

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

A. 510(k) Number:

k053653

B. Purpose for Submission:

This is a new device.

C. Measurands:

Anti-SS-A, anti-SS-B, anti-Sm, anti-Sm/RNP, anti-dsDNA, anti-Scl-70, anti-Jo1, ribosome and centromere

D. Type of Test:

Multiplex bead-based flow cytometric immunoassay

E. Applicant:

Biomedical Diagnostics (bmd) S.A.

F. Proprietary and Established Names:

FIDIS™ Connective 10*

G. Regulatory Information:

1. Regulation section:

21CFR§ 866.5100, Antinuclear Antibody Immunological Test System

2. Classification:

Class II

1. Product code:

LLL, Extractable Antinuclear Antibody, Antigen, and Control

LKJ, Antinuclear Antibody, Antigen, Control

LKO, Anti-RNP Antibody, Antigen, Control

LKP, Anti-Sm Antibody, Antigen, and Control

LSW, Anti-DNA Antibody, Antigen and Control

LJM, Antinuclear Antibody (Enzyme Labeled), Antigen, Controls

MQA, Anti-Ribosomal P Antibodies

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

The FIDIS™ Connective 10* kit is a fluorescent immunoassay for the semi-quantitative simultaneous detection of 10 autoantibody specificities directed against double stranded DNA (dsDNA), SSA (60 kDA and 52 kDA), SSB, Sm, Sm/RNP, Scl-70, Jo-1 ribosome and centromere in human serum. (*Antibodies to dsDNA, SSA, SSB, Sm, Sm/RNP, Scl-70, Jo-1, ribosome and centromere can be reported using this assay).

2. Indication(s) for use:

The FIDIS™ Connective 10* kit is a semi-quantitative homogeneous fluorescent based microparticles immunoassay using flow cytometry readings. It is designed for the simultaneous detection of autoantibody specificities: double stranded DNA (dsDNA), SSA (60 kDA and 52 kDA), SSB, Sm, Sm/RNP, Scl-70, Jo-1 ribosome and centromere in human serum. (*Antibodies to dsDNA, SSA, SSB, Sm, Sm/RNP, Scl-70, Jo-1 ribosome and centromere can be reported using this assay).

The test system is used to screen serum samples and detect the presence of antinuclear antibodies associated with connective diseases systemic lupus erythematosus (SLE), Sjogren's syndrome, mixed connective tissue disease (MCTD), scleroderma, dermatomyositis, and CREST syndrome, in conjunction with clinical findings and other laboratory tests.

3. Special conditions for use statement(s):
This device is for prescription use only.
4. Special instrument requirements:
FIDIS™ Instrument (Luminex 100™ plus FIDIS™ MLX-Booster Software)
CARIS™ (Optional diluting and dispensing device)

I. Device Description:

The device consists of the following: color-coded sets of microspheres (ready-to-use). Each microsphere set is conjugated to one of the following antigens: dsDNA, SSa (60 kDA and 52 kDA), SSB, Sm, Sm/RNP, Scl-70, Jo-1, ribosome and centromere; calibrator (ready to use); positive control (to be diluted); negative control (to be diluted); goat anti-human IgG conjugate coupled phycoerythrin (to be diluted) and 10x concentrated PBS-Tween (to be diluted with distilled water)

J. Substantial Equivalence Information:

1. Predicate device name(s):
Varelisa LA (SS-B) Antibodies, Varelisa RO (SS-A) Antibodies, Varelisa Jo-1 Antibodies, Varelisa Sm Antibodies, Varelisa RNP Antibodies, Varelisa dsDNA Antibodies, Varelisa Scl-70 Antibodies, Varelisa Centromere Antibodies, and QuantaLite Ribosome P ELISA.
2. Predicate 510(k) number(s):
k944168, k944169, k944173, k944170, k993589, k950031, k944172, k944171 and k981237.
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	FIDIS™ Connective 10*	Individual Varelisa ELISA assays for autoantibodies to LA (SS-B), RO (SS-A), Jo-1, Sm, RNP, dsDNA, Scl-70, Centromere and QuantaLite Ribosome P
Intended Use	Individual determination of IgG antibodies to dsDNA, SSA 60 kDA and 52 kDA, SSB, Sm/RNP, Scl-70, Jo-1, ribosome and centromere	Same
Sample type	Serum	Same
Type of test	Semi-quantitative	Same

