hours for INNOVANCE VWF Ac reagent III.

ii. On-Board Stability (Calibrator)

The on-board stability study for calibrator was performed using three Standard Human Plasma (SHP, calibrator) lots representing different time points of the shelf-life. Six to ten replicates of SHP were tested at each time point: 0 (baseline), 2, 4, 6 and 7 hours. On-board stability for the calibrator was determined to be 6 hours (18 to 32°C). However, since the calibrators are intended to be used immediately, on-board stability of SHP is not recommended in the labeling.

iii. Once Opened Stability (Reagent)

The once opened (open vial) stability study was conducted by using three lots of INNOVANCE VWF Ac reagents. The INNOVANCE VWF Ac reagent that represents the entire shelf-life of the reagent were opened, stored for 30 minutes at 15 to 25°C, subsequently recapped and finally stored again at 2 to 8°C for the duration of the study. The following time points were tested: 0 (baseline), 2, 4, 6 weeks for Reagents I and II, and 0 (baseline), 6, 12, 18 weeks for Reagent III. Five plasma pools and three control materials covering the measuring interval (4 to 300% of norm) and medical decision points (MDP1 = 30% of norm, MDP2 = 50% of norm) of INNOVANCE VWF Ac assay were tested with six to twelve replicates at each time point. The INNOVANCE VWF Ac is determined to be stable for 37 days for Reagents I and II, and 113 days for Reagent III when stored open vial at 2–8°C.

iv. Reconstituted Stability of the Calibrator

Reconstituted stability was evaluated by using one lot of INNOVANCE VWF Ac, one lot of calibrator and two lots of Standard Human Plasma (SHP) as calibrators to be investigated. The following conditions and time points were tested: SHP lots were opened, left for 30 minutes at 15 to 25°C, recapped, subsequently stored at 15 to 25°C and finally measured after 4 and 5 hours; SHP lots were opened, left 30 minutes at 15 to 25°C, recapped, stored at ≤ -20°C for 4 and 5 weeks, thawed and measured; frozen SHP at ≤ -20 °C for a period of 4 weeks, after thawing, stored at 15 to 25°C for 2 and 3 hours before measurement. A reference value was established with non-stressed SHP by measuring three replicate determinations of four individual vials of SHP (n = 12). Testing sample SHP was tested with six to twelve replicates at each time point. The stability study result for SHP after reconstitution is determined to be 4 hours when stored at 15 to 25°C, 4 weeks when stored at -20°C and 2 hours at 15 to 25°C once frozen and thawed.

f. Ambient Temperature

The ambient temperature study was to investigate the influence of environmental temperature on test results of the INNOVANCE VWF Ac assay on the BCS XP System. The study was conducted with one BCS XP System, one reagent lot, one calibrator lot, by testing eight test samples covering the measuring interval (4 to 300% of norm) and medical decision points (MDP1 = 30% of norm, MDP2 = 50% of norm) of INNOVANCE VWF Ac assay. Each sample was tested in eight replicates on three days, with each day representing one ambient temperature (18, 22 or 32°C). Results demonstrate that the correctness of the measured results for INNOVANCE VWF Ac is assured within the operating temperature range of the BCS XP System (18°C to 32°C).

g. Transportation Study

The transportation stability study was conducted using one INNOVANCE VWF Ac assay lot and one Standard Human Plasma lot. The transportation conditions were as follows: (1) Ambient Routine (AR1): The products were stored for 36 hours at 30 ºC, then for 12 hours at 35 ºC and finally 4 hours at 45°C. (2) Ambient Routine (AR2): The products were stored for 48 hours at 25 ºC and then for 6 hours at 30 ºC. (3) Ambient Routine (AR3): The products were stored for 54 hours at 15 ºC to 25 °C (manufacturing temperature). (4) Three (3) subsequent one-day freeze/thaw cycles (F/T cycles): The products were frozen at -20 °C, then thawed at 2 to 8 °C and stored for one (1) day at 2 to 8 °C and then frozen again at – 20 °C. After above mentioned (1) to (4) transport simulations (temperature stressing actions) the products were again stored at the regular storage temperature of 2 °C to 8 °C. Five plasma pools as well as three control materials covering the measuring interval (4 to 300% of norm) and medical decision points (MDP1 = 30% of norm, MDP2 = 50% of norm) of INNOVANCE VWF Ac assay were tested in three to six replicates at each test condition. All measurements meet the predefined acceptance criteria for transportation stability for INNOVANCE VWF Ac as well as the calibrator, Standard Human Plasma.

