

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

A. 510(k) Number:

K092693

B. Purpose for Submission:

Substantial equivalence determination for a new device

C. Measurand:

IgG antibodies to *Borrelia burgdorferi*

D. Type of Test:

Western blot test

E. Applicant:

Viramed Biotech AG

F. Proprietary and Established Names:

Borrelia B31 IgG *ViraStripe*[®]

G. Regulatory Information:

1. Regulation section:

21 CFR 866. 3830, Treponema pallidum treponemal test reagents

2. Classification:

Class: II

3. Product code:

LSR; Reagent, Borrelia Serological Reagent

4. Panel:

83- Microbiology

H. Intended Use:

1. Intended use(s):

The Viramed Biotech AG Borrelia B31 IgG ViraStripe® is an in vitro qualitative assay for the detection of IgG antibodies to *Borrelia burgdorferi* in human serum. It is intended for use in the testing of human serum samples which have been found positive or equivocal using an EIA or IFA test procedure for *B. burgdorferi* antibodies. Positive results from this line blot assay are supportive evidence of infection with *B. burgdorferi*, the causative agent for Lyme disease. The Viramed Biotech AG Borrelia B31 IgG ViraStripe® can be used anytime after onset provided the EIA or IFA are positive or equivocal. It should also be used for follow-up when: 1) Only IgM antibodies were found positive in a line blot assay or Western blot, 2) IgG antibodies were found by line blot or Western blot but were not considered significant by the CDC criteria for a positive IgG Western blot, 3) previously tested sero-negative individuals are shown to develop antibodies by an EIA or IFA test.

2. Indication(s) for use:

The Viramed Biotech AG Borrelia B31 IgG ViraStripe® is an in vitro qualitative assay for the detection of IgG antibodies to *Borrelia burgdorferi* in human serum. It is intended for use in the testing of human serum samples which have been found positive or equivocal using an EIA or IFA test procedure for *B. burgdorferi* antibodies. Positive results from this line blot assay are supportive evidence of infection with *B. burgdorferi*, the causative agent for Lyme disease. The Viramed Biotech AG Borrelia B31 IgG ViraStripe® can be used anytime after onset provided the EIA or IFA are positive or equivocal. It should also be used for follow-up when: 1) Only IgM antibodies were found positive in an line blot assay or Western blot, 2) IgG antibodies were found by line blot or Western blot but were not considered significant by the CDC criteria for a positive IgG Western blot, 3) previously tested sero-negative individuals are shown to develop antibodies by an EIA or IFA test.

3. Special conditions for use statement(s):

For prescription use

4. Special instrument requirements:

None

I. Device Description:

This is a line blot assay to detect IgG to individual *B. burgdorferi* antigens. *B. burgdorferi* antigens from a B31 passage tick strain are purified by

electrophoretic and chromatographic methodologies and line striped on a nitrocellulose membrane. *B. burgdorferi* antigens are bound and fixed to the solid phase nitrocellulose membrane. The membrane is blocked, dried and cut into individual test strips.

For each test to be performed, the line blot strip and diluted test serum is added to a line blot strip well. If specific antibodies that recognize an antigen are present, they will bind to the specific antigens on the strip. After incubation the line blot strip is washed to remove unbound antibodies. Alkaline-phosphatase anti-human IgG conjugate is then added to each strip and incubated. If antibody is present, the conjugate will bind to the antibody attached to the specific antigens. The strip is washed to remove unbound conjugate and the substrate solution is added. If the enzyme/antibody complex is present, the substrate will undergo a precipitation and color change. After an incubation period, the reaction is stopped and the presence of precipitated substrate is visualized at specific locations on the strip. The presence of a colored precipitation at various locations on the line blot strip is an indirect measurement of *Borrelia burgdorferi* specific antibodies in the patient specimen. A uniform band locator is given on the evaluation protocol and used to locate and identify specific *Borrelia burgdorferi* B31 antibodies on the line blot test strip. Every strip has an integrated control system including function control and conjugate control. Visualized bands from the reaction are compared for intensity with a separate strip containing the Cut-off control band for evaluation. Any band found having a visual intensity equal to or greater than the Cut-off control band intensity is considered as a significant band.

