SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Electrical Impedance Spectrometer

Device Trade Name: Nevisense

Device Procode: ONV

Applicant's Name and Address: SciBase AB
Kammakargatan 22
SE-111 40 Stockholm
Sweden

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150046

Date of FDA Notice of Approval: June 28, 2017

II. INDICATIONS FOR USE

Nevisense is indicated for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. Nevisense should not be used on clinically obvious melanoma. The Nevisense result is one element of the overall clinical assessment. The output of Nevisense should be used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy.

Nevisense is indicated only for use on:

- primary skin lesions with a diameter between 2 mm and 20 mm;
- lesions that are accessible by the Nevisense probe;
- lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions);
- lesions that do not contain a scar or fibrosis consistent with previous trauma;
- lesions not located in areas of psoriasis, eczema, acute sunburn or similar skin conditions;
- lesions not in hair-covered areas;
- lesions which do not contain foreign matter;
- lesions not on special anatomic sites (i.e., not for use on acral skin, genitalia, eyes, mucosal areas).

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Nevisense labeling.

V. DEVICE DESCRIPTION

Nevisense measures electrical impedance of skin lesions and provides an output called the electrical impedence spectroscopy (EIS) score. Electrical impedance is a measure of a material's overall resistance to the flow of alternating electric currents of various frequencies. The principle is that electrical impedance is different in normal versus abnormal tissue.

The Nevisense device is comprised of:

- Control Unit: processes examination data and presents electrical impedance spectra on the display, includes touch screen for user interaction (see Figure 1).
- Probe: holds the electrode used for lesion evaluation (see Figure 1).
- Probe Cable: connects probe to control unit (see Figure 1).
- Examination Electrodes – single patient use, sterile, disposable: Each electrode can be used up to 20 times for a single patient on several lesions in a single session. The electrode head is covered with micro invasive pins (approximately 150 μm high with 170 μm triangular base) that penetrate into the stratum corneum (approximately 10-20 μm), but do not normally reach blood vessels or sensory nerves in the dermis (See Figure 2).
- Training Electrodes – single person use, sterile, disposable: The training electrode is to be used only for training measurements conducted on normal, intact, healthy skin on a single person in a single training session. Each electrode can be used up to 50 times on a single person in a single training session.
- Test Impedance Tool: used for measurement accuracy tests and calibration.
- Lesion Coverage Tool: a template used to determine the number of measurements necessary to cover the entire surface of a lesion.
- Power cord: provides AC power to the control unit.
- Battery, rechargeable (optional): an optional, rechargeable Li-ion battery, 11.1V 6.6Ah battery may be used instead of the power cord.
- USB flash drive: used to archive or export data.

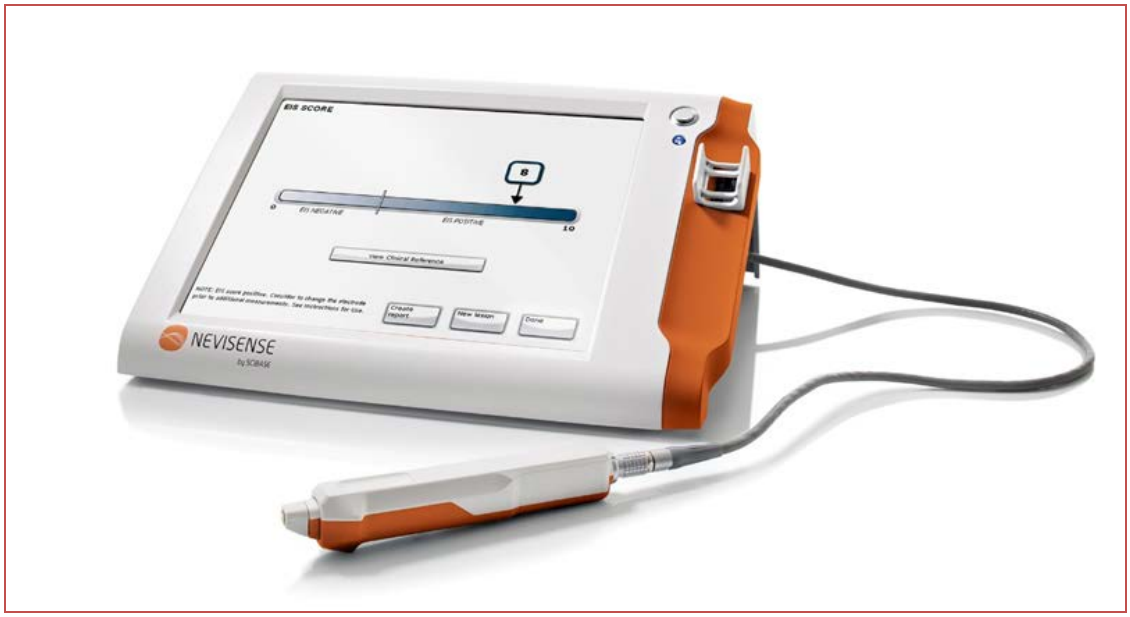


Figure 1: Control unit, Probe, and Probe Cable.

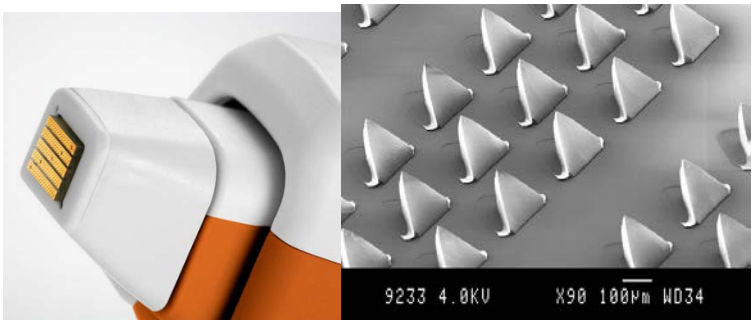


Figure 2: View of electrode tip at end of probe (left image); electron micrograph of electrode micropins, which are 150 um long with 170 um triangular base (right image)

Nevisense is not to be used on lesions already determined to require biopsy based on clinical evaluation. This device is an adjunct tool for lesions prior to the decision to biopsy.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the detection of melanoma including: a dermatologist's visual examination, dermoscopy, and Melafind (P090012). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Nevisense has been CE Marked since 2013, and is currently commercially available in Europe including in Sweden, Germany, Switzerland, Australia, United Kingdom, Belgium, and Austria. Nevisense has Therapuetic Goods Administration TGA

approval in Australia. The Nevisense has not been withdrawn from marketing in any country for any reason related to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects of any skin examination for melanoma may include: false negative results, which may lead to delays in diagnosis and treatment of melanoma, potentially increasing morbidity and mortality; and false positive results, which may result in unnecessary medical intervention including more frequent screening and invasive skin biopsy procedures.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Biocompatibility: The final finished patient-contacting components of the Nevisense system (disposable electrode, probe housing, lesion coverage tool) were tested for biocompatibility in accordance with ISO 10993-1 and FDA Blue Book Memorandum #G95-1. All testing was conducted in accordance with GLP. The Nevisense electrode samples were sterilized by EtO for testing as on the final finished device. The Probe housing and Lesion Coverage Tool are not intended to be provided sterile in clinical use, but were cleaned and disinfected according to the recommended methods prior to testing.

The following testing confirms the Nevisense components are biocompatible for their intended use:

Table 1: Biocompatibility -- Patient Exam/Training Electrode and Probe Housing

Standard	Method	Findings
ISO 10993-5, Biological evaluation of medical devices – Part 5: Tests for *in vitro* cytotoxicity.	ISO Elution Method- Single test extract 1x MEM, in vitro Mammalian Cell Culture	No evidence of cell lysis or toxicity
ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.	ISO Intracutaneous Study in Rabbits- local dermal irritation following intracutaneous injection	Test article met the requirements at 24, 48 and 72 hrs.
ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.	ISO Guinea Pig Maximization Sensitization Study - Extracts	No evidence of causing delayed dermal contact sensitization in the guinea pig.

Table 2: Biocompatibility -- Lesion Coverage Tool

Standard	Method	Findings
ISO 10993-5, Biological evaluation of medical devices – Part 5: Tests for *in vitro* cytotoxicity.	ISO Direct Contact Method/ L-929 mouse fibroblast cells	The test article showed evidence of causing mild cell lysis or cytotoxicity to L-929 cells. The test article met the requirements of the test since the grade was equal to a grade 2 (mild reactivity).
ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.	ISO Skin Irritation Study in Rabbits- Topical application of test article	No erythema or edema observed at 24, 48 or 72 hrs.
ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.	ISO Closed Patch Sensitization Study in Guinea Pigs	No evidence of causing delayed dermal contact sensitization in the guinea pig.