h. Freeze/thaw tolerance Study

The freeze/thaw tolerance study was conducted to assure that the procedure of freezing and thawing does not significantly affect the outcome of the long-term stability studies for the reagent and calibrator. Three Standard Human Plasma lots and three INNOVANCE VWF Ac lots were evaluated. The Standard Human Plasma lots and the INNOVANCE VWF Ac lots were stored for at least one day at ≤ -74 °C. Five plasma pools as well as three control materials covering the respective measuring interval of INNOVANCE VWF Ac (4 to 300% of norm) and the medical decision points (MDPs, MDP1 = 30% of norm, MDP2 = 50% of norm) were used. For the freeze/thaw tolerance investigation of the calibrator, three Standard Human Plasma lots were measured in parallel as unstressed material (no freeze/thaw cycle) and as stressed material (one freeze/thaw cycle). For the freeze/thaw tolerance investigation of the reagent, three INNOVANCE VWF Ac lots were measured in parallel as unstressed material (no freeze/thaw cycle) and stressed material (one freeze/thaw cycle). Each sample was tested in three replicates at each condition. Result demonstrates the INNOVANCE VWF Ac assay kit is stable for one freeze/thaw cycle.

i. Sample Stability

i. Sample Stability

Sample stability study was conducted using one reagent lot INNOVANCE VWF Ac and one lot calibrator on one BCS XP System. A total of at least 20 samples were tested in quadruplicate. Each sample collected was measured in the primary cup and in the secondary cup within 4 hours after blood draw (time point: T0) for evaluation of the baseline value (unstressed sample). Samples were evaluated under the following storage conditions: 1) Storage at 15 to 25°C in 3.2% citrate blood collecting tubes (primary cups); plasma stored on cells; 2) Storage at 15 to 25 °C after transition from primary cups into secondary cups; plasma siphoned from cells; 3) Storage at ≤ -20°C in secondary cups; 4) Storage at ≤ -74 °C in secondary cups. In addition, sample stability for storage at 15 to 25°C of once frozen plasma samples, was investigated. The result from each time point was compared to the respective baseline result. Results demonstrate that samples are stable for 3 months at ≤ -20°C for centrifuged plasma removed from the cell suspension, 12 months at ≤ -74°C for centrifuged plasma removed from the cell suspension, 4 hours at 15–25°C for centrifuged plasma stored on the cell suspension (primary cups) and centrifuged plasma removed from the cell suspension (secondary cups) and 4 hours stability at 15 to 25 °C (once frozen at ≤ -20°C, secondary cups).

ii. Frozen versus Fresh Samples

The frozen versus fresh sample study was conducted to demonstrate equivalence between fresh and frozen citrated plasma samples. The study was conducted by using one INNOVANCE VWF Ac lot and one calibrator lot on one BCS XP system. Sixty fresh samples covering 80% of the AMI (4 to 300% of norm) were measured with one replicate on the BCS XP System within 4 hours after blood collection. One aliquot of each sample was stored for at least 7 days at ≤ -74°C.

The aliquots were thawed within 10 minutes at 37°C in a water bath, gently mixed and measured again within 2 hours after thawing. Results were analyzed using Passing-Bablok regression analysis and Bland-Altman plots. Results meet the predefined acceptance criteria and demonstrate the comparability between fresh and frozen samples.

6. Detection Limit:

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) for the test system were determined following the CLSI EP17-A2 guideline. Each study design included three reagent lots, two BCS XP Systems, one calibrator lot, one single determination of four to five individual aliquots of each sample on three to five days with one trained operator.

The LoB was determined using five-independent analyte-free samples prepared with three different VWF deficient plasmas and tested in four replicate measurements per sample on three different days on two different instruments for n=60 determinations per reagent lot per instrument. The LoB was determined to be 1.131% of norm.

