SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Optical diagnostic device for melanoma detection
Device Trade Name:	MelaFind
Applicant's Name and Address:	MELA Sciences, Inc. 50 South Buckhout St. Suite 1 Irvington, NY 10533
Date of Panel Recommendation:	November 18, 2010
Premarket Approval Application (PMA) Number:	P090012
Date of FDA Notice of Approval:	November 1, 2011
Expedited:	Granted expedited review status on October 3, 2006 because the device met the criteria of a device intended to affect a condition that is life-threatening and is irreversibly debilitating.

II. INDICATIONS FOR USE

MelaFind is intended for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. MelaFind is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy. MelaFind should NOT be used to confirm a clinical diagnosis of melanoma.

MelaFind is only for use by physicians trained in the clinical diagnosis and management of skin cancer (i.e., dermatologists) who have also successfully completed a training program in the appropriate use of MelaFind.

The MelaFind result is one element of the overall clinical assessment. MelaFind positive lesions (which may include malignant melanoma, melanoma in situ, high grade dysplastic nevi and atypical melanocytic proliferation/hyperplasia) should be considered for biopsy; the biopsy decision of a MelaFind negative lesion should be based on the

remainder of the entire clinical context. Lesions that are "non-evaluable" by MelaFind should be carefully re-evaluated for biopsy.

MelaFind is indicated only for use on lesions with a diameter between 2 mm and 22 mm, lesions that are accessible by the MelaFind imager, lesions that are sufficiently pigmented (i.e. not for use on non-pigmented or skin-colored lesions), lesions that do not contain a scar or fibrosis consistent with previous trauma, lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions), lesions greater than 1 cm away from the eye, lesions which do not contain foreign matter, and lesions not on special anatomic sites (i.e., not for use on acral, palmar, plantar, mucosal, or subungual areas). MelaFind is not designed to detect pigmented non-melanoma skin cancers, so the dermatologist should rely on clinical experience to diagnose such lesions.

III. CONTRAINDICATIONS

None

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

MelaFind® is a multi-spectral, non-invasive and automated (objective) computer-vision system that classifies the image of a pigmented skin lesion and classifies them based upon degree of 3-dimensional morphological disorganization: MelaFind Positive (high degree of morphological disorganization) or MelaFind Negative (low degree of morphological disorganization). MelaFind consists of:

- A hand-held imager that for every skin lesion acquires 10 multi-spectral [from 430 nm (blue) to 950 nm (near infrared)] digital images (1280 × 1024 pixels) using 91% isopropyl alcohol for refractive index matching;
- A password-protected computer connected to the imager;
- A monitor for displaying multi-spectral and reconstructed Red Green Blue (RGB) digital images of clinically atypical pigmented skin lesions and MelaFind results;
- A removable media for storing acquired images and MelaFind results;
- Fixed algorithms for automatic image analysis:
    1. calibration algorithms that reduce noise and artifacts in the images and determine the diffuse reflectance (the fraction of the incident light that is reflected) of skin and lesions relative to a target of known reflectance;
    2. image quality control algorithms that automatically detect problems (overexposure, underexposure, lesion too big, lesion too small, too much hair on the lesion, too many bubbles on the lesion, motion of the hand-held imager during imaging, etc) and, when appropriate, request the operator to re-image the lesion; only images that pass these algorithms are accepted for further processing and are considered evaluable;

3. lesion segmentation algorithm that identifies image pixels that belong to the lesion;
4. feature extraction algorithms that compute parameters characterizing lesions;
5. lesion classification algorithm that differentiates lesions with high level of 3-dimensional morphological disorganization (MelaFind Positive) from lesions with low level of disorganization (MelaFind Negative).

Figure 1: Hand Held Imaging Device (Probe)

Figure 2: MelaFind System

Principles of Operation:
MelaFind System Workflow:
(1) Operator's enters patient data; (2) Operator removes or trims any hair from the lesion area, cleans area with alcohol, then squirts a few drops of 91% isopropyl alcohol over the lesion to be imaged; (3) The operator views the preview image and presses the trigger on the hand-held imaging device and holds it steady for 2-3 seconds (until a beep is heard and "Done" appears); (4) Software on the base computer checks that all hardware diagnostic status data are within normal operating ranges, and the probe then transfers the ten-band image to the base computer.; (5) Once an image is accepted, it is calibrated in each spectral band and then segmented, following which values are calculated for a set of lesion features. The computer sends a result message to the monitor, for display to the operator (6). This output provided is either "MelaFind POSITIVE" or "MelaFind NEGATIVE."

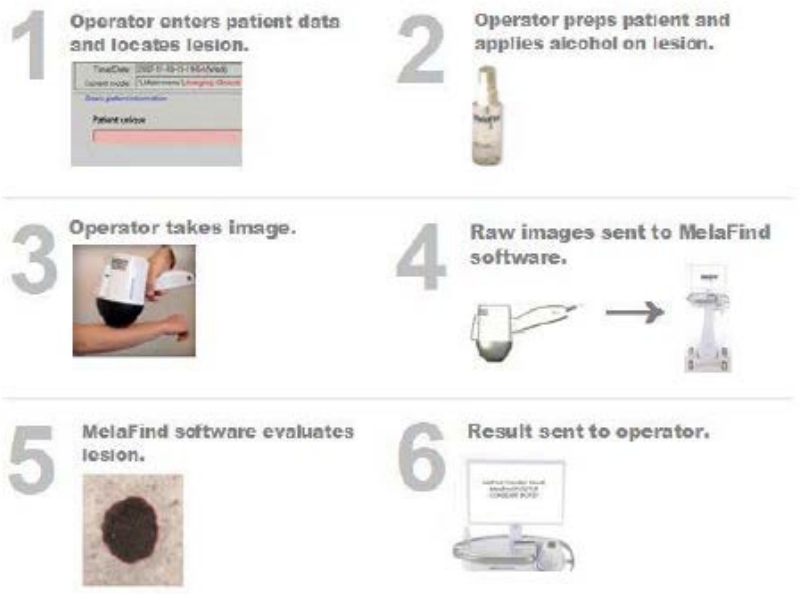

Figure 3: MelaFind Work Flow

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the detection of melanoma: a dermatologist's un-aided visual examination of a lesion with or without dermoscopy, and there are several 510(k) cleared devices that provide digital dermoscopic images that help in observing the skin lesion as it evolves. 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

MelaFind has obtained the CE Mark allowing the company to market its device within the European Union (EU).

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No direct adverse events were reported for the patients enrolled in the MelaFind pivotal study. However, 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.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Electrical Safety Testing

Table A: Electrical Safety Testing

Test	Purpose	Results
UL 60601-1:2006	Electrical Safety	Pass
IEC60601 2nd Ed.+A1+A2	Electrical Safety	Pass
CAN/CSA-C22.2, No. 601.1-M90, 2005	Electrical Safety	Pass
IEC 60529	Electrical Safety	Pass
IEC 60721-4	Electrical Safety	Pass
IEC 60601-1-2:2007	EMC Safety	Pass

B. Software Testing

The sponsor has provided acceptable software documentation to demonstrate functionality, user interface, safety checks and performance accuracy, which included the hand held imaging device and the image analysis software running on the PC.

Table B: Software Testing

Test	Purpose	Results
Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 11, 2005	Software Functionality	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDY (Protocol 20061)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of detecting malignant melanoma and high grade lesions with MelaFind for use on clinically atypical cutaneous pigmented lesions with one or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

MelaFind's classifier algorithm was developed and tested in six clinical studies, which enrolled a total of 9439 images of 9078 lesions from 6931 patients, including 630 melanomas, at 40 clinical study sites in the United States and abroad over seven years. Five of these – Protocols 20011, 20012, RCP2007-05, 20031-A, and 20031-B – were pre-pivotal clinical studies to develop the automatic MelaFind image analysis algorithm. The

last, Protocol 20061, was the pivotal trial to evaluate the safety and effectiveness of MelaFind. Adjunctively, two web-based (electronic) physician reader studies were performed based upon stored images and case histories collected by live assessment in pivotal study (Protocol 20061). The effect of electronic lesion assessment compared to live lesion assessment was not evaluated in studies conducted with this device.