Electrical Safety: The Nevisense demonstrated compliance with applicable clauses of IEC 60601-1:2005 + CORR. 1(2006) + CORR. 2 (2007) Medical electrical equipment Part 1: General requirements for basic safety and essential performance for ratings of 100-240 VAC, 50-60 Hz, 70 VA, Class I, Type BF. Testing performed and findings included the following:

Table 3: Electrical Safety Tests

AAMI ES 60601-1 (Clause and name of test)	Result
Clause 4) General requirements	Pass
Clause 5) General requirements for testing ME equipment	Pass
Clause 6) Classification of ME equipment and ME systems	Pass
Clause 7) ME equipment identification, marking, and documents	Pass
Clause 8) Protection against electrical hazards from ME equipment	Pass
Clause 9) Protection against mechanical hazards of ME equipment and ME systems	Pass
Clause 11) Protection against excessive temperatures and other hazards	Pass
Clause 12) Accuracy of controls and instruments and protection against hazardous outputs	Pass
Clause 13) Hazardous situations and fault conditions	Pass
Clause 14) Programmable electrical medical systems (PEMS)	Pass
Clause 15) Construction of ME equipment	Pass
Clause 17) Electronic compatibility of ME equipment and ME systems	Pass

Electromagnetic Compatibility (EMC): The product demonstrated compliance with EN 55 011 (2009) + A1; Electromagnetic disturbances - Requirements and

tests for class B group 1 devices. Applicable requirements and results are as follows:

Table 4: EMC Tests

Description	**Result**
Radiated electromagnetic field in the frequency range 30 MHz to 1000 MHz, 230 V AC 50 Hz	Pass
Radiated electromagnetic field in the frequency range 30 MHz to 1000 MHz, 100 V AC 60 Hz	Pass
Electrostatic discharge	Pass
Radiated electromagnetic fields in the frequency range 80 – 2500 MHz	Pass
Fast transient/burst	Pass
Conducted disturbances induced by radio frequency (RF)-fields in the frequency range 0.15 MHz – 80 MHz	Pass

Software: Scibase performed verification and validation testing on the Nevisense. Verification testing consisted of software unit testing, software integration testing, and software system testing. The purpose of the verification testing was to assure that the software application satisfied the software requirements. Verification testing was successfully completed. It was found that minor anomalies remain in the software application. These anomalies have no impact on the safety and effectiveness of the device and no impact on the operator usage. Nevisense software has a major level of concern, and Nevisense has provided adequate software documentation in accordance with FDA's "Guidance for FDA Reviewers and Industry, Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" for a major level of concern.

Verification of Nevisense System Requirements: Verification tests for the Nevisense system were conducted. The purpose of the acceptance tests is:

- To ensure that the sensitivity and specificity for the SIMPS-study is acceptable.
- To ensure that it is possible to manufacture a Nevisense system that fulfills the product requirements.
- To ensure that the Nevisense system has specified measurement accuracy.
- To ensure usability of the system.

Several minor changes were made to the device after the pivotal studies, including a new printed circuit (PC) board, change to an optional battery source, and changes to the PC boards of the electrode, probe, and test impedance tool. Comparative bench testing has demonstrated that these minor changes do not affect the device performance as demonstrated in the pivotal study in any substantial manner.

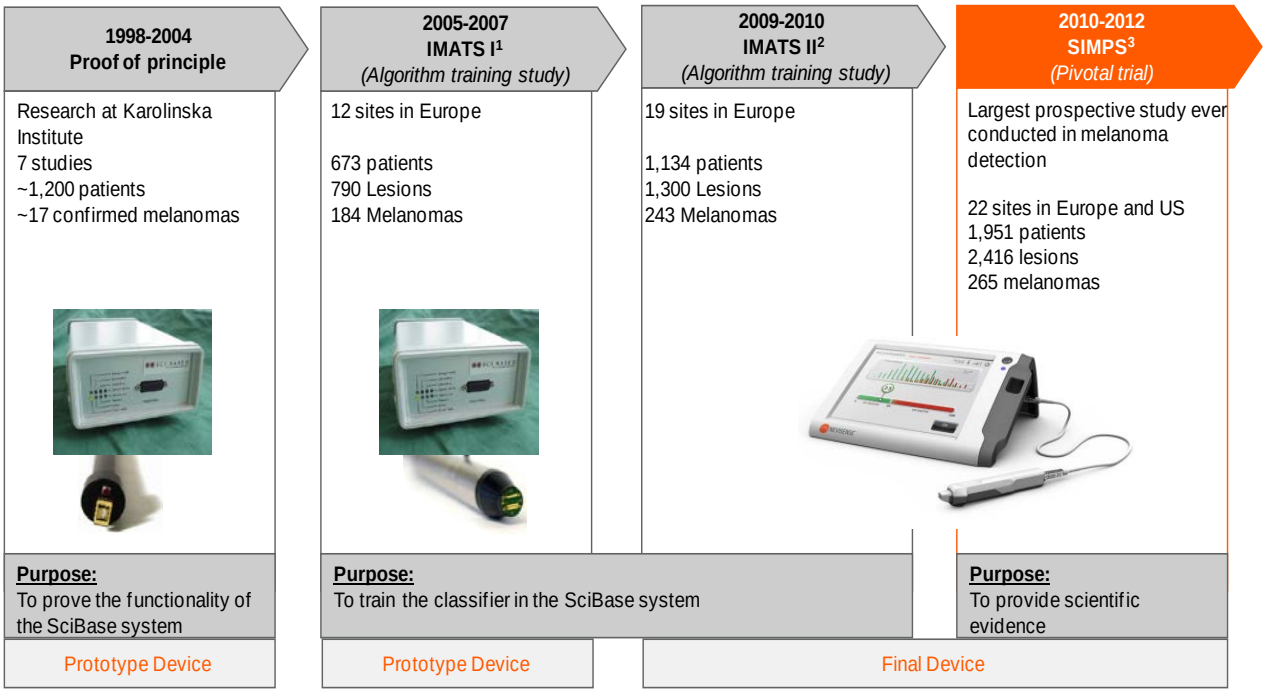
Sterilization and Shelf Life: The examination and training electrodes are sterilized using EtO to a Sterility Assurance Level (SAL) of 10^{-6}. Sterilization validation was conducted in accordance with ISO 11135:2014 "Sterilization of Health Care Products – Ethylene Oxide: Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Device". The ability of the package to maintain sterility for the labeled shelf life was successfully validated per

ISO 11607-1 “Packaging for Terminally Sterilized Medical Devices - Part 1 Requirements for Materials, Sterile Barrier Systems, and Packaging systems” and ISO 11607-2 “Packaging for terminally sterilized medical devices - Part 2 Validation requirements for forming, sealing and assembly processes.” Distribution simulation testing was successfully conducted according to ASTM D4169-16, “Standard Practice for Performance Testing of Shipping Containers and Systems.” Results from testing conducted in accordance with these standards on the Nevisense electrodes after 1 year simulated aging support an initial shelf life of 12 months.

Cleaning and Disinfection Validation: Cleaning and Disinfection validations were conducted to validate the cleaning and disinfecting instructions for the reusable device components of the Nevisense system. The probe unit and lesion coverage tool are validated for cleaning and intermediate level disinfection. The control unit, probe cable, and mains cable are validated cleaning and low level disinfection.

B. Algorithm Development Studies

Beginning in 1998, a Nevisense prototype underwent seven (7) initial proof of principle studies involving 1,200 patients. The classifier in Nevisense, used for classifying the lesion, has been developed with measurement data collected during training studies with nearly 2,000 patients at more than 19 sites in Europe. The final classifier was developed primarily based on data from the International Melanoma Algorithm Training Study II (IMATS II). The sequence of pre-pivotal studies leading to the pivotal study is illustrated in Figure 3.



1) International Melanoma Algorithm Training Study I
2) International Melanoma Algorithm Training Study II
3) SciBase International Melanoma Pivotal Study

Figure 3: Development of the Nevisense device.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

Two (2) clinical studies, conducted under IDE #G090108 demonstrate the safety and effectiveness of the Nevisense device for the proposed indication for use. See Table 5 below for information on the Pivotal Study and the Reader Study.

Table 5: Clinical Studies

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects/Lesions
Pivotal	International, multi-center, prospective, blinded clinical study comparing Nevisense device readings to pathology. Dermatologists were blinded to the Nevisense reading.	To determine the safety and effectiveness of the Nevisense device designed to distinguish between malignant melanoma and benign lesions, using electrical impedance spectrometry, relative to histology (gold standard for diagnosis of melanoma)	22	1951/2416
Reader	A Multiple-Reader, Multiple-Case (MRMC) study, in which readers evaluate each case both with and without the aid of the Nevisense output (EIS negative/positive and score).	To assess how Nevisense output is incorporated into dermatologist's considerations when diagnosing melanoma.	41 readers	141 lesion images and EIS scores

Pivotal Study

A. Study Design

The Pivotal Study was an international, multicenter, prospective, blinded, clinical study conducted at 22 sites with 1951 subjects with 2416 lesions. Nevisense readings were compared to pathology findings. However, dermatologists were blinded to Nevisense readings.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Pivotal Study was limited to patients who met the following inclusion criteria:

   - Men or women of any ethnic group aged ≥18 years
   - Primary lesions (i.e., not metastases or recurrent lesions) that the physicians choose to excise.
   - Lesion ≥ 2 mm in diameter and ≤ 20 mm in diameter

- In subjects with multiple skin lesions, all lesions destined for excision must be identified for purposes of study participation. Note: a subject may only be entered into the study once.
- The subject is willing and able to read, understand, and sign the study specific informed consent form.