The LoD was determined using five independent low-analyte samples prepared by dilution of a normal plasma pool with 80% to 120% of norm VWF activity. Dilution of the normal plasma pool to levels equal to approximately 1-fold, 2-fold, 3-fold, 4-fold, and 5-fold of the LoB value (1.131% of norm) was performed with VWF deficient plasmas. Each of the five plasma pools were tested in five replicates on five different days on two different instruments for n=50 determinations per sample. The LoD was determined to be 1.738% of norm.

The LoQ was determined using five independent low-analyte samples prepared by dilution of a normal plasma pool with 80% to 120% of norm VWF activity. Each of the five plasma pools were tested in four replicates on three different days on two different instruments for n=60 determinations per reagent lot per instrument. The LoQ was determined to be 3.72% of norm.

7. Normal Range and Assay Cut-Off:

Reference Interval

Reference interval studies for the two subgroups investigated (blood group O and non-O) were conducted at three clinical sites in the U.S. at different geographic locations to reflect the U.S. population. Citrated plasma samples were obtained from 302 apparently healthy individuals (150 blood group O and 152 blood group non-O) ≥ 18 years of age. At each site the plasma samples were measured with one INNOVANCE VWF Ac lot, one Standard Human Plasma lot, on one BCS XP System, in single determination. Results from all sites were pooled and all reference intervals were established by calculating two-sided 95% central interval (2.5th / 97.5th percentiles) as the 97.5th percentile was found within the measuring interval. The result for the generic VWF activity reference interval (pooled data of the multicenter study) is 50.7 to 203.5% of norm. The ABO blood group-specific reference intervals are: 49.0 to 178.9% of norm for blood group O and 60.7 to 214.1% of norm for Blood group non-O.

Descriptive statistics of the reference interval study of INNOVANCE VWF Ac on the BCS XP System pooled over all sites (n=3); the 95% central interval (2.5th to 97.5th percentile) is considered as reference interval.

ABO Blood Group	n	Unit	2.5th Percentile (95% confidence range)	97.5th Percentile (95% confidence range)
ABO blood groups combined	302	% of norm	50.7 (46.8, 57.5)	203.5 (189.1, 220.6)
Blood group O	150	% of norm	49.0 (42.9, 56.3)	178.9 (156.8, 196.9)
Blood group non-O	152	% of norm	60.7 (49.5, 72.3)	214.1 (200.8 – *)

* The upper 95% confidence limit for the 97.5th percentile cannot be stated for this subgroup, because corresponding to the sample size of n=152, the highest observation represents the upper limit of the 95% confidence range for the 97.5th percentile. The highest observation in this subgroup was above the measuring interval of INNOVANCE VWF Ac (> 300 % of norm).

The gender specific reference intervals are: 55.4 to 181.3% of norm for female and 48.8 to 210.7% of norm for male.

Descriptive statistics of the reference interval study of INNOVANCE VWF Ac on the BCS XP System pooled over all sites (n=3); specific analysis for females and males.

Gender	n	Unit	2.5th Percentile (95% confidence range)	97.5th Percentile (95% confidence range)
Gender combined	302	% of norm	50.7 (46.8, 57.5)	203.5 (189.1, 220.6)
Female	154	% of norm	55.4 (49.5, 61.6)	181.3 (164.7, 220.6)
Male	148	% of norm	48.8 (42.9, 57.1)	210.7 (199.0 – *)

* The upper 95% confidence limit for the 97.5th percentile cannot be stated for this subgroup, because corresponding to the sample size of n=148, the highest observation represents the upper limit of the 95% confidence range for the 97.5th percentile. The highest observation in this subgroup was above the measuring interval of INNOVANCE VWF Ac (> 300% of norm).

Measurements of VWF in healthy pediatric population

The VWF activity in healthy pediatric population study for the two subgroups investigated (blood group O and non-O) was conducted at two U.S. clinical sites. Citrated plasma samples were obtained from 85 apparently healthy pediatric individuals (44 blood group O and 41 blood group non-O) with > 4 weeks to < 18 years of age. At each site the plasma samples

were measured with one INNOVANCE VWF Ac lot, one Standard Human Plasma lot, on one BCS XP System, in single determination. Results from all 85 pediatric healthy subjects in the age range between > 4 weeks to < 18 years demonstrated values between 37.4 and > 300.0% of norm (78 out of 85 within the reference interval for individuals ≥ 18 years of age). A statement indicating that the outcome of the study is not to be used as a pediatric reference interval is provided in the labeling.