A. Study Design

Patients were treated between Jan 31, 2007 and July 7, 2008. The database for this PMA reflected data collected through July 7, 2008 and included 1383 patients having 1831 pigmented skin lesions (PSLs). Of the 1831 lesions enrolled, 1632 lesions considered to be eligible and evaluable for analysis. There were 7 investigational sites.

Protocol 20061 was a prospective, multi-center, blinded clinical study. Examining dermatologists were blinded to the MelaFind results, dermatopathologists were blinded to both the dermatological diagnoses and MelaFind results, and MelaFind was blinded to both dermatological and histological diagnoses. Enrollment was to proceed until at least 93 eligible and evaluable dermato-histologically confirmed melanomas were enrolled among lesions receiving dermatological diagnosis of either 'melanoma cannot be ruled out' or not melanoma', with a minimum total number of lesions of 1200. Sensitivity and specificity as primary endpoints were determined to be appropriate metrics for evaluating safety and effectiveness of MelaFind to correctly identify malignant melanoma. The sponsor used exact method to calculate the sample size based on one-sided alpha=0.05 and used the "mid-P exact method" to compute a one-sided 95% confidence interval (CI) on sensitivity for their statistical analysis.

Procedures:
Three high resolution digital photographs of the lesions were obtained – two clinical views (from 21 inches and 8 inches away) and a dermoscopic image – using standard cameras. Enrolled lesions were to be assessed by MelaFind as 1 (positive) or 0 (negative), by dermatologists based upon clinical and dermatoscopic (if performed) pre-biopsy lesion categorization as definite melanoma (100% likely melanoma), melanoma cannot be ruled-out (likely, 67-99%; possible, 34-66%; and unlikely, 1-33%), and not melanoma (0% likely) and by dermatopathologists using histologic diagnosis of biopsy specimens.

Population Schema:
Lesions atypical for suspicion of melanoma (F1) were given the clinical diagnosis: "Melanoma" (F2) and "Melanoma cannot be ruled-out" (F3) are considered clinically positive. Atypical and not-atypical lesions undergoing biopsy for "Non-Melanoma Concerns" (F5 and F7) are considered clinically negative.

The following figure describes the population schema for Protocol 20061.

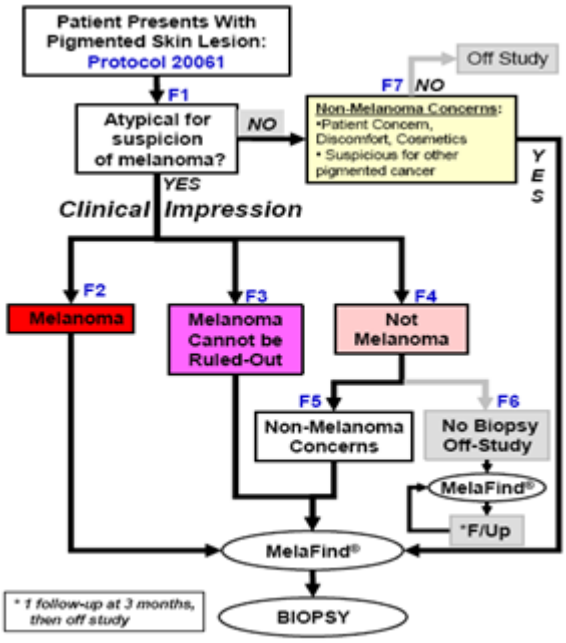

Figure 4: Population Schema:

Protocol 20061 also evaluated the "Uncertain" category by drawing patients from the "Melanoma cannot be ruled-out" (F3) group, which represents the "Uncertain" lesions that were biopsied. Additional "Uncertain" lesions that were biopsied were derived from the "Non-Melanoma Concerns" (F5) category of the "Not Melanoma" group of atypical lesions (F4). The sponsor initially proposed that "Uncertain" lesions from the F4 "Not Melanoma" that are NOT biopsied would be followed (F6). However, no investigational site enrolled any lesions in the follow up group.

All study lesions were biopsied; no study lesions were followed to assess lesion change with time (evolution). Biopsies were reviewed by at least two central dermatopathologists; the positive class of lesions consisted of melanomas (in situ and invasive), and high grade lesions (high grade dysplastic nevi, atypical melanocytic proliferation/hyperplasia). Breslow thicknesses of invasive melanomas were recorded.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Pivotal study was limited to patients with lesions that met the following inclusion criteria:

Cutaneous lesions examined with MelaFind had to satisfy all of the following inclusion criteria:

1. The lesion is pigmented (i.e., melanin, keratin, blood)
2. Clinical management of the lesion by the examining dermatologist is either:
   -Biopsy of the lesion *in toto*,
   OR -
   -3-month follow-up of the lesion
3. The diameter of the pigmented area is not < 2 mm, and not > 22 mm
4. The lesion is accessible to the MelaFind probe
5. The patient, or a legally authorized representative, has consented to participate in the study and has signed the Informed Consent Form

Patients were <u>not</u> permitted to enroll in the Pivotal study if they met any of the following exclusion criteria:

Cutaneous lesions that meet any of the following exclusion criteria will not be accepted:

1. The patient has a known allergy to isopropyl alcohol
2. The lesion has been previously biopsied, excised, or traumatized
3. The skin is not intact (e.g., open sores, ulcers, bleeding)
4. The lesion is within 1 cm of the eye
5. The lesion is on mucosal surfaces (e.g., lips, genitals)
6. The lesion is on palmar hands
7. The lesion is on plantar feet
8. The lesion is on or under nails
9. The lesion is located on or in an area of visible scarring
10. The lesion contains foreign matter (e.g., tattoo, splinter, marker)

2. <u>Follow-up Schedule</u>
   The patient became a prospective candidate for the clinical trial when upon evaluation of a patient presenting with one or more pigmented skin lesions, the examining dermatologist either decided to have a lesion(s) biopsied, or decided that a patient's lesion(s) should be evaluated again in **3** months. Since all lesions enrolled in the study were determined to be suspicious all lesions were biopsied and therefore no lesions were enrolled in the 3-month follow up.

3. <u>Clinical Endpoints</u>
   With regards to safety, effectiveness, and success/failure criteria, the sponsor met the following primary endpoints:

   Primary Aim 1: To demonstrate that MelaFind's sensitivity to malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is at least 95% at a 95% confidence level.

   Primary Aim 2: To demonstrate that, along with this high level of sensitivity, the specificity of MelaFind for lesions that are not malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is superior to the specificity of study dermatologists.

B. Accountability of PMA Cohort

At the time of database lock, of 1383 patients and 1831 lesions enrolled in PMA study, 99% patients and 89% of lesions were available for analysis at the completion of the study. Table 1 summarizes the enrollment of patients and lesions on all clinical studies. Of the 1831 lesions enrolled, 1632 lesions considered to be eligible and evaluable for analysis (Table 2).