Positivity: The criteria for a positive Western blot result defined by the CDC are followed. For *B. burgdorferi* IgG positivity, the blot should be positive for at least 5 of 10 bands: 93, 66, 58, 45, 41, 39, 30, 28, 23, and 18kDa

J. Substantial Equivalence Information:

1. Predicate device name(s):

Viramed Biotech AG Borrelia B31 IgG ViraBlot

2. Predicate 510(k) number(s):

K051071

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The Viramed Biotech AG Borrelia B31 IgG ViraStripe® is an in vitro qualitative assay for the detection of IgG antibodies to Borrelia burgdorferi in human serum. It is intended for use in the testing of human serum samples which have been found positive or equivocal using an EIA or IFA test procedure for <i>B. burgdorferi</i> antibodies.	The Viramed Biotech Borrelia B31 IgG ViraBlot® is an in vitro qualitative assay for the detection of IgG antibodies to Borrelia burgdorferi in human serum. It is intended for use in the testing of human serum samples which have been found positive or equivocal using an EIA or IFA test procedure for <i>B. burgdorferi</i> antibodies.
Assay	Western blot	Western blot
Specimen Type	Serum	Serum
Procedure	Qualitative; <i>B. burgdorferi</i> IgG antibodies to specific protein bands	Qualitative; <i>B. burgdorferi</i> IgG antibodies to specific protein bands.
Differences		
Item	Device	Predicate
Protein antigens	Blot with purified proteins (line blot)	Blot with proteins separated by electrophoresis

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition and CLSI M34-A, Western Blot Assay for Antibodies to *Borrelia burgdorferi*, Approved Guidance

L. Test Principle:

Western blot

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Eight serum samples (low negative, high negative, low positive and

moderate positive) were tested in duplicate over 5 working days (twice) by separate technicians at a single site (Viramed Biotech AG) using one lot. The serum panel specimens were selected to represent negative to high-positive immune-reactivity levels. For this study, two different readers within the three different laboratories assessed the band identification for each sample on the same blot. There was identical testing of all bands by each reporter for each sample.

Study Summary	Day 1- 5				All Technicians Agreement
	Tech 1		Tech 2		
Sample ID	Rep 1	Rep 2	Rep 1	Rep 2	
Low negative	-	-	-	-	100%
High negative (1)	41, 23, 18	41, 23, 18	41, 23, 18	41, 23, 18	100%
High negative (2)	41, 23, 18	41, 23, 18	41, 23, 18	41, 23, 18	100%
Low Positive (1)	66, 41, 39, 28, 23, 18	66, 41, 39, 28, 23, 18	66, 41, 39, 28, 23, 18	66, 41, 39, 28, 23, 18	100%
Low Positive (2)	93, 45, 41, 28, 18	93,45,41,28,18	93,45,41,28,18	93,45,41,28,18	100%
Low Positive (3)	66, 58, 45, 41, 39, 23, 18	66, 58, 45, 41, 39, 23, 18	66, 58, 45, 41, 39, 23, 18	66, 58, 45, 41, 39, 23, 18	100%
Moderate Positive (1)	93, 66, 58, 45, 41, 39, 30, 28, 23, 18	93, 66, 58, 45, 41, 39, 30, 28, 23, 18	93, 66, 58, 45, 41, 39, 30, 28, 23, 18	93, 66, 58, 45, 41, 39, 30, 28, 23, 18	100%
Moderate Positive (2)	93, 66, 58, 41, 39, 30, 28, 18	93, 66, 58, 41, 39, 30, 28, 18	93, 66, 58, 41, 39, 30, 28, 18	93, 66, 58, 41, 39, 30, 28, 18	100%

The Precision/Reproducibility study was satisfactory for this type of assay.

b. Linearity/assay reportable range:

Not applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Not applicable

d. Detection limit:

Not applicable

e. Analytical specificity:

CROSS REACTIVITY

Seventy-five sera determined to contain antibodies to other infectious disease

agents were tested. Cross-reactivity data for *Ehrlichia chafeensis* and *Babesia microti* may represent an actual co-infection with *B. burgdorferi*. All three tick borne organisms have been found to reside in the geographic location where the 12 clinical specimens were obtained. Both of the specimens found positive by the Borrelia B31 IgG ViraStripe[®] were also found to be positive in a commercially available Lyme Western blot test system.

The proposed insert includes the following, which is slightly altered from the text of the submission: “Seventy-five sera determined to contain antibodies to other infectious disease agents are presented in Table 8. Cross-reactivity data for *Ehrlichia chafeensis* and *Babesia microti* may represent an actual co-infection with *B. burgdorferi*. All three tick borne organisms have been found to reside in the geographic location these 12 clinical specimens were obtained. Both of the specimens found positive in the Viramed Biotech AG Borrelia B31 IgG ViraStripe[®] were also found to be positive in a commercially available Lyme Western blot test system. See Limitations for list of untested, potentially cross-reactive organisms.”