8. Carry-Over:

a. Sample Carryover

To evaluate whether a sample could cause contamination by being carried over into the subsequent test sample, two plasma pools with low VWF concentrations were investigated as acceptor samples (low analyte sample 1 and low analyte sample 2). The low analyte sample 1 was investigated using the BCS XP System's Medium-Setting (used for samples of > 20 to 150% of norm VWF activity) of the INNOVANCE VWF Ac test setting (no sample dilution is used). The low analyte sample 2 was investigated using the Low-Setting (used for samples of 4 to 20% of norm VWF activity) of the INNOVANCE VWF Ac test setting on the BCS XP System (higher volume of the sample is pipetted onto the reaction mixture). Both low analyte samples were prepared by diluting a normal plasma pool with VWF deficient plasma that was internally produced by immunoaffinity chromatography. A plasma pool with a high VWF concentration (high carryover test sample) was prepared by spiking a normal plasma pool with VWF concentrate and 1:4 dilution was carried out with dilution buffer when the target range of the donor test sample was beyond the measuring range interval (MRI). The study was conducted by using one reagent lot and one calibrator lot on one instrument. The study data shows that there is no carryover caused by one sample into another.

b. Reagent Carryover

To evaluate the accuracy bias from reagent carryover via the analyzer dispensers on the BCS XP System, the INNOVANCE VWF Ac carryover study was performed on one BCS XP System, with one respective reagent lot and one calibrator lot. To investigate INNOVANCE VWF Ac as acceptor assay, four different samples were determined to investigate the measuring interval adequately: A low sample (~10% of norm), a sample representing the medical decision level (~30% of norm), a normal plasma pool (~100% of norm) and a high pool (~170% of norm). When investigating the other assays (PT seconds with Dade Innovin, APTT with Dade Actin FSL, Antithrombin with INNOVANCE Antithrombin and D-dimer with INNOVANCE D-Dimer) as acceptor assays two different samples were determined— a normal sample and a pathologic sample. The reagent carryover study data shows that there is no cross-contamination caused by one application into another.

B. Clinical Studies:

1. Diagnostic Accuracy:

Method Comparison with the BC von Willebrand Assay

Method comparison studies were performed at four clinical laboratory sites located in the U.S. to compare the performance of the INNOVANCE VWF Ac assay with the BC von Willebrand Reagent (K972116) on the BCS XP System (K013114). The studies were performed with fresh and frozen samples (17 fresh samples, 124 frozen samples, 3 diluted samples, total N=144). To support the intended use population, patient samples with various demographics (i.e., race, gender, and age), were included in the study. The patient cohort included patients previously diagnosed with von Willebrand disease (VWD) (VWD type 1, VWD type 2 (type 2A, 2B, 2M and 2N), VWD type 3, and patients with acquired VWD), patients with hemophilia A, patient with platelet dysfunction and patients without final VWD related diagnosis at the time of enrollment. All samples were collected in 3.2% sodium citrate anticoagulant and tested in singlet with both methods (subject and comparator). Patient sample demographics included 103 females and 41 males, ≥ 6 months of age. Based on the inclusion and exclusion criteria for the method comparison, 140 patient samples were included into the study. From these, 102 (14 fresh samples, 88 frozen samples) were inside the measuring interval of the BC von Willebrand Reagent and the subject device and thus included in the statistical evaluation. Linear regression analyses were performed for the dataset collected for each site.

Passing-Bablok regression analysis was performed for all sites combined (results summarized below).

Site	N	Pearson Correlation Coefficient (r)	Coefficient of Determination (r^2)	Slope (95% confidence interval (CI))	Intercept (95% CI)
Combined Sites	102	0.916	0.839	1.037 (0.959, 1.137)	3.497 (-2.893, 8.257)

A summary of device performance at different medical decision points throughout the reportable range for the combined dataset is shown below.