Table 1. Summary of Patient and Lesion Enrollment by Protocol

Protocol No.	All Images Acquired (n = 9439)[a]	All Lesions Imaged (n = 9078)	All Patients Enrolled (n = 6931)
20011	5794	5488	4180
20012	856	802	644
RCP2007-05	208	208	122
20031-A	223	223	170
20031-B	526	526	432
20061	1832	1831	1383

[a] Multiple images of the same lesion could be acquired

Table 2: Protocol P20061, Lesion Accounting

Total Lesion Registration				**1835**	
	Mis-Registrations			4	
		Demo lesion enrolled as real patient – Invalid data point			2
		Wrong lesion imaged – Invalid data point			1
		Duplicate lesion registration – Invalid data point			1
Lesions Enrolled				**1831**	
	Patient withdrew from Study			1	
Lesions Enrolled and Not Withdrawn				**1830**	
	Determined to be ineligible due to violation of inclusion/exclusion criteria			3	
		Patient did not sign Informed Consent Form			2
		Lesion was previously biopsied excised or traumatized			1
	Determined to be ineligible during central dermatohistopathology			14	
		Lesion biopsied but biopsy not in toto			1
		Lesion was not pigmented			1
		Lesion biopsied but biopsy not in toto; Lesion was not pigmented			1
		Lesion contained dermal scar/fibrosis consistent with previous trauma			11
Eligible Lesions				**1813**	
	Determined to be non-evaluable due to CRF or dermatohistopathology			19	
		Slides not received, or received late			16
		Slides not received, or received late; MelaFind image not acquired			1
		Slides not received, or received late; Image disqualified by MelaFind quality control algorithms			1
		Inadequate histology – poorly prepared slide not prepared			1
Eligible Lesions with CRF and Reference Standard (RefStd)				**1794**	
	Determined to be non-evaluable due to unsuccessful imaging attempts			162	
		Irretrievable electronic data loss – eCRF, MelaFind images, clinical images			4
		MelaFind image not acquired			9
		Phantom self-test failure			7
		Phantom self-test failure; Image disqualified by MelaFind quality control algorithms			2
		Image disqualified by MelaFind quality control algorithms			140
Eligible and Evaluable				**1632**	

C. Population Demographics and Baseline Parameters

Of the 1831 lesions enrolled, 1632 lesions considered to be eligible and evaluable for analysis. Table 3 presents lesion demographics for Protocol 20061 sub-divided by investigating dermatologist pre-biopsy diagnosis of F2, F3, and F4.

Table 3: Protocol 20061, All Enrolled Lesions, Demographics

Demographics		All Enrolled Subject Population			
		Atypical			All Pigmented Lesions
		Melanoma (F2)	Melanoma Cannot Be Ruled Out (F3)	Not melanoma (F4)	All Populations***
N, Lesions from Patients Enrolled		25	1702	103	1831
Gender*	Female	11	920	61	993
	Male	14	782	42	838
Age*	<21 years	0	102	5	107
	21 – 55 years	13	1082	46	1142
	>55 years	12	518	52	582
Anatomic Location*	Face	1	51	7	59
	Posterior Torso	7	745	34	787
	Anterior Torso	0	358	18	376
	Extremity: Arm/ Leg	16	491	30	537
	Neck	0	32	8	40
	Scalp	1	25	6	32
Fitzpatrick Skin Type*	I	3	112	2	117
	II	11	897	73	981
	III	8	610	24	642
	IV	3	75	3	82
	V	0	5	1	6
	VI	0	3	0	3
Geographic Sites, Patients***	US – sun belt	22	1349	88	1459
	US – non-sun belt	3	353	15	372
	Non - US	0	0	0	0

* Table presents total lesion counts. Patients who contributed more than one lesion to the study are represented in more than one population when those lesions occur in more than one population

** Geographic sites were tabulated based on clinical study site. US – sun belt included Alabama, California, Florida, and North Carolina. US – non-sun belt included Pennsylvania and Illinois. All

clinical study sites were in the US.
*** Total eligible and evaluable lesions include 1 lesion from the Not Atypical for suspicion of Melanoma (F7)

Table 4 presents melanoma characteristics among the eligible and evaluable lesions.

Table 4. Protocol 20061 Eligible and Evaluable Lesion, Malignant Melanoma Dermatohistopathology

	Melanoma Type (N = 127)	
Melanoma invasive	n = 70	55.1%
Superficial Spreading	60	85.7%
Lentigo Maligna Melanoma	7	10.0%
Nodular	2	2.9%
Unclassified	1	1.4%
Melanoma in situ	n = 57	44.9%
Superficial Spreading	31	54.4%
Lentigo Maligna	25	43.9%
Unclassified	1	1.8%

Table 5 summarizes data on Breslow thickness of eligible and evaluable invasive melanomas in the pivotal study. Almost all melanomas in the pivotal clinical study were early lesions that can be successfully treated with surgical excision, but may be difficult to differentiate from benign look-alikes.

Table 5. Protocol 20061 Eligible and Evaluable Invasive Melanoma Breslow Thickness

Breslow Thickness	n = 70
Mean	0.41 mm
Std. Deviation	0.20 mm
Median	0.36 mm
Range	0.12 – 1.2 mm
Number of Lesions <1 mm	68 (97.1%)
Number of lesions 1 - 2 mm	2 (2.9%)
Number of lesions 2.1 – 4 mm	0
Number of lesions >4 mm	0

Table 6 compares dermatological categorization and the histological reference standard for all eligible and evaluable lesions. Most histologically verified melanomas were diagnosed prior to biopsy as “Melanoma cannot be ruled out;” about a third of

melanomas were considered unlikely (likelihood between 1 and 33 %), thirteen were considered 'definitive melanoma' (likelihood 100%) and one was considered 'not melanoma (likelihood 0%). Study investigators enrolled these lesions based upon inclusion / exclusion criteria including management plan for lesion excision in toto. Inclusion / exclusion criteria were not based upon dermatologist categorization of the likelihood of lesion to be melanoma (in situ, invasive), high grade dysplastic nevus or atypical melanocytic proliferation or hyperplasia.

Table 6. Protocol 20061, Eligible and Evaluable Lesion (n=1632), Dermatologist Likelihood Estimate and Dermatopathology

Dermatological Diagnosis	Histological Diagnosis		
	MM	HGDN*	OTHER
Melanoma	13	1	6
Melanoma Can Not Be Ruled Out			
Likely melanoma (67-99%)	30	4	46
Possible melanoma (34-66%)	44	14	471
Unlikely melanoma (1-33%)	38		
Not melanoma			
Clinical concern (dermoscopy only)	1	1	27
Non-melanoma skin cancer	0	0	13
Patient's concern	1	1	55
Physical discomfort	0	0	8
Cosmetic purposes	127	48	1457
Total	127	48	1457
*Also includes AMP and AMH			

Prevalence of clinical and historical characteristics of melanoma among eligible and evaluable lesions in the pivotal study is shown in Table 7. Classic characteristics such as ABC (asymmetry, border irregularity, and color variegation) have high sensitivities (over 80%) to positive lesions (melanoma and high-grade). About 30% of positive and 60% of negative lesions are small (diameter < 6 mm). Three melanomas were identified only as "ugly ducklings", i.e., these melanomas had no ABCDE characteristics. Eleven of 1632 lesions did not have any of these characteristics and these were all benign.

Table 7. Protocol 20061: Prevalence of Clinical and Historical Characteristics of Melanoma Among Eligible and Evaluable Lesions

Lesion ABCDEPRU Criteria	Atypical						Not Atypical	
	Melanoma (F2)		Melanoma Cannot Be Ruled Out (F3)		Not melanoma (F4)		Non-atypical pigmented lesion (F7)	
N, Eligible and Evaluable Lesions	20		1528		83		1	
ABCDEPRU n (# recorded); N (# pt = # lesion) % = n / N	n	%	n	%	n	%	n	%
Asymmetry: when one half of the mole does not match the other half	19	95% (19/20)	1202	78.7% (1202/1528)	36	43.4% 36/83)	0	0% (0/1)
Border: when the edges of the mole are ragged or irregular	19	95% (19/20)	1142	74.7% (1142/1528)	35	42.2% (35/83)	0	0% (0/1)
Color: when the color of the mole varies throughout	18	90%(18/20)	1188	77.8% (1188/1528)	45	54.2% (45/83)	0	0% (0/1)
Diameter: if mole's diameter is larger than a pencil eraser (> 6mm)	17	85%(17/20)	620	40.6%(620/1528)	40	48.2% (40/83)	0	0% (0/1)
Evolving: changing size, shape or color over a short period of time	14	70%(14/20)	487	31.9%(487/1528)*	39	47% (39/83)	0	0% (0/1)
Patient concern	11	55%(11/20)	481	31.5%(481/1528)	69	83.1% (69/83)	0	0% (0/1)
Regression: areas of hypo- or de-pigmentation, sometimes resulting in scar-like white or blue grey areas	4	20% (4/20)	85	5.6% (85/1528)	1	1.2% (1/83)	0	0% (0/1)
Ugly duckling: distinct from other nevi on the same patient	14	70% (14/20)	693	45.4% (693/1528)	27	32.5% (27/83)	0	0% (0/1)
Number of ABCDEPRU criteria per patient lesion)								
1	0	0% (0/20)	72	4.7% (72/1528)	14	16.9% (14/83)	0	0% (0/1)
2	2	10% (2/20)	180	11.8% (180/1528)	12	14.5% (12/83)	0	0% (0/1)
3	0	0% (0/20)	392	25.7% (392/1528)	16	19.3% (16/83)	0	0% (0/1)
4	2	10% (2/20)	403	26.4% (403/1528)	16	19.3% (16/83)	0	0% (0/1)
5	2	10% (2/20)	243	15.9% (147/1528)	15	18.1% (15/83)	0	0% (0/1)
6	6	30% (6/20)	147	9.6% (147/1528)	3	3.6% (3/83)	0	0% (0/1)
7	6	30% (6/20)	67	4.4% (67/1528)	7	8.4% (7/83)	0	0% (0/1)
8	2	10% (2/20)	14	0.9% (14/1528)	0	0% (0/83)	0	0% (0/1)
0	0	0% (0/20)	10	0.7% (10/1528)	0	0%(0/83)	1	100% (1/1)