Patients were not permitted to enroll in the Pivotal Study if they met any of the following exclusion criteria:

- Skin surface not measurable (e.g., lesion on a stalk).
- Skin surface not accessible (e.g., inside ears, under nails).
- Lesion located on acral skin (e.g., sole or palms).
- Lesion located on areas of scars, crusts, psoriasis, eczema, or similar skin conditions.
- Lesion on hair-covered areas (e.g., scalp, beards, moustaches, or whiskers).
- Lesion located on genitalia.
- Lesion located in an area that has been previously biopsied or subjected to any kind of surgical intervention or traumatized.
- Lesion located on mucosal surfaces.
- Skin is not intact (measurement area) (e.g., bleeding or with clinical noticeable ulceration).
- Lesion with foreign matter (e.g., tattoo, splinter).
- Lesion and/or reference located on acute sunburn.

2. Follow-up Schedule and Study Sequence

All patients were scheduled to return for follow-up examinations at day 7 post biopsy. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in Table 6 and Figure 4 below summarizing the study schedule and safety and effectiveness parameters.

Table 6: Nevisense Evaluation

Assessment / Visit	Pre-Evaluatio	Evaluation	Day 7 +/- 3days	Post-Evaluatio n
Informed Consent	X			
Inclusion / Exclusion	X			
Demographic information	X			
Medical History and Physical Examination	X			
Skin Lesion Information		X		
SciBase III Evaluation		X		
Lesion Excision		X		
Histopathology Evaluation				X

Assessment / Visit	Pre-Evaluatio	Evaluation	Day 7 +/- 3days	Post-Evaluatio n
Histopathology re-evaluation (PAD board member 1)				X
Histopathology re-evaluation (PAD board member 2)				X
Histopathology re-evaluation (PAD board member 3)				X
Consensus board† (Consensus board member 1)				X
Consensus board† (Consensus board member 2)				X
Visual evaluation board				X
Adverse Event Reporting	X	X	X	

† If significant disagreement among PAD (panel of three histopathologists) Board evaluations

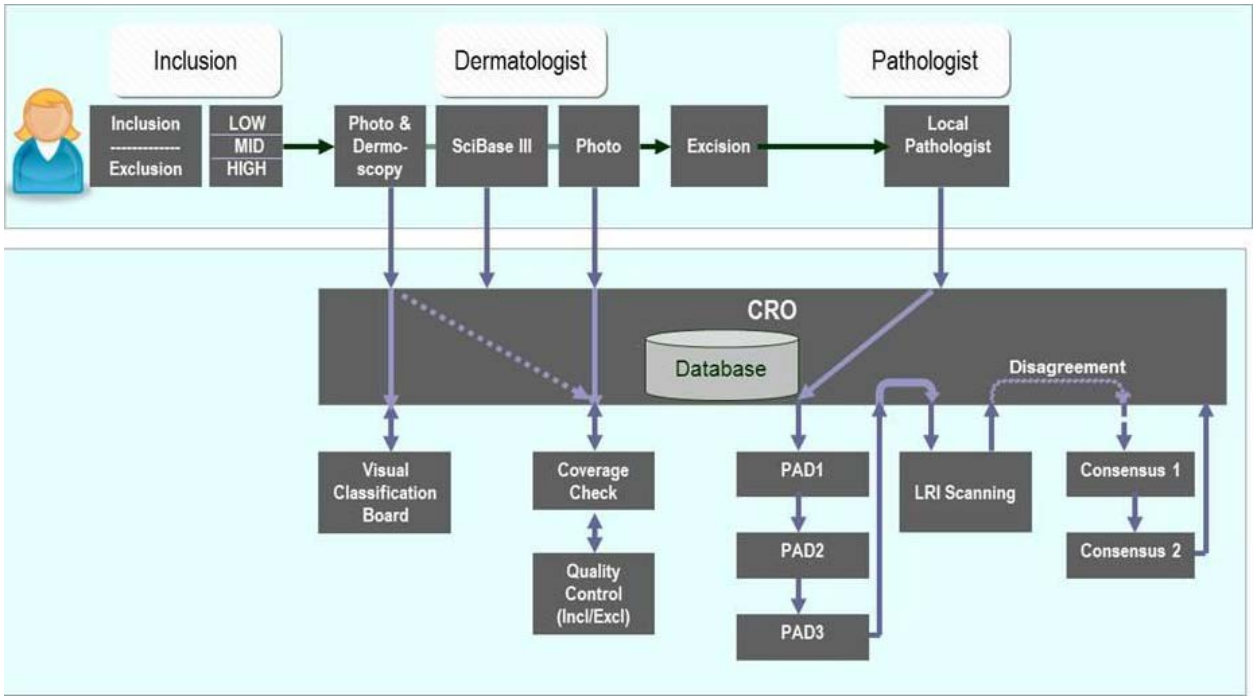


Figure 4: Pivotal Study Sequence

3. Clinical Endpoints

With regards to safety, safety was evaluated by the occurrence and incidence of all adverse events (AEs) reported for study subjects throughout their participation in the study. The primary safety endpoint was the absence of serious device-related events.

With regards to effectiveness, the primary effectiveness endpoint of the study consisted of two (2) co-endpoints aiming to show sensitivity ≥ 0.90 to detect malignant melanoma and non-randomness (odds ratio greater than 1). For the

primary co-endpoints, a lesion is considered positive according to histology only in cases of malignant melanoma.

The secondary effectiveness endpoints included the same co-endpoints for sensitivity and non-randomness as the primary endpoint; however, for the secondary endpoint, a lesion was considered positive by histology (in cases of melanoma, carcinomas (including squamous cell carcinoma (SCC), basal cell carcinoma (BCC), Merkel Cell Carcinoma, and actinic keratosis), and Severe Dysplastic Nevi. The secondary effectiveness endpoints were pre-specified in the Pivotal Study protocol.

B. Accountability of PMA Cohort

In total, 1951 subjects were recruited into the study. Of 1951 subjects, 1915 (98.2%) were included in the Safety analysis population and these subjects provided 2372 lesions. Of the 2372 lesions, 1951 (82.3%) were included in the Primary Effectiveness analysis population and 1961 (82.7%) were included in the Secondary Effectiveness analysis population. To be in the primary effectiveness population, a subject/lesion must not have been subject to a major protocol deviation and the lesion must have had a result for both the test and primary reference diagnoses needed for the primary effectiveness endpoint. To be in the secondary effectiveness population, a subject/lesion must not have been subject to a major protocol deviation and a lesion must have had a result for both the test and secondary reference diagnoses needed for the secondary effectiveness endpoint. The accountability of subjects/lesions in the PMA cohort is summarized in Table 7 below.

Table 7: Accountability of Subjects/Lesions

	Subjects		Lesions	
Recruited	**1951**		**2416**	
Excluded from safety[1]	*36*		*44*	
Safety Analysis Population	**1915**		**2372**	
Excluded from effectiveness populations[2]:	Primary Effectiveness[3]		Secondary Effectiveness[3]	
	Subjects	Lesions	Subjects	Lesions
Patient/Lesion exclusions due to:				
1. Signed informed consent form not present	*0*	*0*	*0*	*0*
2. Withdrawal (patient or investigator)	*10*	*19*	*10*	*19*
3. Inclusion/Exclusion criteria violation	*40*	*53*	*40*	*53*
No valid pathologyand/or Nevisensemeasurement due to:				
4. Measurement failure (due to device malfunction)	*23*	*28*	*23*	*28*
5. No device measurements performed	*7*	*8*	*7*	*8*
6. No reference measurement acquired	*9*	*16*	*9*	*16*
7. Reference measurement failure (≥4 rejected reference measurements)	*59*	*80*	*59*	*80*
8. No lesion measurement acquired	*2*	*2*	*2*	*2*
9. Measurement not performed according to protocol	*10*	*11*	*10*	*11*

10. Insufficient lesion coverage (less than 75% of the lesion was covered with measurements)	*57*	*89*	*57*	*89*
Histopathology, final diagnosis missing or excision not done correctly due to:				
11. Lesion not excised (therefore no histopathology reference)	*3*	*7*	*3*	*7*
12. Excision day >7 days after the measurements were performed	*5*	*6*	*5*	*6*
13. Inability to map histology to excised lesion	*4*	*7*	*4*	*7*
14. Missing lesion histology	*23*	*39*	*23*	*39*
15. Ineligible histopathology (preparation quality)	*7*	*8*	*7*	*8*
16. No Consensus on final diagnosis[4]	*36*	*44*	*32*	*34*
Exclusion due to other reasons:				
17. Other Reason (invalid measurements due to lesion bleeding or suspected mix-up of lesion histology)	*2*	*4*	*2*	*4*
Effectiveness Analysis Populations	**1618**	**1951**	**1622**	**1961**
Excluded due to measurement taken completely outside the lesion (on fully healthy skin)	*7*	*8*	*7*	*8*
Updated Effectiveness Analysis Populations	**1611**	**1943**	**1615**	**1953**

Note: *Italics* indicate number of subjects/lesions excluded.

