



**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY**

I Background Information:

A 510(k) Number

K242952

B Applicant

Siemens Healthcare Diagnostic Products GmbH

C Proprietary and Established Names

INNOVANCE Antithrombin

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JBQ	Class II	21 CFR 864.7060 - Antithrombin III Assay	HE - Hematology

II Submission/Device Overview:

A Purpose for Submission:

Expansion of the indications for use

B Measurand:

Antithrombin Activity (%)

C Type of Test:

Quantitative chromogenic test

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

INNOVANCE Antithrombin is a chromogenic assay for the automated quantitation of functionally active antithrombin in human citrated plasma and can be used as an aid in the diagnosis of antithrombin deficiency.

INNOVANCE Antithrombin is indicated as an aid in monitoring antithrombin activity to support QFILTIA (fitusiran) dosing in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Expanded indications for use only on Siemens BCS XP System

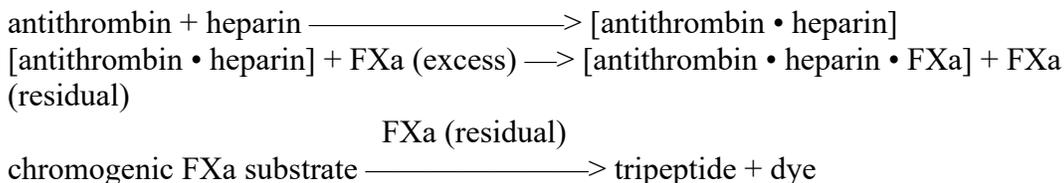
IV Device/System Characteristics:

A Device Description:

INNOVANCE Antithrombin is a chromogenic assay kit containing three reagents used for the determination of antithrombin activity. The reagents are in liquid form and are composed of human Factor Xa, bovine serum albumin, heparin, hirudin, aprotinin and preservatives, chromogenic substrate, and buffer.

B Principle of Operation:

The INNOVANCE Antithrombin assay utilizes a chromogenic measuring principle. An excess of human factor Xa is added to citrated plasma. In the presence of heparin, a portion of the enzyme is complexed and inactivated by the antithrombin present in the sample. Excess, uninhibited factor Xa then cleaves a specific chromogenic substrate, causing the release of a dye. The rate of the substrate cleavage is determined by the increase in the absorbance value at 405 nm.



The release of dye is inversely proportional to the inhibiting activity of antithrombin in the plasma sample, i.e., the smaller the concentration of functionally active antithrombin, the higher the absorbance signal per time unit.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Berichrom Antithrombin III (A)

B Predicate 510(k) Number(s):
K933125

C Comparison with Predicate(s):

Device & Predicate Device(s):	<u>K242952</u>	<u>K933125</u>
Device Trade Name	INNOVANCE Antithrombin	Berichrom Antithrombin III (A)
General Device Characteristic Similarities		
Intended Use/Indications For Use	<p>INNOVANCE Antithrombin is a chromogenic assay for the automated quantitation of functionally active antithrombin in human citrated plasma and can be used as an aid in the diagnosis of antithrombin deficiency.</p> <p>INNOVANCE Antithrombin is indicated as an aid in monitoring AT activity to support QFITLIA (fitusiran) dosing in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.</p>	<p>Berichrom Antithrombin III (A) is intended for the determination of the functional activity of antithrombin III in plasma for the diagnosis of diminished ATIII synthesis, increased consumption and for monitoring substitution therapy.</p>
Sample Type	Human citrated plasma	Same
Analyte	Antithrombin III	Same
Reporting Units	% of the norm	Same
General Device Characteristic Differences		
Test Methodology	Chromogenic substrate, human Factor Xa	Kinetic test, thrombin-specific substrate
Test Platform	BCS XP System	Siemens CA
Reagent Composition	Liquid	Lyophilized

Device & Predicate Device(s):	<u>K242952</u>	<u>K933125</u>
Therapy	QFITLIA (fitusiran)	Substitution Therapy

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition.*

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

CLSI EP17: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures, Second Edition*

CLSI EP39: *A Hierarchical Approach to Selecting Surrogate Samples for the Evaluation of In Vitro Medical Laboratory Tests, First Edition.*

VII Performance Characteristics:

Analytical Performance:

1. Precision/Reproducibility:

Refer to K081769 for the original Precision Study report.