Of the 1632 eligible and evaluable lesions, 645 had dermoscopic evaluations. Table 8 reports prevalence of dermoscopic characteristics of these 645 lesions.

Table 8. Protocol 20061, Eligible and Evaluable Lesions, Comparison of Melanoma Dermoscopic Characteristic Prevalence, Dermatopathology

Dermoscopic Characteristic	Histological Diagnosis		
	Any (n = 645)	MM/HGDN* (n = 88)	Non-MM/HGDN* (n = 557)
Multicomponent pattern	184 (28.5%)	29 (33.0%)	155 (27.8%)
Streaks/pseudopods	41 (6.4%)	11 (12.5%)	30 (5.4%)
Blue-white veil	34 (5.3%)	6 (6.8%)	28 (5.0%)
Branched streaks	59 (9.1%)	11 (12.5%)	48 (8.6%)
Asymmetry	395 (61.2%)	62 (70.5%)	333 (59.8%)
Multiple colors	430 (66.7%)	66 (75.0%)	364 (65.4%)
Regression structures/peppering	97 (15.0%)	27 (30.7%)	70 (12.6%)
Atypical dots/globules	162 (25.1%)	24 (27.3%)	138 (24.8%)
Atypical network	242 (37.5%)	41 (46.6%)	201 (36.1%)
Atypical vasculature	40 (6.2%)	8 (9.1%)	32 (5.7%)
Border sharpness	63 (9.8%)	8 (9.1%)	55 (9.9%)
Scar-like depigmentation	37 (5.7%)	12 (13.6%)	25 (4.5%)
*Includes diagnoses of Atypical Melanocytic Proliferation/Hyperplasia (AMP/AMH)			

Melanoma risk factors among patients with eligible and evaluable lesions in the pivotal study are shown in Table 9. Over 30% of patients had a history of dysplastic nevi, 17% had a personal history of melanoma, over 20% had a family history of melanoma, and about 15% had more than 50 nevi. However, of 127 patients with eligible and evaluable melanomas, 57 (45%) had none of these factors.

Table 9. Protocol 20061, Eligible and Evaluable Lesions, Melanoma Risk Factors

Melanoma Risk Factor		Histological Diagnosis					
		Any (n = 1632)		MM/HGDN (n = 175)		Non-MM/HGDN* (n = 1457)	
		Prevalence (%)	No. of Responses	Prevalence (%)	No. of Responses	Prevalence (%)	No. of Responses
Personal history of basal cell carcinoma		21.0	1612	33.5	173	19.5	1439
Personal history of squamous cell carcinoma		13.5	1611	26.0	173	12.0	1438
Personal history of dysplastic nevi		36.0	1567	26.2	172	37.2	1395
Personal history of melanoma		18.9	1619	24.7	174	18.2	1445
Family History of Melanoma		25.1	1507	25.3	162	25.1	1345
Fitzpatrick Skin Type	I.	6.5	1632	5.7	175	6.6	1457
	II.	53.7		65.7		52.3	
	III.	35.2		26.9		36.2	
	IV.	4.2		1.7		4.5	
	V.	0.2		0.0		0.3	
	VI.	0.1		0.0		0.1	
Natural red/blond hair		39.5	1632	49.1	175	38.4	1457
Blue/Green Eyes		67.8	1632	73.1	175	67.1	1457
Sunburns prior to age 20	0	13.9	1599	13.6	169	14.0	1430
	1-2	26.5		24.3		26.7	
	3-4	14.6		11.2		15.0	
	≥5	45.0		50.9		44.3	
Sunburns after age 20	0	32.2	1537	34.7	167	31.9	1370
	1-2	33.1		32.9		33.1	
	3-4	12.4		7.2		13.0	
	≥5	22.4		25.1		22.0	
Outdoor summer jobs as a teenager		42.0	1618	43.9	173	41.8	1445
Nevi ≥ 2mm	0	0.1	1632	0.6	175	0.1	1457
	1-10	37.4		51.4		35.7	
	11-30	30.5		22.3		31.4	
	31-50	14.8		10.9		15.3	
	>50	17.2		14.9		17.5	
Atypical Pigmented Skin Lesions	0	1.2	1632	0.6	175	1.3	1457
	1	47.5		67.4		45.2	
	2	21.4		16.6		22.0	
	3	7.7		4.0		8.1	
	4	4.5		1.7		4.9	
	>4	17.6		9.7		18.5	
Use of Tanning Beds	0	56.3	1632	65.7	175	55.2	1457
	1-10	17.6		11.4		18.3	
	11-24	9.3		10.9		9.1	
	>24	16.8		12.0		17.4	
History of UVA/UVB Treatment		3.7	1632	2.9	175	3.8	1457

All fields exclude entries of "n'a" or "unknown"
* Includes diagnoses of Atypical Melanocytic Proliferation/Hyperplasia

Anatomic sites for eligible and evaluable lesions in the pivotal study are shown in Table 10. The majority of lesions were from the trunk.

Table 10. Protocol 20061, Eligible and Evaluable Lesions, Anatomic Sites

Anatomic Site	Histologic Diagnosis		
	Any (N = 1632)	MM/HGDN* (N = 175)	Non-MM/HGDN* (N = 1457)
Head/neck	84 (5.1%)	24 (13.7%)	60 (4.1%)
Trunk	1074 (65.8%)	93 (53.1%)	981 (67.3%)
Upper limbs	227 (13.9%)	34 (19.4%)	193 (13.2%)
Lower limbs	247 (15.1%)	24 (13.7%)	223 (15.3%)
*Includes diagnoses of Atypical Melanocytic Proliferation/Hyperplasia			

Age distribution of patients with eligible and evaluable lesions in the pivotal study is shown in Table 11. Majority of melanomas are from adult patients; seven melanomas (all correctly identified by MelaFind) are from pediatric patients, with age ranging from 11 to 20 years. Ninety eight eligible and evaluable lesions in patients under the age of 21, including 7 melanomas, were enrolled and all of the melanomas were read correctly by MelaFind.

Table 11. Protocol 20061, Eligible and Evaluable Lesions, Subject Age Distribution

Age (years)	Histologic Diagnosis		
	Any (N = 1632)	MM/HGDN* (N = 175)	Non-MM/HGDN* (N = 1457)
0 - 20	98 (6.0%)	7** (4.0%)	91 (6.2%)
21 - 64	1268 (77.7%)	106 (60.6%)	1162 (79.8%)
65 +	266 (16.3%)	62 (35.4%)	204 (14.0%)
*Includes diagnoses of Atypical Melanocytic Proliferation/Hyperplasia ** MelaFind correctly identified all 7 melanomas enrolled on patients < 21			

D. Safety and Effectiveness Results

1. Safety and Effectiveness Results

Sensitivity and specificity as primary endpoints were determined to be appropriate metrics for evaluating safety and effectiveness of MelaFind to correctly identify malignant melanoma.