[1]Thirty-six (36) subjects with 44 lesions were excluded from the safety population. In 34 of these subjects, device use was not initiated. In two (2) subjects (from a site which was terminated by the sponsor for lack of GCP), the device use had been initiated, but no adverse events were reported.

[2]Subjects/lesions may satisfy more than one exclusion category; however, in this table, each excluded subject/lesion is counted only once according to the first exclusion reason satisfied, using the exclusion hierarchy represented (from 1 – 17). For example, a subject who had insufficient lesion coverage and missing lesion histology would be counted in this table under insufficient lesion coverage.

[3]Primary effectiveness endpoint uses reference diagnosis definition where positive = melanoma;
Secondary effectiveness endpoint uses reference diagnosis definition where positive = melanoma, severe dysplastic nevi, and carcinomas.

[4]Because primary and secondary endpoints had different definitions of reference diagnosis, it was possible for consensus to be reached for primary and not secondary, or vice versa.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for the population that develops melanoma in the U.S.

Below are tables describing the study population demographics, the study population risk factors for melanoma, and the distribution of lesion sites.

Table 8.a: Statistics for Age

	N subject	**Mean**	**Std**	**Min**	**Median**	**Max**
Age (Years)	1915	50.3	16.8	18.2	48.7	91.2

Table 8.b: Distribution of Gender, Race, Fitzpatrick Scale

Characteristic	**N Subject**	**%**
Gender		
Male	914	47.7
Female	1001	52.3
All	1915	100.0
Race		
White	1867	97.5
Asian	5	0.3
Hispanic	29	1.5
Black or African American	2	0.1
Other	12	0.6
All	1915	100.0
Fitzpatrick Scale		
1. Always burns easily; never tans	134	7.0
2. Always burns easily; tans minimally	934	48.8
3. Burns moderately; tans gradually	624	32.6
4. Burns minimally; always tans well	191	10.0
5. Rarely burns; tans profusely	28	1.5
6. Never burns; deeply pigmented	1	0.1
Missing	3	0.2
All	1915	100.0

Table 9: Number of Lesions per Subject

	N	Mean	Std	Min	Median	Max
Number of Lesions	1915	1.2	0.7	1.0	1.0	10.0

Table 10: Distribution of Possible Risk Factors for Melanoma

Melanoma Risk Factors	**Yes**		**No**		**Unknown**		**Total**	
	N	%	N	%	N	%	N	%
History of extensive exposure to ultraviolet radiation	683	35.7	1157	60.4	75	3.9	1915	100.0
History of sunburns, especially during childhood	1136	59.3	588	30.7	191	10.0	1915	100.0
Previous melanoma	511	26.7	1395	72.8	9	0.5	1915	100.0
Previous BCC or SCC	310	16.2	1581	82.6	24	1.3	1915	100.0

Melanoma Risk Factors	Yes		No		Unknown		Total	
	N	%	N	%	N	%	N	%
Previous Dysplastic Nevi	587	30.7	1260	65.8	68	3.6	1915	100.0
Family history of melanoma	285	14.9	1562	81.6	68	3.6	1915	100.0
Family history of FAM-M syndrome	29	1.5	1742	91.0	144	7.5	1915	100.0
Impaired immune system	57	3.0	1845	96.3	13	0.7	1915	100.0
Xeroderma pigmentosum	8	0.4	1899	99.2	8	0.4	1915	100.0

Table 11: Distribution of Risk for Melanoma based on Number of Lesions on Patient

Melanoma Risk Factor	<50		≥50		Total	
	N	%	N	%	N	%
Number of lesions on patient	1021	53.3	894	46.7	1915	100.0

Table 12: Distribution of Site of Lesion

Site of Lesion		Number of Lesions	
		N_{Lesion}	%
Head	Scalp	12	9.6
	Forehead	34	27.2
	Cheek or Nose	64	51.2
	Chin	2	1.6
	Other	13	10.4
	All	125	100.0
Arm	Upper Arm	169	65.0
	Elbow	7	2.7
	Forearm	73	28.1
	Hand	11	4.2
	All	260	100.0
Leg	Upper leg	216	47.4
	Lower leg	176	38.6
	Knee	24	5.3
	Foot	40	8.8
	All	456	100.0
Trunk	Neck	49	3.2
	Chest	224	14.7
	Back Upper	596	39.0
	Back Lower	318	20.8
	Abdomen	283	18.5
	Pubic, Inguinal Area	20	1.3

Site of Lesion		Number of Lesions	
		N_{Lesion}	%
	Buttocks	39	2.6
	All	1529	100.0
All	Head	125	5.3
	Arm	260	11.0
	Leg	456	19.2
	Trunk	1529	64.5
	Missing	2	0.1
	All	2372	100.0

D. Safety and Effectiveness Results

Pivotal Study

1. Safety Results

Twenty-eight (2)8 subjects (1.5% of all subjects) experienced a total of 36 adverse events (AEs). No serious adverse event, serious adverse device effect or unanticipated adverse device effect was observed throughout the study. Most AEs were of mild severity (33 of 36). The one severe event (migraine headache) was considered unrelated to the device. Two (2) events of moderate severity (both for wound infection following excision) were considered unlikely to have been related to the device. Twelve (12) subjects (0.6% of all subjects) experienced 14 events that were considered by investigators to be possibly, probably, or definitely related to the device. These events involved bleeding during measurement (n=6); itching (n=1) at the measurement site; pain, soreness, or bruising (n=3) or slight tingling sensation (n=2) at the measurement site; and headache (n=2).

2. Effectiveness Results

a. Primary Effectiveness Analysis (on Primary Effectiveness Population, using Primary Reference Diagnosis (positive = melanoma only))

Co-Primary endpoint 1: Sensitivity of Nevisense for Detecting Melanoma
For the primary effectiveness analysis, in accordance with the primary endpoint definition, disease positive means lesions declared by the histology as melanoma (positive = melanoma only). In the primary effectiveness population, 267 or 13.7% of lesions were by histology, diagnosed as melanoma. The Nevisense device correctly identified 256 melanoma lesions out of 267 melanoma lesions, yielding sensitivity of 95.9%. Of 1,684 lesions that were not melanoma, 527 were diagnosed Negative by Nevisense, yielding specificity of 31.3% (not accounting for dependency between lesions within a subject, which is addressed in the analyses for the co-primary endpoints 1 and 2 below).

Table 13: Frequency Distribution of Nevisense Result by Primary Reference Diagnosis (Positive = melanoma only) – Primary Effectiveness Population

	Reference Positive	Reference Negative
Nevisense Positive	256	1157
Nevisense Negative	11	527

Nevisense observed sensitivity was 95.9%, with a 95% confidence interval lower limit of 93.3% (when using a one-sided interval) and 92.7% (when using a two-sided interval). The observed specificity was 31.1%, with a 95% confidence interval lower limit of 29.2% (one-sided interval) and 28.8% (for the two-sided interval). For sensitivity and specificity, the confidence interval computations were performed using a random effects model, with the following form: Test = Subject ID, with Subject ID treated as a random effect to account for correlated data (i.e., multiple lesions selected from the same set of subjects – about 15% of all lesions in SIMPS come from the same set of subjects – the other 85% are unique lesions from unique individuals). For the computation of sensitivity, the data set includes all positive lesions and excludes all subjects with no positive lesions (i.e., only those lesions declared by the reference method as melanoma were included). For the computation of specificity, the data set includes all negative lesions and excludes all subjects with no negative lesions (i.e., only those lesions declared by the reference method as not melanoma were included).

Co-Primary Endpoint 2: Sensitivity + Specificity > 1 for Melanoma Detection by Nevisense

This endpoint assessed whether the Nevisense is better at detecting melanoma than randomly flipping a coin to decide whether lesions contain Melanoma. In order to statistically assess this, the odds ratio from statistical logistic regression modelling was used. An odds ratio statistically greater than 1 from this model means that the sum of sensitivity and specificity is also statistically greater than 1. Some of the subjects in the pivotal study contributed multiple lesions (about 15% of all lesions fall in this situation). To account for this, the statistical logistic regression modelling treated subject as a random effect. All lesions were included for this analysis. The results are given in the following table. The odds ratio is 10.5 ($P < 0.0001$), meaning that odds ratio is statistically greater than 1, which means that sum of sensitivity and specificity is statistically greater than 1.

Table 14: Results from mixed logistic model for co-primary endpoint 2

Odds Ratio			
Estimate	Two-Sided 95% Lower CL	Two-Sided 95% Upper CL	P-Value
10.5	5.6	19.5	<.0001

b. Secondary Effectiveness Analysis (on Secondary EffectivenessEffectivenessPopulation, using Secondary Reference Diagnosis (positive = melanoma, carcinomas, or severe dysplastic nevi))

The secondary effectiveness endpoints included the same co-endpoints for sensitivity and non-randomness as the primary endpoint; however, for the secondary endpoint, a lesion was considered positive (according to histology) in

cases of melanoma, carcinomas (including SCC, BCC, Merkel Cell Carcinoma, and actinic keratosis), and Severe Dysplastic Nevi.