Method Comparison, all sites combined	n	Slope	Intercept (% of norm)	Predicted bias at MDP1 (30% of norm)	Predicted bias at MDP2 (50% of norm)	Pearson correlation coefficient (r)
	102	1.04	3.50	4.60% of norm	10.14% (relative)	0.916

The observed predicted bias at the medical decision points for all sites combined met the predefined acceptance criteria. The result demonstrates that INNOVANCE VWF Ac shows acceptable comparability to the BC von Willebrand Reagent on the BCS XP System.

Method Comparison with HemosIL von Willebrand Assay

An additional method comparison evaluation between the INNOVANCE VWF Ac on the BCS XP System versus HemosIL VWF (K200033) on the ACL TOP 500 CTS (K160276)

was conducted. Test results from the INNOVANCE VWF activity test performed at four different clinical sites were compared with the results from the HemosIL VWF test performed at one external site (Duke University Health Systems). A total of 144 samples (17 fresh samples, 124 frozen samples, 3 diluted samples, total N=144) were included in this study. The patient cohort included patients previously diagnosed with VWD (VWD type 1, VWD type 2 (type 2A, 2B, 2M and 2N), VWD type 3, and patients with acquired VWD), patients with hemophilia A, patient with platelet dysfunction and patients without final VWD related diagnosis at the time of enrollment. A total of 97 samples were inside the measuring interval of both devices (19 – 300% of norm) and thus included in the statistical evaluation. Linear regression analyses were performed for the dataset collected for each site.

Passing-Bablok regression analysis was performed for all sites combined (results summarized below).

Site	N	Pearson Correlation Coefficient (r)	Coefficient of Determination (r^2)	Slope (95% CI)	Intercept (95% CI)
Combined Sites	97	0.971	0.943	0.955 (0.89, 1.02)	-0.552 (-4.83, 3.84)

A summary of device performance at different medical decision points throughout the reportable range for the combined dataset is shown below.

Method Comparison, all sites combined	n	Slope	Intercept (% of norm)	Predicted bias at MDP1 (30% of norm)	Predicted bias at MDP2 (50% of norm)	Pearson correlation coefficient (r)
	97	0.96	-0.55	-1.90% of norm	-5.76% (relative)	0.971

The observed predicted bias at the medical decision points for all sites combined met the predefined acceptance criteria. The result demonstrates that INNOVANCE VWF Ac on the BCS XP System shows acceptable comparability to the HemosIL VWF on the ACL TOP 500 CTS.

Method Comparison Study (Patzke et al. (2014) data re-analysis)

The method comparison study INNOVANCE VWF Ac versus BC von Willebrand Reagent on the BCS XP System presented in Patzke et al. (2014) was performed at three clinical sites (Germany, Switzerland and USA). A total of 618 samples were included in the method comparison study, and n=580 samples (n=29 diluted samples, no spiked samples) were included in the statistical evaluation. The patient cohort included patients previously diagnosed with VWD (VWD type 1, VWD type 2 (type 2A, 2B, 2M and 2N), and patients with acquired VWD), patients before or after treatment with DDAVP (Desmopressin) and patients without final VWD related diagnosis at the time of enrollment. The statistical evaluation of the method comparison INNOVANCE VWF Ac versus BC von Willebrand Reagent on the BCS XP System (Passing-Bablok regression analysis) presented in Patzke et

al. (2014) included all samples with results found within the AMI for INNOVANCE VWF Ac (AMI outside the U.S. = 4 to 600% of norm) and within the AMI for BC von Willebrand Reagent (AMI outside the U.S. = 10 to 600% of norm). Linear regression analyses were performed for the dataset collected for each site.

Passing-Bablok regression of Method Comparison INNOVANCE VWF Ac versus BC von Willebrand Reagent on the BCS XP for samples with INNOVANCE VWF Ac results from 20 to 150% of norm.

Site	N	Pearson Correlation Coefficient (r)	Coefficient of Determination (r^2)	Slope (95% CI)	Intercept (95% CI)
Combined Sites	417	0.972	0.944	0.954 (0.936, 0.974)	2.505 (1.147, 3.558)

A summary of device performance at different medical decision points throughout the reportable range for the combined dataset is shown below.