The dermatopathology, MelaFind output, and dermatologist pre-biopsy lesion categorization among all eligible and evaluable lesions are demonstrated in Table 12.

Table 12. Protocol 20061, Eligible and Evaluable Lesion Population

Lesion Assessment per Dermatologists, MelaFind Dermatopathology				Population						
				Atypical						All Pigmented Lesions
				Melanoma (F2)		Melanoma Cannot Be Ruled Out (F3)		Not melanoma (F4)		All Populations
N, Lesions Enrolled				25		1702		103		1831
N, Lesions Biopsied				25		1702		103		1831
N, Eligible and Evaluable Lesions				20		1528		83		1632
MelaFind Result[1] =				1	0	1	0	1	0	Total[2]
N[3]	By Dermatologist (MD)			20	0	1528	0	0	83	1632
	By MelaFind (MF)			20	0	1383	145	68	15	1632
	By Dermatopathology (DP)			14	6	159	1369	2	81	1632
	DP	MM[4] Type	*in situ*	4	NA	52	NA	1	NA	57
			Invasive	9	NA	61	NA	0	NA	70
		Breslow Thickness	< 1 mm	8	NA	60	NA	0	NA	68
			1 - 2 mm	1	NA	1	NA	0	NA	2
			2.1 - 4 mm	0	NA	0	NA	0	NA	0
			> 4 mm	0	NA	0	NA	0	NA	0
		HGDN		1	NA	41	NA	1	NA	43
		AMP/AMH		0	NA	5	NA	0	NA	5
		Dysplastic nevi, low grade		NA	5	NA	978	NA	15	998
		Other nevi		NA	0	NA	189	NA	28	218
		Non-melanoma skin cancers		NA	0	NA	23	NA	10	33
		Other non-melanocytic lesions		NA	1	NA	179	NA	28	208
by DP & MD & MF				NA	0	NA	0	NA	15	15
by DP & MD & not MF				NA	0	3	0	NA	66	70
by DP & MF & not MD				NA	0	NA	142	NA	0	142
by DP & not MF & not MD				NA	6	NA	1227	NA	0	1233
by DP & MD				NA	0	NA	0	NA	81	82
by DP & MF				14	0	156	142	2	15	329

[1] MelaFind 1 = MM/HGDN/AMP/AMH, MelaFind 0 = Not MM/HGDN/AMP/AMH

[2] Total eligible and evaluable lesions include 1 lesion from the Not Atypical for suspicion of Melanoma (F7)

[3] Number of lesions, [4] Melanoma

Table 13a reports the summary of the diagnostic performance for MelaFind on all eligible and evaluable lesions. The lesion population consists of lesions selected by the Investigating dermatologist for biopsy prior to MelaFind use. Dermatopathology diagnosis (Dx) was positive if a lesion was malignant melanoma (MM), high-grade dysplastic nevus (HGDN), or atypical melanocytic proliferation/hyperplasia (AMP/AMH). Every eligible and evaluable lesion was reviewed by, at least, two central dermatopathologists. If a lesion has one positive and one negative histological Dx, the histological slide will be sent to a third dermatopathologist to break the tie. To minimize clerical errors in pathology reports, if one histological Dx is melanoma and the other two are negative, the histological slide was sent to the dermatopathologist that diagnosed the lesion as melanoma for a blind re-review (fourth dermatohistopathology review). The lesion was placed in the positive category if the Dx of melanoma was duplicated and in the negative category otherwise.

Table 13a. Protocol 20061, Summary of Diagnostic Performance of MelaFind for MM/HGDN/AMP/AMH

Assessment including all lesions based upon dermatopathology	MelaFind
True Positive (TP)	172
False Negative (FN)	3
True Negative (TN)	157
False Positive (FP)	1300
Sensitivity*: P20061 lesion cohort	(172/175) 98.3%**
Specificity*: P20061 lesion cohort	(157/1457) 10.8%**
* This does not represent true (per subject) sensitivity or specificity.	
**The sensitivity and specificity are based on all eligible and evaluable lesions selected for biopsy by the investigating dermatologist and does not include all possible candidate lesions per subject.	

Based upon dermatopathology, sensitivity of MelaFind to detect melanomas (in situ and invasive), and high grade lesions (high grade dysplastic nevi, atypical melanocytic proliferation/hyperplasia) in the population of study lesions was 98.3% (172/175) and specificity was 10.8% (157/1457). One melanoma in situ, one invasive melanoma (Breslow thickness 0.28 mm), and one high grade lesion were not detected by MelaFind.

Table 13b reports the summary of the diagnostic performance of the Investigating Dermatologists on all eligible and evaluable lesions. Please note the lesion population consisted of lesions that were pre-selected by the investigating dermatologist for biopsy, thus, true and false negatives could not be assessed since those lesions were not included in the lesion population and were not biopsied. Table 13b measured sensitivity and specificity based upon the following pre-biopsy lesion

categorization (refer to Figure 4): Lesions categorized by dermatologists before biopsy as melanoma (F2) or melanoma cannot be ruled out (F3) are considered to be Positive; lesions categorized by dermatologists before biopsy as not melanoma (F4) are considered to be Negative.

Table 13b. Protocol 20061, Summary of Diagnostic Performance of the Investigating Dermatologist for MM/HGDN/AMP/AMH

Assessment including all lesions based upon dermatopathology	Investigators
True Positive (TP)	173
False Negative (FN)	2
True Negative (TN)	82
False Positive (FP)	1375
Sensitivity*: P20061 lesion cohort	(173/175) 98.9%**
Specificity*: P20061 lesion cohort	(82/1457) 5.6%**
*This does not represent true (per subject) sensitivity or specificity.	
**The sensitivity and specificity are based on all eligible and evaluable lesions selected for biopsy by the investigating dermatologist and does not include all possible candidate lesions per subject.	

Based upon dermatopathology, sensitivity of the Investigating Dermatologist using the pre-biopsy lesion categorization to detect melanomas (in situ and invasive), and high grade lesions (high grade dysplastic nevi, atypical melanocytic proliferation/hyperplasia) in the population of study lesions was 98.9% (173/175) and specificity was 5.6% (82/1457). According to their pre-biopsy lesion categorization (F4 'not melanoma') the Investigating Dermatologist did not detect one melanoma in situ, and one high grade lesion.

Analysis of Primary Aims:
The primary analysis was performed on 1612 eligible and evaluable lesions among lesions with a pre-biopsy lesion categorization of "melanoma cannot be ruled out" (F3) and "not melanoma" (F4) and excluded 20 eligible and evaluable lesions from "melanoma" (F2).

Analysis of Primary Aim 1:

Table 14 reports that MelaFind has met Primary Aim 1 using the "mid-P exact method" with a sensitivity of 98.3% (112/114) in the detection of Melanoma among lesions with a pre-biopsy lesion categorization of "melanoma cannot be ruled out" (F3) and "not melanoma" (F4). Both 90% and 95% two-sided confidence intervals are computed using Blythe-Still-Casella method by FDA. The Primary Aim 1 is met with 90% Confidence Interval (CI) where 1-sided 95% Lower confidence bound is greater than 95% but not met with 95% CI (2-sided 95% LCB). The difference is

sensitivity is -0.9% and the 95% or 90% CI of the difference is based on inverting 2 one-sided exact tests using standardized statistics.

Table 14. Analysis of Primary Aim 1

	Sensitivity+	95% CI		90% CI	
MelaFind†	98.3%	94.1%	99.7%	95.0%	99.5%

†CI computed with Blythe-Still-Casella method
*CI is exact based on inverting 2 one-sided tests using standardized statistic
+Sensitivity is based on all eligible and evaluable lesions selected for biopsy by the investigating dermatologist and does not include all possible candidate lesions per subject.