Other than the change in definition of positive lesions, the statistical approach for the secondary effectiveness endpoints is the same as the primary effectiveness endpoints. In the secondary effectiveness analysis, 26.0% of lesions are positive by histology. The Nevisense device correctly identified 472 Positive lesions of the 510 in the sample, yielding a sensitivity of 92.5%. Of 1451 Negative lesions, 500 were diagnosed Negative by Nevisense, yielding specificity of 34.5% (not accounting for dependency between lesions within a subject, which is addressed in the analyses for the co-secondary endpoints 1 and 2 below).

Table 15: Frequency Distribution of Nevisense Result by Secondary Reference Diagnosis (Positive = melanoma, carcinomas, or severe dysplastic nevi) – Secondary Effectiveness Population

	Reference Positive	Reference Negative
Nevisense Positive	472	951
Nevisense Negative	38	500

Co-Secondary Endpoint 1 (sensitivity >90%)
For the secondary effectiveness analyses, the sensitivity is 92.5%, with 90.4% for lower limit of the one-sided 95% confidence interval and 89.9% for the lower limit of the two-sided 95% confidence interval. The specificity is 34.3%, with 32.2% for the lower limit of the one-sided 95% confidence interval and 31.8% for the lower limit of the two-sided 95% confidence interval.

Co-Secondary Endpoint 2 (non-randomness)
The odds ratio is 6.4, significantly greater than 1 ($P < 0.0001$), indicating, as in the primary effectiveness analysis, that the Nevisense outcome is not random. The estimate of the sum of sensitivity and specificity is 1.27 with a lower 95% confidence interval of 1.236.

Table 16: Results from mixed logistic model for co-secondary endpoint 2 for SIMPS

Odds Ratio			
Estimate	Two-Sided 95% Lower CL	Two-Sided 95% Upper CL	P-Value
6.4	4.5	9.2	<.0001

The negative and positive predictive value (NPV/PPV) will vary depending on the Nevisense score. PPV is the probability that lesions with a positive Nevisense score truly are melanoma, whereas NPV is the probability that lesions with a negative Nevisense score truly are not melanoma. Both PPV and NPV are affected by the prevalence of melanoma in the population. For the pivotal clinical study, the prevalence of melanoma was 13.7%, which may be higher than the prevalence in the intended population at a dermatologist's specific practices. In order to account for the differing levels of prevalence, Table 17 depicts the dependence of the Nevisense PPV and NPV upon prevalence. Table 17 was derived by using the primary endpoint results (sensitivity (95.9%) and specificity (31.3%)) for the overall cohort in the pivotal clinical study and the formulas for

adjusting PPV and NPV from Altman, DG and Bland, JM. Statistics Notes: Diagnostic tests 2: predictive values *BMJ* 1994; 309:102. doi: https://doi.org/10.1136/bmj.309.6947.102

Table 17: PPV and NPV of Nevisense Adjusted for Prevalence. Last row depicts the PPV and NPV of Nevisense for the Prevalence Observed in the Pivotal Clinical Study

Prevalence	PPV	NPV
3%	4.14%	99.6%
5%	6.84%	99.3%
7%	9.50%	99.0%
9%	12.1%	98.7%
11%	14.7%	98.4%
13%	17.3%	98.1%
13.7%	18.1%	97.9%

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Pivotal Study Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 69 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

Reader Study

A. Study Design

The Reader Study was designed as a Multiple-Reader, Multiple-Case (MRMC), in which readers evaluate each case both with and without the aid of the Nevisense output (EIS negative/positive and score). The study used a subset of images collected during the pivotal study. Each image had a documented reference diagnosis (final diagnosis by the histopathology board) and dermatologist decision. Readers were provided with photographic images and pertinent clinical data; readers did not have access to the dermatoscopic images. The study provided information about the adjunctive use of the device. Readers were not aware of whether the patient whose image is presented was sent out for biopsy/referral, and were not aware of the established lesion diagnosis. None of the dermatologist that participated in the Reader Study participated in the Pivotal study.

B. Eligibility and Accountability

Reader Eligibility Criteria

Readers participating in this study were considered eligible if: 1) he/she was a board certified dermatologist, 2) he/she was a practicing dermatologist in the United States, 3) he/she had not previously participated in the SciBase International Melanoma Pivotal Study (SIMPS) trial, 4) at most 1 reader had previously participated in the study from the same site, and 5) he/she completed the survey for at least 60% out of the lesions included in this study within a set timeframe of 4 weeks.

Reader Selection, Enrollment, Accountability

Forty-two (42) board-certified dermatologists (all U.S.) enrolled in in the Reader study, and 41 dermatologists completed the study and contributed the data for the analysis. One dermatologist reviewed only eight (8) images, and therefore did not meet the reader eligibility criteria requiring that he/she complete the survey for at least 60% of the lesions within a 4 week period. The remaining 41 dermatologists completed the review of the entire dataset. The dataset for each reviewer consisted of the same set of 141 cases, selected to include both negative (benign) and positive (malignant) lesions from low risk, intermediate risk, and high risk categories.

For each image, the reader completed the following two steps in sequence:

1. Reader reviewed the lesion image with relevant patient clinical information;
2. Reader reviewed the lesion image with relevant patient clinical information, and the EIS score between 0 and 10, and the EIS Negative or Positive

The EIS score provided to the Reader was the same score used in the Pivotal Study, from which the images were provided. After each step, the readers decided whether or not they believed it was a melanoma and whether or not they would biopsy the lesion. This review sequence allows comparison of the use of an EIS score to a dermatologist's assessment of malignancy and whether they would consider excision/referral of a suspected lesion.

The Reader Study had two (2) co-primary endpoints. The first co-primary study hypothesis tests whether dermatologists' sensitivity when diagnosing melanoma is superior with Nevisense information than without Nevisense information. The second co-primary study hypothesis endpoint tests whether the dermatologists' sensitivity + specificity with Nevisense is greater than 1, meaning that the dermatologists' decision with Nevisense's aid is not random. Sensitivity and specificity are derived from the dermatologists' assessments of whether they believe the lesions to be a melanoma, rather than whether or not they would biopsy/refer the lesions. The primary effectiveness analysis was conducted on the population of eligible readers.

C. Reader and Lesion Characteristics

Readers (dermatologists) in the study were 81% male. Readers' ages were about equally distributed in the 10-year intervals from 30 to 59, with few readers in age groups 60-69 (9.5%) or >70 (2.4%). Readers had an average of 15.8 years of experience (range 2 – 41 years). Dermatologists with specialized focus on skin care comprised 40.5% of the readers, and without specialized focus in skin care comprised 57.1%, while the remaining 2.4% reported another specialist focus (described as melanoma and patch testing). The readers' practice settings were private clinic/group practice (52.4%), university clinic (11.9%), combination private and university clinic (2.4%), and private clinic/one person (33.3%). Fifty percent (50%) of readers reported spending >50% of their time per week diagnosing skin lesions suspect for skin cancer. The majority of readers reported being comfortable examining and diagnosing melanoma using only the naked eye (71.4%), and being comfortable examining and diagnosing melanoma using a dermoscope (76.2%).

The study made use of images collected during the pivotal study. Following the selection scheme presented in this study protocol, 141 lesion images were randomly selected to the reader study, with only one lesion per subject selected. Thus, the number of subjects is the same as the number of lesions. The subjects' average age was 49 years (range 19 to 85), and 45.4% of subjects were male. Most subjects (97.2%) were white. Most subjects were Fitzpatrick scale 2 (57.4%), and 3 (28.4%); and about half the subject (53.9%) had less than 50 lesions.

There were 141 lesions: 81 non-melanoma and 60 melanoma. The lesions represented a mix of clinical suspicion levels for melanoma: low (29.8%), intermediate (36.9%), and high (33.3%). The frequency distribution of Nevisense dichotomous outcomes, and the EIS scores for the lesions are summarized in Table 18 and Table 19. The Nevisense sensitivity in this subset of lesions is 96.7%, and specificity is 30.9%, which is consistent with accuracy reported in the pivotal study that was based on a greater sample of lesions.

Table 18: Distribution of EIS Dichotomous Outcome

EIS Dichotomous Outcome	Reference Status				All	
	Non-Melanoma		Melanoma			
	N	%	N	%	N	%
Negative	25	30.9	2	3.3	27	19.1
Positive	56	69.1	58	96.7	114	80.9
Total	81	100.0	60	100.0	141	100.0

Table 19: EIS Scores

Reference Status	EIS Score					
	Mean	Standard Deviation	Minimum	Median	Maximum	N
Non-Melanoma	4.5	2.2	0.0	5.0	10.0	81
Melanoma	6.4	2.1	2.0	6.0	10.0	60
Total	5.3	2.3	0.0	5.0	10.0	141

D. Reader Study Safety and Effectiveness Results

The sensitivity of dermatologists in detecting melanoma was 77.2% when using clinical information alone, compared to a sensitivity of 83.6% when dermatologists used the Nevisense plus additional clinical information. The difference (Without – With) was estimated at -6.4%, with two-sided 95% confidence interval of (-9.6%, -3.3%). This improvement was statistically significant with a p-value less than 0.001. Both the p-value and two-sided 95% confidence interval were derived by using a mixed model. The study succeeded in demonstrating an increase in readers' sensitivity with the aid of Nevisense information. Therefore, the first co-primary hypothesis was met.