Method Comparison, all sites combined	n	Slope	Intercept (% of norm)	Predicted bias at MDP1 (30% of norm)	Predicted bias at MDP2 (50% of norm)	Pearson correlation coefficient (r)
	417	0.97	2.51	1.14% of norm	0.45% (relative)	0.972

Passing-Bablok regression of Method Comparison INNOVANCE VWF Ac versus BC von Willebrand Reagent on the BCS XP for samples with INNOVANCE VWF Ac results from 4 to 300% of norm.

Site	N	Pearson Correlation Coefficient (r)	Coefficient of Determination (r^2)	Slope (95% CI)	Intercept (95% CI)
Combined Sites	556	0.985	0.970	0.955 (0.940, 0.971)	1.110 (0.349, 2.018)

A summary of device performance at different medical decision point throughout the reportable range for the combined dataset is shown below.

Method Comparison, all sites combined	n	Slope	Intercept (% of norm)	Predicted bias at MDP1 (30% of norm)	Predicted bias at MDP2 (50% of norm)	Pearson correlation coefficient (r)
	556	0.96	1.11	-0.23% of norm	-2.26% (relative)	0.985

The results demonstrate that the additional evaluations of the method comparison INNOVANCE VWF Ac versus BC von Willebrand Reagent on the BCX XP System (for the

ranges from 20 to 150% of norm and 4 to 300% of norm) confirm the acceptable comparability between the devices shown in the publication of Patzke et al. (2014) for the entire U.S. AMI (4 to 300% of norm).

2. Diagnostic Concordance:

The diagnostic concordance study was conducted to compare the use of the subject device instead of using the study site specific standard of care (SOC) VWF-activity assay within the initial evaluation of VWF disorders. A total of 138 patients were included in the diagnostic concordance study of which 108 patients were tested by Beckman Coulter von Willebrand Reagent as the SOC VWF activity assay at three sites, and 30 patients were tested by HemosIL VWF Activity Reagent as its SOC VWF activity assay at one site. This initial evaluation is most commonly accomplished using the following assays (NIH Publication No 08-5832): VWF antigen (VWF:Ag), VWF activity and coagulation factor VIII (FVIII) activity (called 'initial VWD testing panel'). The overall percent agreement, the positive percent agreement (PPA: any type of VWD) and the negative percent agreement (NPA: VWD excluded) with 95% Confidence Limits were calculated.

Diagnostic Concordance: Percent Agreements and 95% Confidence Limits.

Agreement Measures	Agreement (%)	Lower Limit of 95% Score Confidence Interval	Upper Limit of 95% Score Confidence Interval
Positive Percent Agreement 'any type'	74.29	57.93	85.84
Positive Percent Agreement 'low' VWF	52.63	31.71	72.67
Negative Percent Agreement 'VWD excluded'	95.77	88.30	98.55
Overall Percent Agreement	83.33	76.23	88.63

An overall percentage agreement of more than 80% between the INNOVANCE VWF Ac and the SOC activity assays was found. This result demonstrates that for the majority of patients (> 80%), use of the subject device instead of currently available assays to measure VWF activity will not alter diagnosis.

3. Real-world evidence

A comprehensive review of published scientific literature describing studies evaluating the subject device is presented in this De Novo classification request to provide real-world evidence (RWE) from literature. The original publications (no reviews) include method comparison data between INNOVANCE VWF Ac and other VWF activity assays performed by independent research or clinical organizations. The real-world evidence further demonstrates the safety and effectiveness of the new device INNOVANCE VWF Ac.