A single-site repeatability study and a multi-site reproducibility study were performed in accordance with the CLSI EP05-A3 ‘Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition’ to characterize precision performance in the lower end of the measuring range for INNOVANCE Antithrombin on the BCS XP System. Whole blood samples collected from patients on fitusiran were processed to create citrated plasma pools at two concentrations near the medical decision points (i.e., 10% and 15% antithrombin activity).

The single-site precision study was carried out on one BCS XP System over twenty days, by three operators, with two runs per day, two replicates per run, in combination with three reagent lots and one calibrator lot. All results are within the acceptable limits.

Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Lot		Between Operator		Total	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
10% Pool	240	9.75	1.36	13.94	0.79	8.06	0.24	2.42	0.09	0.97	0.0	0.0	1.59	16.31
15% Pool	240	15.73	1.38	8.77	0.48	3.08	0.40	2.57	0.39	2.45	0.0	0.0	1.57	9.95

The reproducibility study was performed on three BCS XP analyzers, one per site, one operator per site, using one reagent lot with three replicates in combination with one standard lot and one control lot with two runs per day over five days. All results are within the acceptable limits.

Reproducibility Study Results												
Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
10% Pool	90	11.05	0.81	7.31	1.56	14.16	0.00	0.00	1.30	11.79	2.19	19.82
15% Pool	90	15.54	0.92	5.93	0.12	0.75	0.31	2.02	0.97	6.21	1.38	8.85

2. Linearity:

Refer to K081769.

3. Analytical Specificity/Interference:

Refer to K081769 for the original Interference Study report.

Analytical specificity testing was performed using potential exogenous interferents specific to patients with hemophilia A or B with or without factor VIII or IX inhibitors. Citrated plasma samples were pooled to assess the interference at the medical decision point for fitusiran dosing schematic around 15% antithrombin activity (low plasma pool) and around the normal range of antithrombin activity between 90–100% (high plasma pool). For both low and high plasma pools, control samples were spiked with solvent and test samples were spiked with each potential interferent, tested in replicates of eight, and the differences of the mean measured antithrombin activity was calculated. The test results are summarized in the table below.

Interferent	Highest Concentration without Interference
Desmopressin	0.0144 µg/mL
Tranexamic Acid	0.48 mg/mL
Recombinant Factor VIIa	2.16 µg/mL
Coagulation Factor VIII	0.96 IU/mL
Coagulation Factor IX	1.44 IU/mL
activated Prothrombin Complex Concentrate (aPCC)	2.4 IU/mL

4. Assay Reportable Range:

The assay reportable range is 7.32–127.9% antithrombin activity.

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

Refer to K081769.

6. Detection Limit:

Refer to K081769 for Limit of Blank and Limit of Detection studies.

The limit of quantitation (LoQ) was determined according to the CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition. Plasma samples with concentrations ranging from approximately 6–10% of antithrombin activity were prepared. Four replicates per sample were run once per day for three days using two INNOVANCE Antithrombin reagent lots on one BCS XP System totaling in n=120 determinations. The LoQ estimates were evaluated separately for each reagent lot. The LoQ is defined as 7.32% of antithrombin activity.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Refer to K081769.

2. Matrix Comparison:

Refer to K081769.

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

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

The safety and effectiveness of the INNOVANCE Antithrombin assay as an aid in monitoring patients on QFITLIA was demonstrated in the ATLAS-OLE study (NCT03754790), an open-label, long-term safety and efficacy study. A total of 227 patients in ATLAS-OLE rolled over from two clinical studies (ATLAS-INH, NCT03417102 and ATLAS A/B, NCT03417245) and ATLAS-PPX. The ATLAS-INH enrolled adult and pediatric males (aged ≥ 12 years) with hemophilia A or B with inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX), who previously received on-demand (episodic) treatment with bypassing agents (BPAs) for bleeding. The ATLAS A/B study enrolled adult and pediatric males (aged ≥ 12 years) with hemophilia A or B without inhibitory antibodies to FVIII or FIX, who previously received on-demand (episodic) treatment with clotting factor concentrate (CFC) for bleeding. The ATLAS-PPX study is a crossover study in patients previously on CFC or BPA prophylaxis, and were treated with QFITLIA in a multicenter study which was initiated as an open-label extension study to evaluate the long-term safety

and efficacy of QFITLIA in adult and pediatric males aged ≥ 12 years with hemophilia A or B, with or without inhibitory antibodies to FVIII or FIX.