With Nevisense aid, the sum of dermatologists' sensitivity and specificity is 1.33 with the two-sided 95% confidence interval (1.24, 1.42), which is significantly greater than 1, as indicated by the confidence interval. This confidence interval was derived by using a mixed model. This result demonstrates that the readers' decision regarding whether a lesion is melanoma or not when using Nevisense device is not random. Therefore, the second co-primary hypothesis was also met.

Dermatologists' sensitivity without Nevisense ranged from 50% to 96.7%, with median sensitivity of 80%. Dermatologists' sensitivity with Nevisense increased and ranged from 51.7% to 98.3%, with median sensitivity of 86.7%. On average, there was an increase of 6.4% in per-reader melanoma sensitivity. The difference in readers' individual sensitivities ranged from 0% (no change) to 20%. Note that sensitivity did not decrease for any reader.

Dermatologists' specificity without Nevisense ranged from 8.6% to 93.8%, with median specificity of 53.1%. Dermatologists' specificity with Nevisense decreased on average by 4%. The difference in readers' individual specificities ranged from -17.3% to 18.5%.

The difference in sensitivity was always positive, whereas the difference in specificity had both positive and negative values (depending on the reader), with an average difference in specificity of -4.0%.

Tables 20 and 21 depict the results when readers were deciding whether or not a lesion was melanoma (primary endpoint).

Table 20: Reader Sensitivity & Specificity for Deciding Whether or Not Melanoma

	Without Nevisense (Standard Deviation)	With Nevisense (Standard Deviation)	Difference (Standard Deviation)
Sensitivity	77.2% (13.6%)	83.6% (13.2%)	6.4% (5.1%)
Specificity	53.1% (21.2%)	49.1% (20.2%)	-4.0% (7.5%)

Table 21: By Reader Sensitivity & Specificity for Deciding Whether or Not Melanoma

	Minimum across Readers	Maximum across Readers	Median
Sensitivity without Nevisense	50.0%	96.7%	80.0%
Sensitivity with Nevisense	51.7%	98.3%	86.7%
Difference between the above Sensitivities	0.0%	20.0%	6.7%
Specificity without Nevisense	8.6%	93.8%	53.1%
Specificity with Nevisense	17.3%	93.8%	49.4%
Difference between the above Specificities	-17.3%	18.5%	-4.9%

Tables 22 and 23 depict the results when readers were deciding whether or not to biopsy lesions.

Table 22: Reader Sensitivity & Specificity for Deciding Whether or Not to Biopsy

	Without Nevisense (Standard Deviation)	With Nevisense (Standard Deviation)	Difference (Standard Deviation)
Sensitivity	91.4% (7.8%)	96.3% (4.6%)	4.9% (5.0%)
Specificity	26.4% (16.5%)	20.2% (13.1%)	-6.2% (9.2%)

Table 23: By Reader Sensitivity & Specificity for Deciding Whether or Not to Biopsy

	Minimum across Readers	Maximum across Readers	Median
Sensitivity without Nevisense	70.0%	100.0%	93.3%
Sensitivity with Nevisense	75.0%	100.0%	96.7%
Difference between the above Sensitivities	-3.3%	18.3%	3.3%
Specificity without Nevisense	0.0%	65.4%	24.7%
Specificity with Nevisense	2.5%	64.2%	19.8%
Difference between the above Specificities	-21.0%	16.0%	-6.2%

Tables 24 - 27 provide the results from the Reader Study for those at or above the age of 30.

Table 24: Reader Sensitivity & Specificity for Deciding Whether or Not Melanoma, Age group ≥ 30

	Without Nevisense (Standard Deviation)	With Nevisense (Standard Deviation)	Difference (Standard Deviation)
Sensitivity	77.5% (13.4%)	84.5% (13.2%)	7.0% (5.1%)
Specificity	52.2% (21.0%)	46.9% (20.6%)	-5.3% (7.3%)

Table 25: By Reader Sensitivity & Specificity for Deciding Whether or Not Melanoma, Age group ≥ 30

	Minimum across Readers	Maximum across Readers	Median
Sensitivity without Nevisense	50.8%	96.6%	81.4%
Sensitivity with Nevisense	52.5%	98.3%	88.1%
Difference between the above Sensitivities	0.0%	20.3%	6.8%
Specificity without Nevisense	10.9%	93.8%	48.4%
Specificity with Nevisense	15.6%	93.8%	46.9%
Difference between the above Specificities	-20.3%	14.1%	-4.7%

Table 26: Reader Sensitivity & Specificity for Deciding Whether or Not to Biopsy, Age group ≥ 30

	Without Nevisense (Standard Deviation)	With Nevisense (Standard Deviation)	Difference (Standard Deviation)
Sensitivity	91.4% (7.6%)	96.9% (4.3%)	5.5% (5.2%)
Specificity	25.5% (16.2%)	18.8% (12.0%)	-6.8% (9.4%)

Table 27: By Reader Sensitivity & Specificity for Deciding Whether or Not to Biopsy, Age group ≥ 30

	Minimum across Readers	Maximum across Readers	Median
Sensitivity without Nevisense	69.5%	100.0%	93.2%
Sensitivity with Nevisense	76.3%	100.0%	93.8%
Difference between the above Sensitivities	-1.7%	18.6%	5.1%
Specificity without Nevisense	0.0%	62.5%	23.4%
Specificity with Nevisense	1.6%	59.4%	17.2%
Difference between the above Specificities	-23.4%	14.1%	-6.3%

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Reader Study Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The reader study included 42 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Exploratory Effectiveness Analyses

The following additional analysis of the primary co-endpoints was conducted in analysis populations not prospectively defined in the Statistical Analysis Plan (SAP).

Primary Effectiveness Endpoints (with Updated Primary Effectiveness Analysis Population)

The primary effectiveness endpoints analyses were repeated on an Updated Primary Effectiveness analysis population, which excluded eight additional lesions due to an invalid measurement procedure (measurements completely outside the border of the lesion on healthy skin), a major protocol deviation, which was discovered after database lock. In this population, which reflects device accuracy for lesions assessed according to device instructions for use,

- Melanoma sensitivity was 96.6% with lower one-sided 95% confidence limit of 94.2%.
- The outcome of Nevisense device remained highly related to the reference outcome (P<0.0001), i.e. non-random. The obtained odds ratio of the device versus reference was 12.9, with a two-sided 95% confidence interval of 6.5 to 25.4.

Therefore, both co-primary hypotheses of this study were also met for the updated primary effectiveness population.

An additional analysis investigating the dependency between accuracy and lesion type was performed using the Updated Primary Effectiveness Analysis population. This analysis excluded the eight (8) lesions previously mentioned and used for Reference Diagnosis the definition of the secondary confirmatory endpoint. Table 28 presents sensitivity and specificity for different lesion types. As can be seen from this table, the overall sensitivity for melanoma is 96.6%.

The sensitivity for high stage melanoma (thickness T2, T3 and T4) is 100%, and sensitivity for melanoma with thickness T1 is above 98%. Sensitivity for in-situ is, as expected, lowest at 93.8%. Overall specificity is 34.4%, which includes mild to moderate nevi, melanocytic nevi, and other lesions. In this analysis, severe dysplastic nevi, carcinomas, and actinic keratosis are counted as positives. Carcinomas are malignant lesions and are therefore presented as positive. Severe dysplastic nevi are presented in a separate category because they can be considered positive or negative, depending on the clinical conventions adopted in different countries. This analysis was done to help communicate the numbers for lesion subcategories to the clinical community.

Table 28: Updated Primary Effectiveness Analysis Population: Sensitivity and Specificity by Lesion Type

Sensitivity and Specificity Analyses (Assuming Independency)										
Reference Diagnosis (Secondary)	**Sensitivity**	**Specificity**	**TP***	**FN***	**TN***	**FP***	**Total N**	**95% Two-sided LCL**	**95% Two-sided UCL**	**95% One-sided LCL**
Melanoma (Total)	**96.6**		**256**	**9**			**265**	**93.65**	**98.44**	**94.15**
Melanoma: Tis (In-situ) (= 0mm)	93.8		105	7			112	87.55	97.45	88.58
Melanoma: T1 (0-1 mm)	98.2		111	2			113	93.75	99.78	94.53
Melanoma: T2	100		35	0			35	90	100	91.8

Sensitivity and Specificity Analyses (Assuming Independency)										
Reference Diagnosis (Secondary)	**Sensitivity**	**Specificity**	**TP***	**FN***	**TN***	**FP***	**Total N**	**95% Two-sided LCL**	**95% Two-sided UCL**	**95% One-sided LCL**
(1-2 mm)										
Melanoma: T3 (2-4 mm)	100		4	0			4	39.76	100	47.29
Melanoma: T4 (> 4mm)	100		1	0			1	2.5	100	5
Severe Dysplastic Nevus	**84.1**		**132**	**25**			**157**	**77.4**	**89.42**	**78.48**
Non-MM (BCC+SCC+ AK)	**98.4**		**62**	**1**			**63**	**91.47**	**99.96**	**92.69**
Non-MM Excluding AK	100		55	0			55	93.5	100	94.7
BCC	100		48	0			48	92.6	100	93.9
SCC	100		7	0			7	59.0	100	93.5
AK**	87.5		7	1			8	47.3	99.7	52.9
Merkel Cell Carcinoma	**100**		**1**	**0**			**1**	**100**	**N/A**	**N/A**
Mild to Moderate Dysplastic Nevus		**36,1**			**357**	**631**	**988**	**33,13**	**39,22**	**33.6**
Melanocytic Nevus		**36,7**			**131**	**226**	**357**	**31,68**	**41,93**	**32.45**
Other		**11,6**			**13**	**99**	**112**	**6,33**	**19,03**	**7.0**
Overall Specificity		**34,4**			**501**	**956**	**1457**	**31,95**	**36,89**	**32.33**

*Definitions: TP - True Positive, FN - False Negative, TN - True Negative, FP - False Positive, LCL - Lower Confidence Limit, UCL - Upper Confidence Limit

**Actinic Keratosis (AK) is a precursor lesion to Squamous Cell Carcinoma (SCC), and not an SCC per se.

Subgroup Analyses

The following analyses are conducted on the primary effectiveness population unless otherwise noted.

