Celine Royet
Regulatory Affairs Manager
Resonance Health Analysis Service Pty Ltd
141 Burswood Rd
Burswood 61000
AUSTRALIA

November 30, 2018

Re: K182218
Trade/Device Name: FerriSmart Analysis System
Regulation Number: 21 CFR 892.1001
Regulation Name: Liver iron concentration imaging companion diagnostic for deferasirox
Regulatory Class: Class II
Product Code: PCS
Dated: October 22, 2018
Received: October 26, 2018

Dear Celine Royet:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Michael D. O'Hara For

Robert A. Ochs, Ph.D.
Director
Division of Radiological Health
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
k182218

Device Name
FerriSmart

Indications for Use *(Describe)*
FerriSmart is indicated to:
• measure liver iron concentration in individuals with confirmed or suspected systemic iron overload;
• monitor liver iron burden in transfusion dependent thalassemia patients and patients with sickle cell disease receiving blood transfusions;
• aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(K) SUMMARY

This Summary has been prepared in accordance with 21 CFR 807.92.

GENERAL INFORMATION

Date Prepared	28-Nov-2018
Submitted by	Resonance Health Analysis Service Pty Ltd 141 Burswood Rd Burswood 6100 AUSTRALIA
Main Contact	Mrs Celine Royet Regulatory Affairs Manager celiner@resonancehealth.com Tel: +61 8 9286 5300 Fax: +61 8 9286 5399
US Contact (US Agent)	Rene Van De Zande Director & GM Emergo Global Representation LLC 2500 Bee Cave Road Building 1, Suite 300 Austin, TX 78746 Phone: 512 3279997 Fax: 512 3279998 Email: USAgent@ul.com

DEVICE INFORMATION

Name of Device	FerriSmart
Trade/proprietary Name	FerriSmart
Classification	Class II
Product Code	90-PCS
CFR Section	892.1001 Liver Iron Concentration Imaging Companion Diagnostic For Deferasirox
Panel	Radiology

Description of the Device

FerriSmart is a stand-alone software application that automatically analyses multi-slice, spin-echo MRI data sets encompassing the abdomen to determine the signal decay rate (R_2) that is used to characterize iron loading in the liver, which is then transformed by a defined calibration curve to provide a quantitative measure of liver iron concentrations *in vivo.*

The software application is a measuring medical device intended to be hosted either in a cloud-based or on site hosted platform and used directly by the radiographer. It does not drive the MRI machine and does not come into direct contact with patients.

The key components of FerriSmart are:

- Specific Magnetic Resonance Imaging Protocol: Use of a specific magnetic resonance imaging protocol for acquisition of the raw image data. The imaging protocol is critical to ensure the quality of the end results. Its adherence is verified by the IQC Module, an automated algorithm that checks the correctness of the parameters of the data acquisition protocol.
- FerriSmart AI Analysis Software: Custom-designed image analysis software performing the R_2 measurement based on AI (Artificial Intelligence) technology.
- Liver Iron Measurement: An additional software module (algorithmic) that incorporates a calibration curve relating R_2 to liver iron concentration (LIC) is added to allow production of a liver iron concentration report.

The result report provides the patient's average LIC reported in micromole and milligram per gram dry weight of liver. The images analysed are included in the report for review by the radiologist. The results are intended to assist in clinical diagnosis, and/or in making decisions concerning clinical management.

Intended Use

The intended use of FerriSmart is:

For the measurement of R_2 and iron concentration in the liver from MRI scans.

Indications for Use

FerriSmart is indicated to:

- measure liver iron concentration in individuals with confirmed or suspected systemic iron overload;
- monitor liver iron burden in transfusion dependent thalassemia patients and patients with sickle cell disease receiving blood transfusions;.
- aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox.

PREDICATE INFORMATION

FerriSmart is substantially equivalent to the predicate device FerriScan R_2-MRI Analysis System (Resonance Health Analysis Services) - DEN130012 / K124065.

REFERENCE DEVICE

The reference device is FerriScan R_2-MRI Analysis System (Resonance Health Analysis Services) – K043271.

SUBSTANTIAL EQUIVALENCE INFORMATION

The table below summarizes the main similarities and differences between FerriSmart, the predicate and the reference device.