The sponsor's analysis stated that MelaFind's sensitivity to melanomas in the F3 and F4 populations had to be at least 95% at a 95% lower confidence bound in order to meet the primary aim. Lower confidence bound was computed using the mid-p exact method because of small sample sizes and very high sensitivity. Estimated sensitivity of MelaFind to melanoma from among lesions with a pre-biopsy lesion categorization of "melanoma cannot be ruled out" (F3) and "not melanoma" (F4) was 112/114 (98.25%) with 95% LCB = 95.10, indicating that Primary Aim 1 was met.

Analysis of Primary Aim 2:

Table 15 reports that the sponsor has met Primary Aim 2 since MelaFind Specificity (10.6%) is superior to the study dermatologists (5.5%). FDA's pooled specificity was obtained by pooling all pathology negative lesions. The pooled estimate calculates the specificity per individual and weights these by proportion of pathology negative lesion for that patient out of all pathology negative lesions. The 95% confidence interval are 95% bootstrap percentile intervals which take into account the correlation due to multiple lesion per individual.

Table 15. Analysis of Primary Aim 2

	Specificity†	95% CI††	
MelaFind	10.6%	9.7%	13.2%
Study Dermatologist	5.5%	4.5%	7.3%
Difference	5.1%	3.3%	7.7%

†Pooled estimate of Specificity based on all eligible and evaluable lesions selected for biopsy by the investigating dermatologist and does not include all possible candidate lesions per subject.
††95% Bootstrap percentile intervals,

The sponsor used average specificity which estimated specificity for each investigator and then was averaged across the investigators. Here, estimated specificity of MelaFind was 9.49% (95% CI: 6.06% to 12.92%) and for investigators was 3.71%

(95% CI: 0.77% to 6.65%). The estimated difference between average specificity of MelaFind and average specificity of investigators was 5.78% (95% CI: 0.92% to 10.64%), with p-value = 0.02. This p-value is less than 0.05 indicating that Primary Aim 2 was met.

Analysis of all enrolled lesions:

Of the 1831 enrolled lesions, 162 were deemed to be non-evaluable, including 27 melanomas. Table 16 reports the frequency of MelaFind Positive, MelaFind Negative and MelaFind non-evaluable among lesions that were positive on dermatopathology for malignant melanoma or high grade lesion and among lesions that were negative on dermatopathology for malignant melanoma or high grade lesions. Table 16 reports the MelaFind errors associated with the non-evaluable lesions.

Table 16. MelaFind test results to detect Melanoma or high grade dysplastic nevi among all eligible lesion (n=1794)

MelaFind	N	Melanoma or High grade lesions	Not Melanoma or High Grade lesions	% Melanoma or High grade Lesions of the total
+	1479	173	1306	11.7% (173/1479)
-	160	3	157	1.9% (3/160)
Non-evaluable*	155	29	126	18.7% (29/155)

*155 of 162 non-evaluable lesions did not have a MelaFind reading

Table 17 presents the predictive value of MelaFind readings for MM/HGDN/AMPH on all the eligible lesions in Protocol 20061. The predictive value to detect MM/HGDN/AMPH was 18.7% for a MelaFind non-evaluable test result, 11.7% for a positive test result and 1.9% for a MelaFind negative test result.

Table 17. Protocol 20061 Predictive values of MelaFind test results to detect MM/HGDN/AMPH, All Eligible Lesions (n=1794).

MelaFind	N	MM /HGDN/ AMPH	Not MM /HGDN/ AMPH	Predictive Value for MM/HGDN/AMPH	95% CI
+	1479	173	1306	11.7% (173/1479)	(10.0%, 13.4%)*
–	160	3	157	1.9% (3/160)	(0.5%, 5.3%)†
Non-evaluable	155	29	126	18.7% (29/155)	(12.8%, 25.2%)*

*95% Bootstrap percentile method; †Blythe-Still-Casella method, assuming lesions were independent (even if they came from the same patient).

Dermatopathology identified 205 of the total enrolled lesions as melanoma and high grade of which 30 were found non-evaluable by MelaFind. Lesion non-evaluability was due to investigator, operator, and MelaFind errors which are shown in Table 18. Overall, 30 (14.6%) of positive lesions and 132 (8.3%) of negative lesions were not evaluable.

Table 18. Protocol 20061: Non-Evaluable Lesions

Reason for Non-Evaluability	Melanomas and high grade lesions Number of cases (% of all cases = 205)	Other lesions Number of cases (% of all cases = 1589)
Investigator errors (non-eligible lesions)	6 (2.9%)	30 (1.9%)
Operator errors (bubble, hair, etc)	11 (5.4%)	60 (3.8%)
MelaFind errors (images not acquired, etc)	13 (6.3%)	42 (2.6%)
All errors	30 (14.6%)	132 (8.3%)

2. Subgroup Analyses

   The following preoperative characteristics were evaluated for potential association with outcomes:

   Eligible and evaluable lesions had ABCDEPRU Criteria, MelaFind and Investigating dermatologist assessment as follow (Table 19):

Table 19: Protocol 20061, Eligible and Evaluable Lesion Population

Lesion ABCDEPRU Criteria	Atypical						Not Atypical	
	Melanoma (F2)		Melanoma Cannot Be Ruled Out (F3)		Not melanoma (F4)		Non-atypical pigmented lesion (F7)	
N, Eligible and Evaluable Lesions	20		1528		83		1	
ABCDEPRU n (# recorded); N (# pt = # lesion) % = n / N	n	%	n	%	n	%	N	%
Asymmetry: when one half of the mole does not match the other half	19	95% (19/20)	1202	78.7% (1202/1528)	36	43.4% 36/83)	0	0% (0/1)
Border: when the edges of the mole are ragged or irregular	19	95% (19/20)	1142	74.7% (1142/1528)	35	42.2% (35/83)	0	0% (0/1)
Color: when the color of the mole varies throughout	18	90%(18/20)	1188	77.8% (1188/1528)	45	54.2% (45/83)	0	0% (0/1)
Diameter: if mole's diameter is larger than a pencil eraser (> 6mm)	17	85%(17/20)	620	40.6%(620/1528)	40	48.2% (40/83)	0	0% (0/1)
Evolving: changing size, shape or color over a short period of time	14	70%(14/20)	487	31.9%(487/1528)*	39	47% (39/83)	0	0% (0/1)
Patient concern	11	55%(11/20)	481	31.5%(481/1528)	69	83.1% (69/83)	0	0% (0/1)
Regression: areas of hypo- or de-pigmentation, sometimes resulting in scar-like white or blue grey areas	4	20% (4/20)	85	5.6% (85/1528)	1	1.2% (1/83)	0	0% (0/1)
Ugly duckling: distinct from other nevi on the same patient	14	70% (14/20)	693	45.4% (693/1528)	27	32.5% (27/83)	0	0% (0/1)
Number of ABCDEPRU criteria per patient (lesion)								
1	0	0% (0/20)	72	4.7% (72/1528)	14	16.9% (14/83)	0	0% (0/1)
2	2	10% (2/20)	180	11.8% (180/1528)	12	14.5% (12/83)	0	0% (0/1)
3	0	0% (0/20)	392	25.7% (392/1528)	16	19.3% (16/83)	0	0% (0/1)
4	2	10% (2/20)	403	26.4% (403/1528)	16	19.3% (16/83)	0	0% (0/1)

5	2	10% (2/20)	243	15.9% (147/1528)	15	18.1% (15/83)	0	0% (0/1)
6	6	30% (6/20)	147	9.6% (147/1528)	3	3.6% (3/83)	0	0% (0/1)
7	6	30% (6/20)	67	4.4% (67/1528)	7	8.4% (7/83)	0	0% (0/1)
8	2	10% (2/20)	14	0.9% (14/1528)	0	0% (0/83)	0	0% (0/1)
0	0	0% (0/20)	10	0.7% (10/1528)	0	0%(0/83)	1	100% (1/1)

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

SUMMARY OF READER STUDY

A pilot reader study of 50 randomly-selected pigmented skin lesions from Protocol 20061 using 39 dermatologist readers showed 80% biopsy sensitivity for dermatologists with a kappa score of 0.22.