For the Pivotal Study, the sensitivity for each age group was calculated for all melanoma lesions and for the subset of low stage melanoma (thicknesses Tis and T1). The results are summarized in Table 29 for the updated primary effectiveness population. Of the 265 lesions that were melanomas in the updated primary effectiveness analysis population, very few (n=5, 1.9%) occurred in subjects 18-30 years of age. The true sensitivity in this age group could not be verified due to the small number of melanoma lesions represented. Therefore, the device labeling warns when assessing Nevisense output in patients 30 years of age and below, as the safety and effectiveness of Nevisense has not been adequately studied in this subgroup.

Table 29: Sensitivity and Specificity of Nevisense by Age Group and Melanoma Depth

Set of Melanoma Lesions	Age Group	Sensitivity	Specificity
Tis-T4	<= 30	57%	38%
Tis-T4	31-40	97%	38%
Tis-T4	41-50	98%	38%
Tis-T4	51-60	98%	28%
Tis-T4	61-70	97%	19%
Tis-T4	71-80	98%	14%
Tis-T4	> 81	100%	3%
Tis-T1	<= 30	50%	38%
Tis-T1	31-40	96%	38%
Tis-T1	41-50	97%	38%
Tis-T1	51-60	98%	28%
Tis-T1	61-70	96%	19%
Tis-T1	71-80	97%	14%
Tis-T1	> 81	100%	3%

Table 30: Sensitivity and Specificity of Nevisense for Males and Females

Clinical Suspicion of Risk	Sensitivity for Males	Specificity for Males	Sensitivity for Females	Specificity for Females
Overall	97.9%	25.3%	93.5%	36.8%

For the pivotal study, sensitivity of Nevisense was evaluated by lesion area quantile. Lesion area is calculated from lesion Length x Width, and lesion quantiles defined by Area (mm^2) as shown below:

1^{st} Quantile: Area ≤ 12
2^{nd} Quantile: $12 <$ Area ≤ 24
3^{rd} Quantile: $24 <$ Area ≤ 42
4^{th} Quantile: $42 <$Area

Table 31: Sensitivity by Lesion Area Quantile

Area Group	Estimate
1^{st} quantile	80.1%
2^{nd} quantile	88.0%
3^{rd} quantile	93.5%
4^{th} quantile	98.9%

A lower sensitivity was observed for Nevisense in the 1st quantile (80.1%) as compared with other quantiles (88.0% – 98.9%). The accuracy of Nevisense relative to other methods used to diagnose the same lesions was explored.

Pivotal study

Figure 5 shows the sensitivity by lesion size in the pivotal study primary effectiveness population for Nevisense as compared with assessment by the visual classification board (overall suspicion of malignancy from 0 (benign) to 10 (malignant)), and with

each site's local pathologist determination for the same lesions. Nevisense sensitivity was as good as or better than other methods in every lesion size category.

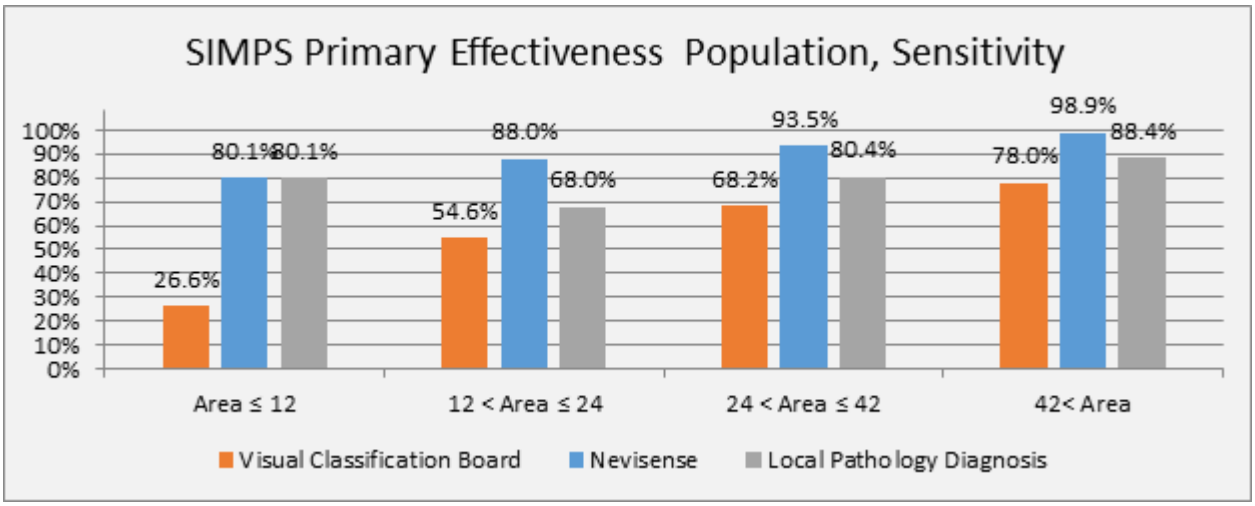


Figure 5: Pivotal Study – Sensitivity by Lesion Size

The Visual Classification Board (VCB) was a panel of dermatologists who evaluated lesion and dermoscopy images according to established clinical protocols (clinical ABCD rule, the dermoscopic ABCD rule, the seven-point checklist, and the overall suspicion of malignancy classified by VCB from 0 (benign) to 10 (malignant)) to ascertain a standardized assessment for study lesions.

Reader Study

Figure 6 shows the sensitivity for reader diagnosis of melanoma without (before) having the Nevisense data versus with (after) considering the Nevisense data for the same lesions. In all lesion size categories, Nevisense meaningfully improved physician detection of melanoma. The largest increase in Reader sensitivity was seen in the smallest lesions: Reader sensitivity improved from 37.6% without Nevisense to 50.5% with Nevisense.

Note that Reader diagnosis of *melanoma with Nevisense* is different than stand-alone Nevisense accuracy. Reader diagnosis of *melanoma with Nevisense* is reader accuracy with (after) considering Nevisense output, and should be compared with reader accuracy without (before) considering Nevisense output.

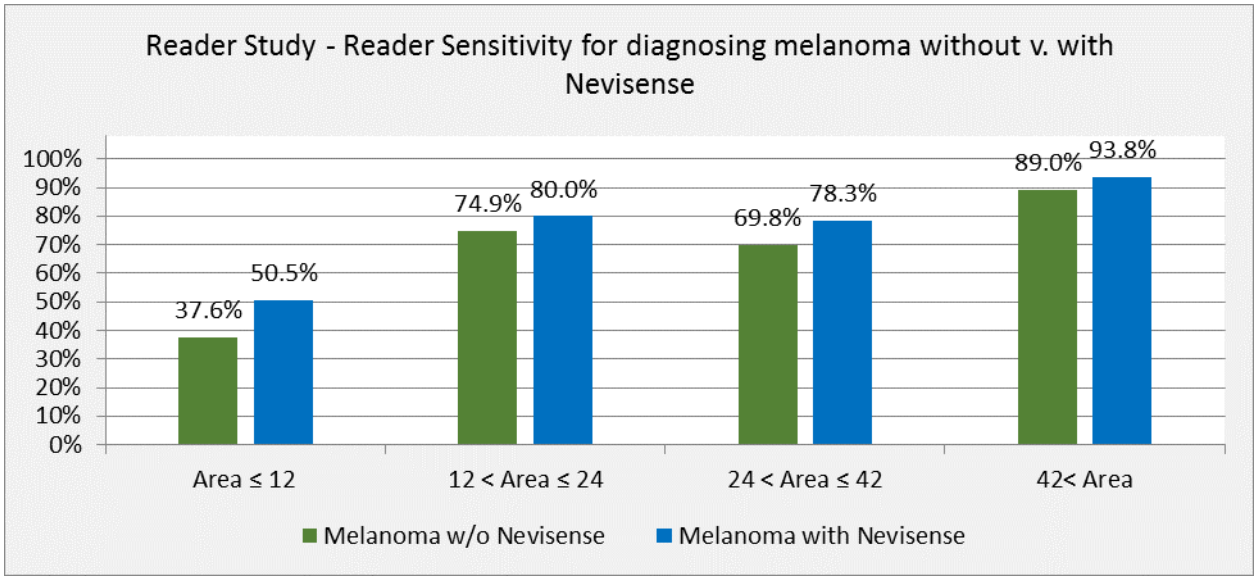


Figure 6: Reader Study, Reader Sensitivity for diagnosis of Melanoma without (before) versus with (after) Nevisense information

