



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

I Background Information:

A 510(k) Number

K231290

B Applicant

The Binding Site Ltd.

C Proprietary and Established Names

Optilite Freelite Kappa Free Kit
Optilite Freelite Lambda Free Kit

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DFH, DEH	Class II	21 CFR 866.5550 - Immunoglobulin (Light Chain Specific) Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

Modification of a previously cleared device: Addition of intended use as an aid in the evaluation of Monoclonal Gammopathy of Undetermined Significance (MGUS) on Optilite Analyzer.

B Measurand:

Kappa (κ) Free Light Chain (FLC)
Lambda (λ) Free Light Chain (FLC)

C Type of Test:

Immuno-turbidimetry; Quantitative

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Optilite Freelite Kappa Free Kit is intended for the quantitative in vitro measurement of Kappa free light chains in serum using the Binding Site Optilite analyzer. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE), and aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted in conjunction with other laboratory and clinical findings.

The Optilite Freelite Lambda Free Kit is intended for the quantitative in vitro measurement of Lambda free light chains in serum using the Binding Site Optilite analyzer. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE), and aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted in conjunction with other laboratory and clinical findings.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Optilite Freelite Kappa Free Kit

Warning: The kappa free light chain results for a given specimen determined with assays from different manufacturers or on different systems can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the kappa free light chain assay used. Values obtained with different assays or systems cannot be used interchangeably. If, in the course of serially monitoring a patient, the assay or system used for determining kappa free light chain levels is changed, additional sequential testing should be carried out. Prior to changing assay or system, the laboratory **MUST** confirm baseline values for patients being serially monitored.

Optilite Freelite Lambda Free Kit

Warning: The lambda free light chain results for a given specimen determined with assays from different manufacturers or on different systems can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the lambda free light chain assay used. Values obtained with different assays or systems cannot be used interchangeably. If, in the course of serially monitoring a patient, the assay or system used for determining lambda free light chain levels is changed, additional sequential testing should be carried out. Prior to changing assay or system, the laboratory **MUST** confirm baseline values for patients being serially monitored.

Optilite Freelite Kappa Free Kit and Optilite Freelite Lambda Free Kit

Precaution:

Evaluation of monoclonal gammopathy of undertermined significance (MGUS):

- The performance has not been sufficiently studied in Light Chain MGUS patients.
- Patients with renal disease or inflammation may have elevated levels of kappa and lambda free light chains (FLC).
- Sample populations excluded MGUS populations that were further diagnosed with a disease/disorder in subsequent testing with another medical device such as neoplasia, and infectious diseases including human immunodeficiency virus. Thus, the specificity of the test may be inflated.
- The performance has not been fully evaluated on all race/ethnicity in the intended use population.

D Special Instrument Requirements:

Optilite Analyzer (K141100)

IV Device/System Characteristics:

A Device Description:

No modification is made to the kit components for the Optilite Freelite Kappa and Lambda Free Kits cleared in K150658. The assays are comprised of the following reagents:

- Latex Reagent: Consisting of polyclonal monospecific antibody coated onto polystyrene latex with preservatives, supplied in stabilized liquid form.
- Calibrator and Controls: Pooled human serum with preservatives, supplied in stabilized liquid form.
- Reaction Buffer: Containing 0.099% sodium azide as a preservative.

B Principle of Operation:

No modification is made to the principle of operation for the Optilite Freelite Kappa and Lambda Free Kits cleared in K150658.

The concentration of the soluble antigen is assessed by turbidimetry. The test sample is added to a solution containing the appropriate antibody in a reaction cuvette. A beam of light is passed through the cuvette and is increasingly scattered by the formation of insoluble immune complexes. Light scatter is monitored by measuring the decrease in intensity of the incident beam of light. The antibody in the cuvette is in excess so the amount of immune complex formed is proportional to the antigen concentration. A series of calibrators of known antigen concentration are assayed to produce a calibration curve of measured light scatter versus antigen concentration. Samples of unknown antigen concentration can then be assayed, and the results read from the calibration curve.

V Substantial Equivalence Information:**A Predicate Device Name(s):**

Freelite Human Kappa And Lambda Free Diagnostic Test Kits For Use On The Roche Cobas Integra 400/400 Plus Analyzer Kit

B Predicate 510(k) Number(s):

K070900

C Comparison with Predicate(s):