Differences		
Item	Device	Predicate
Assay type	Flow Cytometer based	ELISA

Differences		
Item	Device	Predicate
Assay Format	Multiplexed	Individual analytes
Sample Dilution	1:200	1:101
Substrate solution	None	TMB
Instrument	Luminometer (Luminex 2.2)	Spectrophotometer
Detection method	Fluorescence	Colorimetric
Conjugate	Phycoerythrin	HR peroxidase
Solid Phase Capture	Color-coded microspheres	Microwells
Antigens	Recombinant dsDNA, SSA,SSB, Scl70, Jo1, and Centromere; Purified Sm, Sm/RNP and Ribosome P	Recombinant dsDNA, SSA, SSB, Scl70, Jo1, RNP, and Centromere; Synthetic SmD peptide, And Ribosome P

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

None referenced.

L. Test Principle:

FIDIS™ Connective 10* is a multiplexed semi-quantitative, fluorescent immunoassay performed on the FIDIS™ Instrument (Luminex 100™) with the MLX Booster software. Each antigen (dsDNA, SSA [60 kDA and 52 kDA], SSB, Sm, Sm/RNP, Scl-70, Jo-1, ribosome and centromere) is covalently coupled to an individual set of microspheres through its surface functional groups. The different sets of antigen-coupled microspheres are mixed together to constitute the final microspheres reagent and put into wells of a microtiter plate. Prediluted controls and diluted patient sera are added to separate wells allowing autoantibodies to bind to the immobilized antigens on the beads. After incubation, a wash step through a filtration process will remove the unbound antibodies. Then a phycoerythrin labeled anti-human IgG is added to each well and binds to any patient autoantibodies/antigen complexes on the microspheres. The samples are subsequently measured in the FIDIS Instrument. The flow cytometer discriminates the different bead sets as well as measures the fluorescent intensity of the conjugate on each bead. For each sample, the antibody titer for each antigenic specificity is interpolated against a calibration system.

FIDIS™ Connective 10* was optimized by flow cytometry for the average binding capacity at the given dilution (1:200) from the median fluorescence value using 200 microspheres per parameter.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

To evaluate intra-assay and inter assay reproducibility, five samples covering the reportable range of the assay were analyzed on the FIDIS™ Connective 10*. For within-run, the five samples were assayed 10 times in one run and for between-run; the three samples were assayed 2 times per run for 6 runs. Results were as follows:

Antigenic Specificity	Within-run		Between-run	
	Mean value	%CV	Mean Value	%CV
dsDNA	45	6.0	48	14.0
	55	2.5	49	6.6
	71	5.0	67	8.0
	105	6.1	102	7.4
	687	2.6	667	5.1
SSA 60 kDA / SSA52kDA	28	11.0	27	9.0
	50	12.0	46	13.0
	66	13.8	52	8.5
	81	3.5	76	3.9
	248	3.6	241	4.9
SSB	46	8.0	41	11.0
	54	6.0	53	10.0
	56	6.7	45	7.5
	80	3.1	73	9.1
	131	2.5	122	6.2
Sm	25	11.0	26	11.0
	28	9.0	29	8.0
	45	9.7	35	7.1
	90	4.0	87	6.4
	115	2.5	134	6.7
Sm/RNP	20	10.0	31	10.0
	44	5.5	55	8.9
	67	4.0	63	9.0
	89	3.1	88	4.6
	110	2.6	114	7.1
Scl-70	28	9.0	30	14.0
	34	15.0	35	14.0
	49	10.9	76	8.8
	97	8.4	84	5.8
	180	3.5	152	8.5
Jo-1	50	8.0	59	9.0
	60	8.0	59	9.0
	91	7.0	79	4.7
	176	6.2	170	7.8
	285	2.1	266	8.8
Centromere	30	8.0	27	12.0
	54	4.2	44	6.3
	94	3.3	82	7.3
	97	7.0	88	9.0
	181	2.1	156	7.3
Ribosome	51	5.0	49	8.0
	68	3.0	52	8.6
	69	7.0	64	11.0
	87	2.0	79	8.5
	136	2.5	132	5.5