Sensitivity for Nevisense in the pivotal study was lower (80.1%) for the smallest lesions. However, sensitivity is also lower for dermatologists for smaller lesions as seen in the VCB subgroup for Pivotal Study and in the Reader Study. In every lesion size category, sensitivity is as good or better for Nevisense than for the other methods. The largest difference in sensitivity for the Pivotal Study (Nevisense versus VCB subgroup) and the largest improvement in sensitivity for the Reader Study (melanoma diagnosis without versus with Nevisense) were observed in the smallest lesions, which may be more difficult for dermatologists to diagnose, thus supporting the benefit of Nevisense as a diagnostic support tool.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Pivotal Study

Primary Endpoint Effectiveness at the lesion level (Primary Effectiveness Population):

Sensitivity 95.9%
Specificity 31.3%

Table 32: Cross-Tabulation of Results from Lesions Tested by Nevisense and Reference (Histology) for the Primary Effectiveness Analysis

	Reference Positive	Reference Negative
Nevisense Positive	256	1157
Nevisense Negative	11	527

The odds ratio is 10.5 ($P < 0.0001$), meaning that the Nevisense outcome is not random.

Therefore, both co-primary study endpoints were met.

Secondary Endpoint effectiveness at the lesion level:

Sensitivity 92.5%
Specificity 34.5%

Table 33: Cross-Tabulation of Results from Lesions Tested by Nevisense and Reference (Histology) for the Secondary Effectiveness Analysis

	Reference Positive	Reference Negative
Nevisense Positive	472	951
Nevisense Negative	38	500

The odds ratio is 6.4 ($P < 0.0001$), meaning that the Nevisense outcome is not random

Therefore, both co-secondary study endpoints were met.

Primary Endpoint effectiveness at the lesion level (with Updated Primary Effectiveness Population):

Sensitivity 96.6%
Specificity 34.4%

Table 34: Cross-Tabulation of Results from Lesions Tested by Nevisense and Reference (Histology) for the Primary Effectiveness Analysis, Excluding Nevisense Measurements Taken on Healthy Skin

	Reference Positive	Reference Negative
Nevisense Positive	256	956
Nevisense Negative	9	501

The odds ratio is 12.9 ($p<0.0001$), meaning the Nevisense outcome is not random.

Therefore, both co-primary endpoints were also met for the analysis conducted in the updated primary effectiveness population.

Reader Study

Reader sensitivity for identifying melanoma was 77.2% without Nevisense and 83.6% with Nevisense. Reader sensitivity improved on average by 6.4%, which was statistically significant ($P < 0.001$). Therefore, the first co-primary endpoint

was met. Readers' specificity with Nevisense decreased on average by 4%, which was not statistically significant (p=0.14).

With Nevisense aid, the sum of readers' sensitivity and specificity is 1.33, which is statistically significantly greater than 1, meaning the readers' decision when using Nevisense is non-random. Therefore, the second co-primary endpoint was also met.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical studies conducted to support PMA approval as described above. No serious adverse events were noted in the pivotal study.

A portion of the cutaneous melanomas in the pivotal study 4.1% were missed (sensitivity 95.9%). Approximately 69% of lesions were classified as melanoma when they were not melanoma by histological examination (specificity 31.3%). Potential indirect adverse effects of any skin examination for melanoma include: false negative results may lead to delays in the timely diagnosis of melanoma cancer and treatment, allowing an undetected condition to worsen and potentially increasing morbidity, and mortality; false positive results could lead to patients unnecessarily undergoing more frequent screening and potentially invasive procedures such as skin biopsy.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in the clinical studies conducted to support PMA approval as described above. The results of the Pivotal Study and Reader Study suggest that Nevisense, when used as indicated and for the types of lesions indicated, aids dermatologists in the detection of melanoma. This is not to be used on lesions already determined to require biopsy based on clinical evaluation. This device is an adjunct tool for lesions prior to the decision to biopsy.

In the Pivotal Study, Nevisense demonstrated a high sensitivity for detection of melanoma (95.9%), with an observed specificity of 31.1% in the primary effectiveness population. For the same lesion dataset, the observed sensitivity was 71.3% for dermatologists in the visual classification board, and was 84.6% for the diagnosis of the local pathologists. (Note that the reference diagnosis was established by the pathology board, not by the local pathologists.) This suggests that Nevisense can provide benefit as an aid in melanoma detection.

The observed Nevisense sensitivity was 100% for high stage melanoma (thickness T2, T3 and T4), 97.4% for melanoma thickness T1, and 92.9% for in-situ in the primary effectiveness population. The Nevisense sensitivities observed for T1 (97.4%) and for in-situ (92.9%) compare favorably with the observed sensitivity of visual classification board dermatologists (76.6% for T1, and 57.4% for Tis) and with the diagnosis of the local pathologists (92.1% for T1, and 72.6% for in-situ) for the same lesion dataset, suggesting that Nevisense can aid dermatologists

with melanoma detection, particularly in less severe melanomas, which can be more difficult for dermatologists to detect.

In the Pivotal Study, there were few melanomas in patients <30 years of age. The observed Nevisense sensitivity for this subgroup (57.1%) was notably lower than for all other age groups ≥30 years. Although the true sensitivity in this age group could not be verified due to the small number of melanoma lesions represented, the device labeling advises a warning when assessing Nevisense output in patients below age 30.

In the Pivotal Study, there were few melanomas in patients with Fitzpatrick skin types 5 and 6. Because the true sensitivity in these skin type groups could not be verified due to the small number of melanomas represented, the device labeling advises caution when assessing Nevisense output in patients with Fitzpatrick skin types 5 and 6.

Bleeding during measurement was reported after use of the device in 6 (0.3%) of subjects, which may suggest that the electrode can penetrate deeper than the stratum corneum in some cases. The electrode can be used up to 20 times in the same patient. If the electrode comes in contact with a melanoma and then is used for subsequent measurements on the patient, there is a theoretical possible risk of tumor seeding. There are no known cases of melanoma transferred in this way. The risk is estimated to be remote (worst-case probability estimate 0.000007).

The Reader Study evaluated how having Nevisense output as an adjunctive diagnostic support tool affects dermatologists' ability to detect melanoma, by comparing dermatologists' melanoma detection accuracy without versus with Nevisense output. In the Reader Study, physician sensitivity increased from 77.2% without Nevisense to 83.6% with Nevisense (+6.4%), which was statistically significant ($p<0.001$), while physician specificity decreased from 53.1% without Nevisense to 49.1% with Nevisense (-4%), which was not statistically significant ($p=0.14$). These results further support the benefit of the Nevisense as an adjunct to the current clinical practice for detecting melanoma.

Results from the Reader Study for the melanoma question demonstrated a 6.4% increase in sensitivity with Nevisense and a 4% decrease in specificity with Nevisense. Results from the Reader Study for the biopsy question demonstrated a 4.9% increase in sensitivity with Nevisense and a 6.2% decrease in specificity with Nevisense.

Below are the total number of readings that changed, across all readers, when deciding whether the lesion was melanoma and whether they would biopsy lesions.

Change from Not Melanoma to Melanoma for Actual Melanomas: 180
Change from Melanoma to Not Melanoma for Actual Melanomas: 22
Change from Not Melanoma to Melanoma for Non Melanomas: 371
Change from Melanoma to Not Melanoma for Non Melanomas: 239

Change from No Biopsy to Biopsy for Actual Melanomas: 144

Change from Biopsy to No Biopsy for Actual Melanomas: 23
Change from No Biopsy to Biopsy for Non Melanomas: 423
Change from Biopsy to No Biopsy for Non Melanomas: 218

Overall, the device used as an adjunct tool led to 158 more melanoma decisions and 121 more biopsy decisions for actual melanomas.

1. Patient Perspectives

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

In conclusion, given the available information above, the data supports the Nevisense indication for use.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Nevisense provides an objective method, used as a complement to the visual examination, to help the dermatologist decide whether to biopsy the lesion. The device demonstrated a satisfactory safety profile, with few adverse events overall and no serious adverse events. The high observed sensitivity and non-randomness of the device for distinguishing melanomas and non-melanoma malignancies from benign lesions observed in the Pivotal Study, and the improved accuracy relative to standard of care observed in the Reader Study, considered with the indications for use and the warnings, together support the conclusion that the benefits of the Nevisense for use by dermatologists as one element of the overall clinical assessment, used in combination with clinical and historical signs of melanoma to obtain additional information prior to a decision to biopsy, outweigh the risks.

XIV. CDRH DECISION

CDRH issued an approval order on June 28, 2017.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Altman, DG and Bland, JM. Statistics Notes: Diagnostic tests 2: predictive values *BMJ* 1994; 309:102. doi: https://doi.org/10.1136/bmj.309.6947.102