Disease State Sera	Number	Borrelia B31 IgG ViraStripe [®] Positive	Percent cross-reactivity
<i>Ehrlichia chafeensis</i>	7	1	14%
<i>Babesia microti</i>	5	1	20%
<i>Borrelia hermsii</i>	6	0	0%
<i>Leptospira interrogans</i>	10	0	0%
<i>Helicobacter pylori</i>	10	0	0%
<i>Epstein Barr Virus</i>	6	0	0%
ENA Autoimmune	16	0	0%
<i>Treponema pallidum</i>	15	0	0%

INTERFERING SUBSTANCES

There is no discussion regarding interfering substances in the submission. The proposed package insert contains the following:

“Haemolysed, lipemic, or icteric sera should not be used for testing, in addition sera with elevated bilirubin, and triglycerides were not tested. The performance of this assay when testing sera from patients with any immune-deficient diseases such as HIV, HTLV, etc. and sera from patients that have had immune-suppressive therapy with drugs or medications is not known because no studies were conducted to assess the performance. Do not use heat-inactivated sera.”

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

i. Correlations to the CDC Lyme Disease Panel

A Lyme Disease Clinical panel containing 44 clinically defined positives and negative samples was obtained from the Center for Disease Control and Prevention, Fort Collins, Colorado.

Time after Onset	Total	Borrelia B31 IgG ViraStripe®		
		Positive	Negative	% Agreement
Normals	5	0	5	100%
Clinically Undefined	3	1	2	100%
Early Localized	27	6	21	93%
Disseminated Disease	9	8	1	89%
Total	44	15	29	93%

ii. College of American Pathologists 2003 Tick-borne Disease Proficiency Panel

The CAP Tick-borne Proficiency Panel for the year 2003 was tested:

	CAP Published		Borrelia B31 IgG ViraStripe®		Borrelia B31 IgG ViraBlot®	
	IgG Pos	IgG Neg	IgG Pos	IgG Neg	IgG Pos	IgG Neg
	LY-A 2003 TTD01-05	0	5	0	5	0
LY-B 2003 TTD06-10	1	4	1	4	1	4
LY-C 2003 TTD11-15	3	2	3	2	1	4
Total	4	11	4	11	2	13

According to the sponsor, there was 100% concordance (15/15) with the CAP panel (95% Confidence Interval 78.2-100), and 86% (13/15) concordance with the predicate device (95% Confidence Interval 59.5-98.3).

b. *Matrix comparison:*

Not applicable

3. Clinical studies:

a. *Sensitivity:*

A total of 435 samples were prospectively collected and found to be EIA positive were sent to laboratories in California, Wisconsin, and Minnesota for Lyme disease testing. Samples were tested with the Viramed Biotech AG Borrelia B31 IgG ViraStripe[®] and the predicate device (Viramed Biotech AG Borrelia B31 IgG ViraBlot[®] Western Blot). Results are presented in the tables below.

Subjects Sent to the Laboratory for Lyme Disease Testing

Predicate	Borrelia B31 IgG ViraStripe [®]		Total
	Positive	Negative	
Positive	58	3	61
Negative	1	373	374
Total	59	376	435

	Percent Agreement	Exact 95% Confidence Intervals
Positive	98.3% (58/59)	(91.0% – 100%)
Negative	99.7% (373/374)	(98.5% - 100%)
Overall	99.1% (431/435)	(97.7% - 99.7%)

Clinically-defined Lyme disease samples

One hundred (100) sera were obtained from patients that were clinically defined (culture confirmed) with Lyme borreliosis. Of these 100 sera, 40 were paired (20 acute and 20 convalescent) sera from patients diagnosed with Erythema migrans (EM), 20 with early-disseminated Lyme Disease/Carditis/Acute Neuroborreliosis, and 40 with late stage Lyme arthritis. Results are presented in the tables below.

Stage	Borrelia B31 IgG ViraStripe [®]			
	Total	Positive	Negative	Sensitivity (95% Confidence Intervals)
Acute EM 1-21 days from Onset	20	5	15	25% (8.6%- 49.1%)
Convalescent EM 4 weeks after Onset	20	5	15	25% (8.6%- 49.1%)
Early Neurologic	20	13	7	65% (40.8% – 84.6%)
Late Arthritis	40	37	3	92.5% (79.6% – 98.4%)
Total	100	60	40	

Borrelia B31 IgG ViraBlot®	Borrelia B31 IgG ViraStripe®		
	Positive	Negative	Total
Positive	59	1	60
Negative	1	39	40
Total	60	40	100

	Percent Agreement	95% Confidence Intervals
Positive	98.3% (59/60)	91.1% - 100%
Negative	97.5% (39/40)	86.8% - 99.9%
Overall	98.0% (98/100)	93.0% - 99.8%

b. *Clinical specificity:*

The sponsor notes the following for analytic specificity (there is no description of clinical specificity): “For determination of analytical specificity, two hundred of the sera from normal blood donor individuals representing endemic and non-endemic geographic regions of the United States were tested for IgG *Borrelia burgdorferi* antibodies by the Viramed Biotech AG Borrelia B31 IgM ViraStripe®”

Analytical Specificity

	N	Negative	Positive	% Positive
Endemic	100	98	2	2%
Non-endemic	100	99	1	1%

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Not applicable

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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