Precision of the assay using the optional automated CARIS system was assessed. For within-run, seven samples were assayed 10 times in one run and for between-run; seven samples were assayed 4 times per run for 6 runs. Three antigens were chosen for this study. Results were as follows:

Antigenic Specificity	Within-run		Between-run	
	Mean value	%CV	Mean Value	%CV
dsDNA	370	6.0	360	6
SSB	77	12.0	73	11.0
SSA 60 kDA	193	3.0	187	7.0
SSA52kDA	150	6.5	149	9.0
	70	5.0	69	4.0
	56	8.0	53	14.0
	12	8.0	11	10.0

b. *Linearity/assay reportable range:*

Linearity is not claimed for this assay.

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

The dsDNA values in the calibrator are established using the WHO International Standard for anti-double stranded DNA (dsDNA), human code: WO/80. Other calibrator titers are expressed in arbitrary units per mL (AU/mL).

d. *Detection limit:*

Not applicable

e. *Analytical specificity:*

Interfering substances

To evaluate the system for potential cross reactivity to other antibodies and interference from blood components, 52 samples were tested. High level of complement proteins were used but the specific kind of complement was not provided. A statement to avoid the use of abnormal concentration of these samples was added to the Limitations of the Procedure. The following results were obtained:

	Number of Positive Samples								
	dsDNA	SSA 60 & 52kD	SSB	Sm	Sm/RNP	Sci70	Jo1	Centromere	Ribosome
Cryoglobulinemia (6)								1	
Complement (8)	2	1			2				1
Hypergammaglobulinemia (1)									
IgG monoclonal Ig (3)									
IgM monoclonal Ig (8)									
Rheumatoid Factor (8)									
Blood Plasma (6)									
Hemolyzed sera (6)									
Citrated Plasma (6)									

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

The tables below show the comparison of serum samples (N=434) that were

tested with the FIDIS™ Connective 10* and the predicate devices. No information about age, gender, and clinical status was provided.

- 307 positive samples for one or more parameters related to systemic autoimmune diseases
- 227 negative samples

All borderline results with the two devices were considered negative.

		Varelisa dsDNA	
		Pos	Neg
FIDIS dsDNA	Pos	58	8
	Neg	3	365

Positive % agreement: 95.08% (95% CI: 89.7% - 100%)
 Negative % agreement: 97.86% (95% CI: 96.4% - 99.3%)
 Overall % agreement: 97.47% (95% CI: 96.0% - 98.9%)

		Varelisa SS-A	
		Pos	Neg
FIDIS SS-A	Pos	116	30
	Neg	8	283

Positive % agreement: 93.55% (95% CI: 89.2% - 97.9%)
 Negative % agreement: 90.42% (95% CI: 87.2% - 93.7%)
 Overall % agreement: 91.30% (95% CI: 88.7% - 93.9%)

		Varelisa SS-B	
		Pos	Neg
FIDIS SS-B	Pos	49	19
	Neg	3	363

Positive % agreement: 94.23% (95% CI: 87.9%, -100.0%)
 Negative % agreement: 95.03% (95% CI: 92.8 - 97.2%)
 Overall % agreement: 94.93% (95% CI: 92.9% -97.0%)

		Varelisa Sm	
		Pos	Neg
FIDIS Sm	Pos	51	13
	Neg	5	365

Positive % agreement: 91.07% (95% CI: 83.6% - 98.5%)
 Negative % agreement: 96.56% (95% CI: 94.1% - 98.4%)
 Overall % agreement: 95.85% (95% CI: 94.0% - 97.7%)

		Varelisa Sm/RNP	
		Pos	Neg
FIDIS Sm/RNP	Pos	84	18
	Neg	14	318

Positive % agreement: 85.71% (95% CI: 78.8% - 92.6%)