	Proposed Device	**Predicate Device**	**Reference Device**
	FerriSmart	**FerriScan R2-MRI Analysis System**	**FerriScan R2-MRI Analysis System**
Regulatory Class	II	II	II
510(k) number	K182218	DEN130012 / K124065	K043271
Classification Name	Liver Iron Concentration Imaging Companion Diagnostic For Deferasirox	Liver Iron Concentration Imaging Companion Diagnostic For Deferasirox	System, Nuclear Magnetic Resonance Imaging, System, Image Processing Radiological
CFR Section	892.1001	892.1001	892.1000
Product Code and Classification Panel	90 PCS	90 PCS	90 LNH
Description	Standalone software package that automatically analyses multi-slice, spin-echo MRI data sets encompassing the abdomen to provide objective and reproducible determination of liver parameters to support clinicians in the assessment of liver iron status. The software tool determines the signal decay rate (R_2) that is used to characterize iron loading in the liver, which is then transformed by a defined calibration curve to provide a	Software tool to facilitate the import and visualization of multi-slice, spin-echo MRI data sets encompassing the abdomen, with functionality independent of the MRI equipment vendor, to provide objective and reproducible determination of liver parameters to support clinicians in the assessment of liver iron status. The software tool also calculates the signal decay rate (R_2) that is used to characterize iron loading in the liver, which is then transformed	Software tool to facilitate the import and visualization of multi-slice, spin-echo MRI data sets encompassing the abdomen, with functionality independent of the MRI equipment vendor, to provide objective and reproducible determination of liver parameters to support clinicians in the assessment of liver iron status. The software tool also calculates the signal decay rate (R_2) that is used to characterize iron loading in the liver, which is then transformed by a defined calibration

	Proposed Device	Predicate Device	Reference Device
	FerriSmart	**FerriScan R2-MRI Analysis System**	**FerriScan R2-MRI Analysis System**
	quantitative measure of liver iron concentrations *in vivo.*	by a defined calibration curve to provide a quantitative measure of liver iron concentrations *in vivo.*	curve to provide a quantitative measure of liver iron concentrations *in vivo.*
Technology	Convolutional neural networks for the image analysis. Algorithmic for the images quality checks and R_2 conversion into LIC.	Algorithmic, with human interaction for Region of Interest (ROI) selection.	Algorithmic, with human interaction for Region of Interest (ROI) selection.
Intended purpose(s)	1. Supporting clinical diagnoses about the status of liver iron concentration. 2. Supporting the subsequent clinical decision-making processes. 3. Supporting the use in clinical research trials, directed at studying changes in liver iron concentration as a result of interventions.	1. Supporting clinical diagnoses about the status of liver iron concentration. 2. Supporting the subsequent clinical decision-making processes. 3. Supporting the use in clinical research trials, directed at studying changes in liver iron concentration as a result of interventions. 4. It contains an image viewer for importing DICOM images, browsing through patient datasets, viewing images and performing region of interest analysis.	1. Supporting clinical diagnoses about the status of liver iron concentration. 2. Supporting the subsequent clinical decision-making processes. 3. Supporting the use in clinical research trials, directed at studying changes in liver iron concentration as a result of interventions. 4. It contains an image viewer for importing DICOM images, browsing through patient datasets, viewing images and performing region of interest analysis.
Intended Use	Measurement of R_2 and iron concentration in the liver from MRI scans	For the analysis of multi-slice, spin-echo MRI data sets of the liver for the measurement of liver R_2 and liver iron concentration and to assist in the provision of iron chelation therapy	Measurement of R_2 and iron concentration in the liver from MRI scans.
Indications	Indicated to: • measure liver iron concentration in individuals with	Measure liver iron concentration to aid in the identification and monitoring of non-transfusion-dependent	The R2-MRI Analysis System is an accessory diagnostic device to MRI scanners and is intended for diagnostic use to

	Proposed Device	Predicate Device	Reference Device
	FerriSmart	**FerriScan R2-MRI Analysis System**	**FerriScan R2-MRI Analysis System**
	confirmed or suspected systemic iron overload; • monitor liver iron burden in transfusion dependent thalassemia patients and patients with sickle cell disease receiving blood transfusions;. • aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox.	thalassemia patients receiving therapy with deferasirox.	present images that reflect the magnetic resonance spectra for the determination of iron on the liver.
User	Radiologist	Resonance Health's trained analyst	Resonance Health's trained analyst
Hosting platform	Cloud-based or on-site hosting	Resonance Health's internal server	Resonance Health's internal server
Image-type utilized	Magnetic Resonance	Magnetic Resonance	Magnetic Resonance
Image format	DICOM	DICOM	DICOM
Data Acquisition method	Single Spin Echo (SSE)	Single Spin Echo (SSE)	Single Spin Echo (SSE)
Anatomical Sites	Liver	Liver	Liver

Similarities with the predicate:

Both systems are stand-alone software applications, independent of the MRI scanner.