Device & Predicate Device(s):	<u>K231290</u> (Device)	<u>K070900</u> (Predicate)
Device Trade Name	Optilite Freelite Kappa Free Kit Optilite Freelit Lambda Free Kit	Freelite Human Kappa and Lambda Free Kits for use on Roche Cobas Integra 400/400 plus
General Device Characteristic Similarities		
Assay Type	Quantitative	Same
Test Method	Turbidimetry	Same
Detection Antibody	<u>Kappa</u> : Polyclonal sheep anti-human Kappa antibody coated onto latex particles <u>Lambda</u> : Polyclonal sheep anti-human Lambda antibody coated onto latex particles	Same
Reference Interval	Kappa: 3.30–19.40 mg/L Lambda: 5.71–26.30 mg/L Ratio: 0.26–1.65 mg/L	Same
Specimen Type	Serum	Same
Traceability	Internal reference material	Same
Measuring range (Kappa)	0.6–25.3 mg/L (1+1) 2.9–127 mg/L (1+9) 29–1270 mg/L (1+99) 290–12700 mg/L (1+999) 1450 – 63500 mg/L (1+4999)	Same (First 4 dilutions only)
Measuring range (Lambda)	1.3–34.7 mg/L (1+1) 5.2–139 mg/L (1+7) 52–1390 mg/L (1+79) 520–13900 mg/L (1+799) 5200–139000 mg/L (1+7999)	Same
Open-vial Stability	3 months	Same

General Device Characteristic Differences		
Intended Use/ Indications For Use	<p><u>The Optilite Freelite Kappa Free Kit</u> is intended for the quantitative in vitro measurement of Kappa free light chains in serum using the Binding Site Optilite analyser. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinaemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE), and aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted in conjunction with other laboratory and clinical findings.</p>	<p><u>Freelite Human Kappa Kit:</u></p> <p>This kit is intended for the quantitation of kappa free light chains in serum on the Roche Cobas Integra 400, 400plus and 800. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus in conjunction with other laboratory and clinical findings.</p>
	<p><u>The Optilite Freelite Lambda Free Kit</u> is intended for the quantitative in vitro measurement of Lambda free light chains in serum using the Binding Site Optilite analyser. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinaemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus (SLE), and aids in the evaluation of monoclonal gammopathy of undetermined significance (MGUS). Results of the free light chain measurements should always be interpreted in conjunction with other laboratory and clinical findings.</p>	<p><u>Freelite Human Lambda Kit:</u></p> <p>This kit is intended for the quantitation of Lambda free light chains in serum on the Roche Cobas Integra 400 / 400plus and 800. Measurement of free light chains aids in the diagnosis and monitoring of multiple myeloma, lymphocytic neoplasms, Waldenström's macroglobulinemia, AL amyloidosis, light chain deposition disease and connective tissue diseases such as systemic lupus erythematosus in conjunction with other laboratory and clinical findings.</p>
On-board stability	30 days	3 months
Instrument	Optilite analyzer	Roche Cobas Integra
Measuring range (Kappa)	1450–63500 mg/L (1+4999)	2900–127000 mg/L (1+9999)

VI Standards/Guidance Documents Referenced:

Not applicable

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

See K150658

2. Linearity:

See K150658

3. Analytical Specificity/Interference:

See K150658

4. Assay Reportable Range:

See K150658

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

See K150658

6. Detection Limit:

See K150658

7. Assay Cut-Off:

See expected values/reference range below.

B Comparison Studies:

1. Method Comparison with Predicate Device:

See K150658

2. Matrix Comparison:

Not applicable

C Clinical Studies:

MGUS is a clinically asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder. The performance of the Optilite Freelite Kappa and Lambda Free Kits as an aid in the evaluation of MGUS was investigated from the following retrospective clinical studies:

Study 1:

A retrospective study was performed by testing a total of 234 samples from clinically confirmed MGUS patients (with IFE positivity) and a total of 140 samples from clinically defined non-MGUS patients with polyclonal immunostimulation (confirmed with SPEP/SIFE). Clinical diagnostic criteria and classification for MGUS and related plasma-cell disorders were, as practiced clinically, fulfilled, but were not limited to the criteria outlined by the 'International Myeloma Working Group (IMWG)' consensus. The result of the device was compared to the clinical diagnosis for each sample.

The cohort of 234 MGUS samples included 174 non-IgM MGUS, 24 IgM MGUS, 12 light chain (LC) MGUS and 24 Biclonal. All samples were tested for FLC kappa and lambda levels with the Optilite Freelite Kappa and Lambda Free kits on the Optilite Analyzer. FLC κ/λ ratios were also calculated for each sample. The test result for MGUS positive or negative were based on the following criteria:

- For Non-LC MGUS, the test was considered as “MGUS Positive” or “Abnormal” when abnormal FLC κ/λ ratio (outside reference interval, i.e., <0.26 or >1.65) with IFE positivity was determined.
- For LC MGUS, the test was considered as “MGUS Positive” when abnormal FLC κ/λ ratio (outside reference interval, i.e., <0.26 or >1.65) with elevated FLC kappa (>19.40 mg/L) or elevated FLC lambda (>26.30 mg/L) was determined.