Negative % agreement: 94.64% (95% CI: 92.2% - 97.1%)
 Overall % agreement: 92.63% (95% CI: 90.2% - 95.1%)

		Varelisa Sci70	
		Pos	Neg
FIDIS Sci-70	Pos	32	5
	Neg	2	385

Positive % agreement: 94.12% (95% CI: 86.2% - 100%)
 Negative % agreement: 98.75% (95% CI: 97.7% - 99.8%)
 Overall % agreement: 98.4% (95% CI: 97.2% - 99.6%)

		Varelisa Jo1	
		Pos	Neg
FIDIS Jo-1	Pos	34	8
	Neg	0	392

Positive % agreement: 100.0%
 Negative % agreement: 98.00% (95% CI: 96.6% - 99.4%)
 Overall % agreement: 98.16% (95% CI: 96.9% - 99.4%)

		Varelisa Centromere	
		Pos	Neg
FIDIS Centromere	Pos	45	4
	Neg	2	383

Positive % agreement: 95.74% (95% CI: 90.0% - 100.0%)
 Negative % agreement: 98.97% (95% CI: 98.0% - 100.0%)
 Overall % agreement: 98.62% (95% CI: 97.5% - 99.7%)

		QuantaLite Ribosome	
		Pos	Neg
FIDIS Ribosome	Pos	24	4
	Neg	2	404

Positive % agreement: 92.31% (95% CI: 82.1% - 100.0%)
 Negative % agreement: 99.02% (95% CI: 98.1% - 100.0%)
 Overall % agreement: 98.62% (95% CI: 97.5% - 99.7%)

Comparison of the automated CARIS system and manual method

A comparison study between the manual method and the automated CARIS™ system was also performed. The comparison was performed on 36 samples. All borderline results with the two methods were considered negative.

SSA (60kD+52kD)		Manual FIDIS	
		Pos	Neg
CARIS FIDIS	Pos	18	1
	Neg	0	17

Positive % agreement: 100.0%
 Negative % agreement: 94.4%
 Overall % agreement: 97.2%

SSB		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	4	0
	Neg	1	31

Positive % agreement: 80.0%
 Negative % agreement: 100.0%
 Overall % agreement: 97.2%

Sm		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	2	0
	Neg	0	34

Positive % agreement: 100.0%
 Negative % agreement: 100.0%
 Overall % agreement: 100.0%

Sm/RNP		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	6	0
	Neg	0	30

Positive % agreement: 100.0%
 Negative % agreement: 100.0%
 Overall % agreement: 100.0%

Sci70		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	4	0
	Neg	0	32

Positive % agreement: 100.0%
 Negative % agreement: 100.0%
 Overall % agreement: 100.0%

Jo1		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	5	0
	Neg	0	31

Positive % agreement: 100.0%
 Negative % agreement: 100.0%
 Overall % agreement: 100.0%

Centromere		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	7	0
	Neg	0	29

Positive % agreement: 100.0%

Negative % agreement: 100.0%

Overall % agreement: 100.0%

Ribosome		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	0	0
	Neg	0	39

Positive % agreement: 100.0%

Negative % agreement: 100.0%

Overall % agreement: 100.0%

dsDNA		Manual FIDIS	
		Pos	Neg
Caris FIDIS	Pos	7	0
	Neg	0	29

Positive % agreement: 100.0%

Negative % agreement: 100.0%

Overall % agreement: 100.0%

b. Matrix comparison:

Serum is the only recommended matrix.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

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:

The reported expected ranges were estimated from 2 populations:

- 50 samples from blood donors
- 48 samples selected from their potential biological interferences and according to WHO standard for dsDNA specificity

Arbitrary units (AU/mL)	<30 AU/mL	30-40 AU/mL	>40 AU/mL
International units (IU/mL) For dsDNA	<30 IU/mL	30-40 IU/mL	>40 IU/mL
Interpretation	Negative	Equivocal ¹	Positive

The negative thresholds (30 AU/mL or 30 IU/mL) correspond to the 97.9th percentile for dsDNA, SSA, Sm/RNP; 99.0% for centromere and ribosome, and 100% for SSB, Sm, Scl70 and Jo1 for the populations studied.

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.