Dosing in the clinical studies ATLAS-INH and ATLAS-A/B was initiated with QFITLIA at fixed dose of 80 mg monthly. To mitigate the risk of thrombotic events, an AT-DR (antithrombin-based dose regimen) with the target AT activity range of 15–35% was implemented in ATLAS-OLE. The AT-DR was initiated when studies ATLAS-INH and ATLAS-A/B were nearly completed and therefore the efficacy of QFITLIA AT-DR treatment was assessed by comparing the QFITLIA AT-DR treatment data from the long-term extension study ATLAS-OLE to the control data from studies ATLAS-INH and ATLAS-A/B.

A total of 213 patients were subsequently transitioned to an AT-DR with the target AT activity range of 15–35%. In the AT-DR, the QFITLIA starting dose was 50 mg every two months, and dosing was individually adjusted based on AT activity level using the INNOVANCE Antithrombin assay. The dose could be increased to 50 mg every month or 80 mg every month, or decreased to 20 mg every two months or 20 mg every month, or treatment discontinued if AT activity $< 15\%$ at the lowest dose. No patients required escalation to 80 mg every month to achieve the target AT range. The dose required to maintain AT activity 15–35% in patients who initiated dosing on 50 mg every two months was as follows: 35.8% received 50 mg every two months, 15.7% received 50 mg every month, 30.9% received 20 mg every two months, 2.9% received 20 mg every month, and 14.7% discontinued due to more than one AT activity $< 15\%$.

Efficacy of QFITLIA was evaluated for a duration of 7 months (primary efficacy period) following a 6-month dose adjustment period. Median observed annualized bleeding rate (IQR) for treated bleeds was 3.7 (0.0; 7.5) overall, 1.9 (0.0; 5.6) in inhibitor patients and 3.8 (0.0; 11.2) in non-inhibitor patients. The results from the study support the expanded intended use of the INNOVANCE Antithrombin assay in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without FVIII or FIX inhibitors treated with QFITLIA.

Table 1: Annualized Bleed Rate for Treated Bleeds with QFITLIA Prophylaxis versus On-Demand BPA in Patients ≥ 12 Years of Age with Inhibitors

Endpoint	QFITLIA AT-DR	On-Demand BPA
All Treated Bleeds		
ABR (95% CI)*	5.14 (2.78, 9.52)	19.12 (11.80, 30.98)
% reduction	73%	
p-value	p=0.0006	
Treated Spontaneous Bleeds		
ABR (95% CI)*	3.11 (1.78, 5.43)	17.09 (9.87, 29.60)
% reduction	82%	
p-value	< 0.0001	
Treated Joint Bleeds		
ABR (95% CI)*	3.95 (2.50, 6.24)	14.41 (8.98, 23.15)
% reduction	73%	
p-value	p=0.0001	

Table 2: Annualized Bleed Rate for Treated Bleeds with QFITLIA Prophylaxis versus On-Demand CFC in Patients ≥ 12 Years of Age without Inhibitors

Endpoint	QFITLIA AT-DR	On-Demand CFC
All Treated Bleeds		
ABR (95% CI)*	9.01 (5.59, 14.54)	31.42 (20.48, 48.21)
% reduction	71%	
p-value	p<0.0001	
Treated Spontaneous Bleeds		
ABR (95% CI)*	5.40 (3.65, 7.97)	20.99 (13.95, 31.59)
% reduction	74%	
p-value	p<0.0001	
Treated Joint Bleeds		
ABR (95% CI)*	6.18 (4.18, 9.15)	21.56 (14.56, 31.93)
% reduction	71%	
p-value	p<0.0001	

ABR = annualized bleed rate; AT-DR = AT-Dosing Regimen; CFC = clotting factor concentrate; CI = confidence interval.

* Based on negative binomial regression model.

D Clinical Cut-Off:

Not Applicable.

E Expected Values/Reference Range:

Refer to K081769.

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.