One hundred thirty-nine (139) out of 234 MGUS cases were tested positive by the Optilite Freelite Kappa Free Kit and Optilite Freelite Lambda Free Kit with a positive rate of 59.4% (95% CI: 53.0 – 65.5%). The distribution of the cohort and the positivity rate for each clinical type of MGUS are summarized in the following table:

MGUS Type	N	n (n/N%) Freelite positive
Non-IgM MGUS (all)	174	101 (58.0%)
IgG κ	74	52 (70.3%)
IgG λ	62	24 (38.7%)
IgA κ	21	16 (76.2%)
IgA λ	15	9 (60.0%)
IgD κ	0	0 (0%)
IgD λ	0	0 (0%)
Other *	2	0 (0%)
IgM MGUS (all)	24	10 (41.7%)
IgM κ	19	9 (47.4%)
IgM λ	5	1 (20.0%)

MGUS Type	N	n (n/N%) Freelite positive
LC-MGUS (all)	12	12 (100%)
κ	8	8 (100%)
λ	4	4 (100%)
Biclonal	24	16 (66.7%)
TOTAL	234	139 (59.4%)

* λ band (not free light chain) with no obvious corresponding heavy chain. These samples have been categorized as non-IgM MGUS based on associated IFE and FLC results generated for these samples.

The 140 samples from patients with confirmed non-MGUS polyclonal stimulation (polyclonal hypergammaglobulinemia) were comprised of autoimmune diseases (27); diabetes (21); cardiovascular diseases (12); liver diseases (11); renal diseases (8); infection/inflammation (5); endocrine disorders (4); respiratory diseases (3); cancers (2); and other diseases/conditions (anemia, arthralgia, back pain, thigh pain, bone pain, elevated globulin levels, hypocalcemia, iron deficiency, joint pain, leg pain, low Hb, low sodium, malaise, morning stiffness, night sweats, neutrophilia, raised calculated globulin, raised CRP, rash and itch, recurrent UTIs, TATT- tired all the time, tiredness, weight loss) (47). Among 140 non-MGUS samples, 121 of these were determined as negative by the Optilite Freelite Kappa Free Kit and Optilite Freelite Lambda Free Kit, indicating a negative agreement of 86.4% (95% CI: 79.8–91.1%) in this sample cohort. The 19 false positive samples were from patients with the following disorders: diabetes (2); renal diseases (3); infection/inflammation (2); liver diseases (1); autoimmune diseases (6); endocrine disorders (1) and other diseases/conditions (4).

Study 2:

Another retrospective study was performed by testing 45 subjects with clinically stable MGUS and four subjects with progressive clinical status converting from MGUS to multiple myeloma (MM). Among 45 MGUS stable subjects, 39 patients were diagnosed with non-IgM MGUS (20 IgG K, 14 IgG L, two IgA K, and three IgA L), and six patients with IgM MGUS (four IgM K and two IgM L). All four subjects with progressive disease status were initially diagnosed with non-IgM MGUS (one IgG K, and three IgG L).

At least four serial draws were collected from each patient and tested with the Optilite Freelite Kappa Free Kit and Optilite Freelite Lambda Free Kit. FLC κ/λ ratio was calculated for each blood draw sample. Since the MGUS has been identified as a precursor to malignant diseases (multiple myeloma or amyloidosis), but not as a disease which requires treatment, no defined criteria in how to interpret consecutive FLC results are available. Therefore, for device evaluation purposes only, the criteria for stable MGUS and progressive MGUS based on test results in this study is defined as follows:

- FLC stable: Stable MGUS defined as < 25% increase in the concentration of the involved FLC in two assessments taken at least 6 months +/- 2 months apart where possible. This analysis included MGUS patients with and without abnormal FLC κ/λ ratio.
- FLC progressive: Progressive MGUS defined as the FLC κ/λ ratio outside of the reference interval of 0.26 –1.65, and an increase of ≥ 25% in the concentration of the

involved light chain at or preceding the diagnosis of MM, compared to a previous sample taken at least 6 months +/- 2 months where possible.

Forty-two (42) out of 45 clinically stable MGUS subjects except LC MGUS, were determined as stable by the test and two out of four clinically progressive subjects were determined as progressive by these tests.

Limitations

- The performance has not been sufficiently studied in Light Chain (LC) MGUS patients – 12 LC MGUS patient samples were tested in Study 1, no LC MGUS patient samples were tested in Study 2.
- The performance has not been fully evaluated on all race/ethnicity in the intended use population.
- The study included time points of blood draws not indicative of clinical practice. The algorithm using only FLC has not been validated for progression of disease. Furthermore, a small sample size (4 patients) with only one specific subtype (i.e., IgG MGUS only) was used to study progression in Study 2. Risk mitigation strategies include that this test is not a stand-alone test for the evaluation of patients with MGUS and the test is to be utilized in conjunction with serum protein electrophoresis and immunofixation blood tests.

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

See K150658

Kappa FLC reference range: 3.30–19.40 mg/L

Lambda FLC reference range: 5.71–26.30 mg/L

Kappa/Lambda Ratio reference Range: 0.26–1.65 mg/L

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.