A prospective, randomized, and investigator blinded web-based reader study under Protocol 20063 was conducted electronically. The study was intended to assess and compare the biopsy sensitivity and specificity of MelaFind®, to the average biopsy/referral sensitivity and specificity of expert and general dermatologists as well as primary care physicians who did not participate in the pivotal clinical study under Protocol 20061, In this reader study, randomly-selected Protocol 20061 lesions were evaluated by physicians who recorded their biopsy decisions. One-hundred-thirty lesions (65 melanomas and 65 non-melanomas) were selected randomly from the Protocol 20061 database, maintaining the prevalence of non-melanoma lesion types observed in Protocol 20061. Non-melanomas were matched by age and anatomic site to melanomas. All lesion images underwent review by the principal investigator for image quality. Physicians (pigmented skin lesion experts, general dermatologists, and primary care physicians) were recruited until at least 40 participants from each category completed the study. Physician heterogeneity was assessed using kappa statistics.

Procedure. A total of 1690 physicians were invited to participate; 241 agreed and registered for the study. For data to be included in the study, physicians must have completed at least 78 of the 130 cases; 155 of the 241 physicians completed the study. An intake survey was used to assign the physicians to the appropriate caregiver groups. The order in which the cases were presented to the physicians was serially assigned within each caregiver group; the random assignment of cases per 10 different modules was performed in blocks. Reader study physicians reviewed three high resolution digital images taken from standard cameras – clinical images from 21 and 8 inches away from the lesion, and a dermoscopic image. In addition, twenty-four items of information were provided, including clinical history, risk factors for melanoma, and the results of physical examination findings by the Protocol 20061 investigating physician. Reader study physicians answered 6 questions regarding the decision to biopsy or not biopsy the lesion.

Primary Objective. The primary objective of Protocol 20063, the adjunctive reader study, was to test the hypothesis that MelaFind sensitivity to identify melanoma was at least as good as that of investigators using photographs and histories of the same lesions collected by pivotal study investigators by live assessment. Table 20 provides study outcomes. MelaFind sensitivity was 97%, which was statistically significantly superior to that of 110 dermatologists who, on the average, missed (i.e., elected not to biopsy) 28% of melanomas in this electronic study (p-value < 0.0001).

Table 20. Protocol 20063: ANOVA Results for Biopsy/Referral Sensitivity and Specificity with 95% CI, n = 100

	Sensitivity	Std. Dev.	CI	Specificity	Std. Dev.	CI
All Derms	0.72	0.03	(0.66, 0.78)	0.51	0.04	(0.43, 0.58)
MelaFind	0.97	0.15	(0.90, 0.99)	0.09	.19	(0.04, 0.19)
Difference	0.25	0.03	(0.18, 0.32)	-0.41	0.05	(-0.51, -0.31)

Inter-reader variability for biopsy decisions in the reader study was evaluated using kappa statistics (shown in Table 21) and indicates variability in biopsy decisions of dermatologists (kappa: 0.313) and primary care physicians (kappa: 0.200).

Table 21. Protocol 20063: Kappa Statistics for Biopsy/referral for Melanoma

	Lesions	Mean readers per lesion	Kappa	SE0*
Overall	130	154.1	0.256	0.001
Melanomas	65	154.1	0.204	0.001
Non-melanomas	65	154.1	0.235	0.001
PCPs	130	45.0	0.200	0.003
General dermatologists	130	45.6	0.313	0.003
PSL experts	130	63.6	0.276	0.002

*standard error of the kappa statistic under the null hypothesis that kappa = 0

Figure 5 shows 39 reader-dermatologist assessments from pre-Protocol 20063 reader study compared to 23 average live dermatologist assessments (solid diamond), that is, variability between reader study investigators and live pivotal study assessment. Figure 3 shows biopsy decisions by the 155 physicians participating in the P20063 reader (web-

based lesions assessment; open symbols) study compared to MelaFind (black circle), that is, variability between reader study investigators and MelaFind. Figures 2 (solid diamond) and Figure 6 (solid circle) show MelaFind and live assessment.

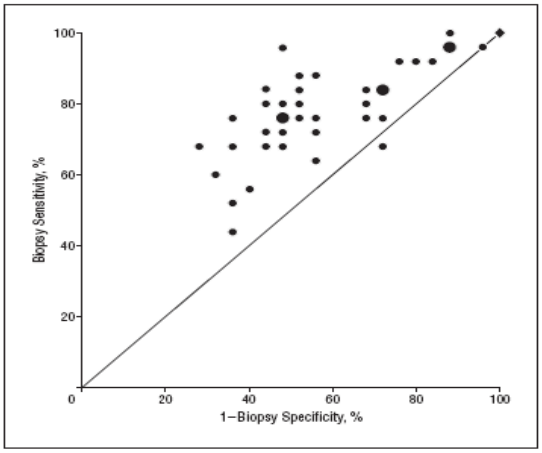

Figure. Biopsy decisions by 39 dermatologists participating in the pilot reader study. Small black circles represent individual readers; big black circles, pairs of readers; and the diamond, examining clinicians in the clinical trial on the same set of lesions.

Figure 5: 39 reader-dermatologist assessments compared to 23 average live dermatologist assessments.

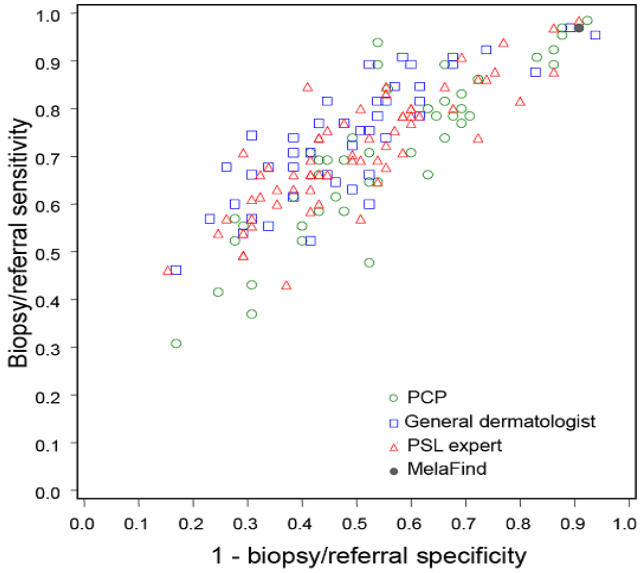

Figure 6: 155 reader assessments compared to average MelaFind assessments.

This data is based upon the 130 lesions randomly selected from 124 patients (age: 11 to 97 years, median 58 years; gender: 60 male and 64 female) in Protocol 20061 and matched as per study design description. Of the 65 melanomas, 29 were in situ and 36 were invasive with a median Breslow thickness of 0.39 mm (range 0.12 mm to 1.2 mm). Of the 65 non-melanomas, 60% were low grade dysplastic nevi. The results from 155 physicians were included in the analysis – 64 pigmented skin lesion experts, 46 general dermatologists, and 45 primary care physicians. The median years in practice of the physicians were 10, 12 and 15 years, respectively. Forty-five percent of physician readers were female and 55% were male. The average biopsy sensitivity of the dermatologists-readers was 72%, which was not statistically significantly different than the average biopsy sensitivity for primary care physician-readers (71%). The biopsy sensitivity of MelaFind® was 97% ($p < 0.0001$ versus dermatologists). On average, the dermatologist-readers detected 47 of 65 melanomas and MelaFind® detected 63/65 melanomas; the invasive (Breslow thickness 0.28 mm) and in situ melanomas not detected by MelaFind® were missed by 71% and 21% of the dermatologist-readers, respectively. The kappa score of the dermatologist-readers was 0.29, indicating only "fair agreement." There was a trend toward lower sensitivity of dermatologists for in situ versus invasive melanomas (69% versus 74%, $p = 0.33$). The biopsy specificity of the dermatologists was 51% versus 9% for MelaFind® ($p < 0.0001$). Four dermatologist-readers had biopsy sensitivities at or above the 95% threshold for MelaFind in the Pivotal Trial (98%, 97%, 97%, and 95%; average 97%); the average biopsy specificity of these four dermatologist readers was 10% (9%, 11%, 14% and 6%, respectively).