VII Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

VIII Identified Risks and Mitigations:

Identified Risks to Health	Mitigation Measures
Falsely elevated von Willebrand factor (VWF) activity results may lead to delayed diagnosis and delayed patient management of von Willebrand disease (VWD). Patients with delayed diagnosis and resulting delayed patient management of VWD are at increased risk of bleeding due to the withholding of appropriate treatment.	Certain design verification and validation identified in special control (1), including documentation of certain analytical studies and clinical studies. Certain labeling information identified in special control (2), including limitations and performance information identified in special control (1).
Falsely depressed von Willebrand factor (VWF) activity results may lead the physician to suspect von Willebrand disease (VWD) in patients who do not have the disease. As a result, the patients may receive unnecessary follow-up testing and unnecessary treatment as well as delays in receiving a correct diagnosis and appropriate patient management. In addition, affected patients may experience mental anxiety because of the erroneous diagnosis.	Certain design verification and validation identified in special control (1), including documentation of certain analytical studies and clinical studies. Certain labeling information identified in special control (2), including limitations and performance information identified in special control (1).
No results may lead to delayed patient management.	Certain design verification and validation identified in special control (1), including documentation of certain analytical studies and clinical studies. Certain labeling information identified in special control (2), including limitations and performance information identified in special control (1).

IX Benefit/Risk Assessment:

A Summary of the Assessment of Benefit:

The INNOVANCE® VWF Ac assay is intended for the quantitative determination of the von Willebrand factor-GPIb-binding activity in patients with suspected or confirmed von Willebrand factor disorders. It is an automated, particle enhanced turbidimetric assay that measures the binding between VWF and gain-of-function mutants of platelet receptor GPIb. The reagents do

not contain ristocetin and platelets, which may affect assay performance due to sourcing variability.

The performance characteristics of the assay are evaluated in analytical studies. In single site internal precision study, the total within-site CVs range from 1.54 to 7.24%. In external multi-center reproducibility study, the total CVs for combined sites range from 2.83 to 6.29%. The CVs for both precision and reproducibility studies meet the predefined acceptance criteria. Although samples around medical decision levels and within normal range are contrived, the sponsor has provided line data and results demonstrating comparability between contrived samples (spiked plasma pool) and native patient samples.

The performance characteristics of the assay are also evaluated in clinical validation studies. In the comparison study between INNOVANCE® VWF Ac assay and BC von Willebrand Reagent, Passing-Bablok evaluation of pooled data (all site combined) show that slope, intercept, predicted bias at medical decision points and Pearson correlation coefficient meet the predefined acceptance criteria. However, samples at individual sites do not adequately cover the AMI. To address the Agency's concern and provide additional comparison data, the sponsor reanalyzed the line data from a published study that compared INNOVANCE® VWF Ac assay to BC von Willebrand Reagent with an additional 580 samples. Passing-Bablok analysis of the additional data shows acceptable performance.

The diagnostic concordance between the INNOVANCE® VWF Ac assay and site-specific standard of care assay is evaluated and shows an overall percent agreement of 83.3% and a negative percent agreement of 95.8%. For low VWF, the positive percent agreement (PPA) is 52.6%. The sponsor has provided benefit risk analysis and clinical justifications for the acceptability of the PPA at low VWF.

Data from above studies show favorable analytical and clinical performance for the proposed indications for use.

B Summary of the Assessment of Risk:

Falsely elevated VWF activity results may lead to delayed diagnosis and treatment of von Willebrand disease (VWD). The patients are at increased risk for bleeding because of the potential delayed appropriate treatment. Falsely depressed VWF activity results may lead the physician to suspect VWD in patients who do not have the disease. As a result, the patients may receive unnecessary follow-up testing and possibly unnecessary treatment as well as delays in receiving a correct diagnosis and appropriate patient management. In addition, the patients may experience unnecessary anxiety because of the erroneous diagnosis. Failed results may cause delayed diagnosis of VWD. Further, no results may lead to delayed patient management.

C Patient Perspectives:

This submission did not include specific information on patient perspectives for this device.

D Summary of the Assessment of Benefit-Risk:

The proposed special controls include requiring device labeling include a statement that results should be used in conjunction with the patient's medical history, clinical presentation, and other laboratory findings. Device labeling addresses the risk of interference (including endogenous and exogeneous substances, HAMA and RF) and includes information on the possibility of failed results possibly caused by interference. Device labeling also contains information on expected values (results of reference interval studies) and characteristics of analytical and clinical performance. Given the performance characteristics, applicable general controls and proposed special controls, including labeling mitigations, the probable benefits outweigh the probable risks of this device.

X Conclusion:

The De Novo request is granted and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code(s): QTY
Device Type: Von Willebrand factor assay
Class: II
Regulation: 21 CFR 864.7293