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

A. Panel Meeting Recommendation

At an advisory committee meeting held on November 18, 2010, the General and Plastic Surgery Devices Panel raised concern regarding MelaFind use by non-dermatologists. The indications for use defined the operator of MelaFind to be at the physician level whereas the pivotal study only used study investigators that were board certified dermatologists. In addition, panelists were concerned that without training in the proper use of MelaFind, operator's would not select the appropriate lesions for MelaFind use and would not correctly use the device to guide their clinical decision to biopsy in order to rule-out melanoma in accordance to the indications and instructions for use. Other concerns involved having a MelaFind negative reading influence a decision to not biopsy a lesion with clinical suspicion of melanoma, which may potentially result in a false negative diagnosis and delay in care; and the guidance that should be provided to users based on the high number of melanomas confirmed by dermatopathology among the non-evaulables.

At the meeting, the Panel voted 10 votes yes and six votes no that there is reasonable assurance the device is safe, and eight votes yes and six votes no that there is reasonable assurance that the device is effective, and eight votes yes, seven votes no and one absente

that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

B. FDA's Post-Panel Action

The sponsor has provided a revised indication for use that defines MelaFind use by physicians trained in the clinical diagnosis and management of skin cancer (i.e. dermatologists) who have also successfully completed a training program in the appropriate use of MelaFind. This addresses the concern regarding the use of MelaFind by a non-dermatologist and the potential concerns regarding the appropriate use of MelaFind according to the indications and instructions for use. In addition, the revised indications for use and labeling also states that MelaFind should not be used to confirm a clinical diagnosis of melanoma and that it is one element of the overall clinical assessment. Also, MelaFind negative lesions should be based on the remainder of the entire clinical context and lesions that are "non-evaluable" by MelaFind should be carefully re-evaluated for biopsy. These indications and labeling were found acceptable to address these outstanding concerns since lesions that are clinically diagnosed to be suspicious for melanoma will not be evaluated by MelaFind and a MelaFind negative reading is only part of the assessment for a clinical decision to biopsy and will not replace clinical judgement. In addition, non-evaluable lesions will now be re-evaluated for biopsy which is supported by the clinical data.

XIII. CONCLUSION.S DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety and Effectiveness Conclusions

The pivotal clinical study conducted by the sponsor has met the primary endpoints regarding safety and effectiveness by achieving a 112/114 (98.3%) MelaFind sensitivity to malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is at least 95% at a 95% confidence level and achieved a superior MelaFind pooled specificity (10.6%) to the study dermatologists (5.1%) using 95% Bootstrap percentile intervals.

To mitigate the safety concern of a MelaFind negative reading influencing a dermatologist's initial decision to not biopsy a lesion with clinical suspicion of melanoma, potentially resulting in a false negative diagnosis and delay in care, the indications for use and labeling state that MelaFind should not be used to confirm a clinical diagnosis of melanoma and that MelaFind negative lesions are a part of the clinical decision process to biopsy and will not replace clinical judgement.

Approximately 9% of lesions were non-evaluable by the device and of those lesions, 18.7% were confirmed melanomas or high-grade lesions by dermatopathology. Labeling has been revised to include device performance on both evaluable lesions and non-evaluable lesions to inform the dermatologist of potential concerns. In addition, the indications for use provides instructions to the dermatologist to indicate that when the

device cannot obtain a reading, the dermatologist must rely on own clinical judgment and is recommended to consider biopsy due to the high prevalence of malignant melanoma as demonstrated in the pivotal study.

By limiting the indications for MelaFind to use by physicians trained in the clinical diagnosis and management of skin cancer (i.e. dermatologists) who have also successfully completed a training program in the appropriate use of MelaFind, the potential concerns regarding incorrect lesion selection for MelaFind use and the possible inadequate use of MelaFind due to lack of training has been mitigated. Physician's will have to successfully complete a training program in the appropriate use of MelaFind and will have the expertise in identifying atypical lesions since they will be physicians trained in the clinical diagnosis and management of skin cancer (i.e. dermatologists).

The performance of MelaFind was determined by the review staff to be sufficient with the latest iteration of the indications for use, that is, for when a dermatologist chooses to obtain additional information for a decision to biopsy. A MelaFind positive reading can be interpreted as a recommendation for biopsy in order to rule-out malignant melanoma and high grade lesions. The risk of a MelaFind negative lesion influencing a decision to not biopsy a lesion with clinical suspicion of melanoma has been mitigated by the latest agreed upon indications for use and labeling. MelaFind non-evaluable readings have also been labeled to inform the user of device performance and instructed by the indications for use to be considered for biopsy which is demonstrated by the pivotal study. A post-approval study to further characterize the safety in a post-marketing setting is warranted and is a condition of approval. Further revisions to the labeling may be necessary from longer-term data.

B. **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. The sponsor has met the primary endpoints regarding safety and effectiveness by achieving a 112/114 (98.3%) MelaFind sensitivity to malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is at least 95% at a 95% confidence level and achieved a superior MelaFind pooled specificity (10.6%) to the study dermatologists (5.5%). The current indications for use and labeling minimizes any potential safety concerns by limiting the device operator to physicians trained in the clinical diagnosis and management of skin cancer (i.e. dermatologists) who have also successfully completed a training program, informs the dermatologist on MelaFind performance, and recommends appropriate biopsy decisions regarding a MelaFind positive, negative, and non-evaluable readings when a dermatologist chooses to obtain additional information for a decision to biopsy in order to rule-out malignant melanoma and high grade lesions. As indicated, MelaFind should not be used to confirm a clinical diagnosis of melanoma and that it is one element of the overall clinical assessment for a decision to biopsy a lesion and will not replace clinical judgement.

XIV. CDRH DECISION

CDRH issued an approval order on November 1, 2011. The final conditions of approval cited in the approval order are described below.

The sponsor must conduct a post approval study that will evaluate whether MelaFind increases the sensitivity of physicians in diagnosing melanomas and high-grade lesions, while the false positive rate of physicians is not substantially elevated.

The study will be a multi-center, single arm, observational, prospective study to gather data on relative sensitivity, among other study endpoints. Data to be collected includes: relative sensitivity comparing physicians' performance before and after using MelaFind as the primary study endpoint; real-world use of MelaFind, i.e., the patient characteristics including age, gender, race/ethnicity, and Fitzpatrick Skin Type, the number of lesions that were examined by MelaFind, the proportion of lesions that meet the labeled Indications For Use among all the lesions examined by MelaFind, the proportions of positive and negative findings of MelaFind among all of the lesions examined, the proportion of lesions that are un-evaluable by MelaFind, the proportion of lesions that are found to be un-evaluable for each user of MelaFind, the number of attempts with MelaFind that were performed for each lesion before a definitive reading resulted or the lesion was declared un-evaluable, and the impact of MelaFind use on the per physician biopsy rate for pigmented lesions; and an evaluation of safety and effectiveness of MelaFind, i.e., the proportion of biopsy from the lesions that MelaFind identifies as positive and the results of those biopsies, the proportion of biopsy among the "unreadable" lesions and the results of those biopsies, the proportion of biopsy from the lesions that MelaFind identifies as negative and the results of those biopsies, and the proportion of the biopsied lesions (from each of the above – MelaFind positive, MelaFind negative, and un-evaluable) returned as melanoma on pathology. This study must enroll 78 patients with one or more eligible and evaluable histologically-confirmed melanoma and/or high-grade lesion based on the null hypothesis that the relative sensitivity is less than or equal to 1.1. The study power will be at least 85%.

Patients with lesions evaluated with MelaFind during the enrollment period, but not biopsied at that time, will be followed at 1 year ±3 months and 2 years ±3 months. At least 50% of the study sites will be new (i.e., they did not participate in the MelaFind pivotal study). The study sites will include a mix of academic centers and private practices.

The applicant's manufacturing facilities were 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

N/A