Both systems have the same MRI data acquisition protocol: Single Spin Echo (SSE).

The anatomical site scanned (liver) is the same.

Both systems produce an output report comprising a quantitative measure of the signal decay rate (R_2), which is then converted using the same calibration curve into Liver Iron Concentration (LIC).

Differences with the predicate:

Analysis technology is different: FerriScan is an algorithm-based technology. FerriSmart uses convolutional neural networks for image recognition and analysis. However FerriSmart AI Analysis Software has been trained on FerriScan data.

The image input quality check is different: parameters checked are the same but FerriSmart uses an algorithm to automatically perform the checks whereas FerriScan requires human input.

Users are different: FerriScan is used in-house by Resonance Health's analysts and results are provided as a service. FerriSmart user is the radiologist.

FerriSmart is cloud-based. FerriScan is kept in-house on Resonance Health's internal server.

Indications: FerriSmart encompasses the Indications of the predicate with additional indications supported by literature and demographics of the validation dataset used during the clinical validation against the predicate.

PERFORMANCE DATA

Resonance Health has followed the principles developed by the IMDRF and recently published by the FDA: *Software as a Medical Device (SaMD): Clinical Evaluation. Final Guidance for Industry and FDA Staff. December 2017*, to design the performance testing that support FerriSmart, using the predicate device FerriScan R_2-MRI Analysis System (DEN130012/ K124065) as the reference standard.

The following performance data were provided in order to support the substantial equivalence determination and comply with the Special Controls defined by 21 CFR 892.1001.

Software Verification and Validation:

FerriSmart software has been developed, verified and validated following the Design Control principles and in accordance with the *General Principles of Software Validation; Final Guidance for Industry and FDA Staff. U.S. Department Of Health and Human Services Food and Drug Administration. January 2002*.

User Testing:

A User Testing study was conducted to assess to the usability of FerriSmart, including readability of the patient report and Instructions for Use. All participants of the study reported the product was easy to use, fast and technically reliable (no bugs).

Literature Review:

The reviewed literature and breakdown of patient population across several US sites have shown that the predicate FerriScan has been used to monitor iron burden in transfusion dependent thalassemia patients and patients with sickle cell disease receiving blood transfusions. These studies published in the scientific literature support the broadening of the indications from the predicate.

Repeatability Study:

Repeatability of FerriSmart was assessed in a study of 60 subjects who were scanned twice and had LIC measured each time using both FerriScan Analysis System and FerriSmart Analysis System. The data give information on the precision of FerriSmart.

Below 3 mg Fe/g dry tissue, FerriSmart has a repeatability that is consistent with that of FerriScan. Above 3 mg Fe/g dry tissue, the upper and lower 95% limits of repeatability ratios of 1.26 (95% CI 1.24-1.28) and 0.79 (95% CI 0.78 – 0.81) are acceptable since they correspond to a standard error on a single measurement of approximately 9% which is somewhat better than the standard error on a measurement of LIC by biopsy which ranges from about 19% in the absence of liver fibrosis to greater than 40% in end stage liver disease (Kreeftenberg et al. 1984; Emond et al. 1999).

Clinical Study:

The clinical study had 971 datasets from multiple makes and models of scanner for:

1. Assessing the performance of the FerriSmart IQC module;
2. Assessing the bias and limits of agreement between FerriSmart and FerriScan measurements of LIC on multiple scanners;
3. Assessing the diagnostic performance of FerriSmart for predicting FerriScan LIC results above various clinically relevant LIC thresholds on multiple scanners.

The sensitivities and specificities results are presented in the Table below.

Sensitivities and specificities of FerriSmart for predicting FerriScan LIC values greater than several clinically relevant thresholds.

LIC threshold (mg Fe/g dry tissue)	Clinical relevance	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
1.8	• The upper 95% limit of normal LIC (Bassett et al. 1986).	96 (94 - 97)	80 (73 - 87)
3.0	• Threshold below which deferasirox treatment for non-transfusion dependent thalassemia (NTDT) patients should be interrupted (FDA 2013).	96 (94 - 97)	95 (92 - 98)
3.2	• Historical phenotypic definition of iron overload for patients with hereditary hemochromatosis. • Suggested lower limit of optimal range for LICs for chelation therapy in transfusional Fe overload (Olivieri and Brittenham 1997).	94 (92 - 96)	95 (92 - 98)
5.0	• Threshold above which iron chelation with deferasirox can be considered for patients with NTDT (FDA 2013).	91 (89 - 94)	97 (95 - 99)
7.0	• Suggested upper limit of optimal range for LICs for transfusional Fe overload and threshold for increased risk of iron-induced complications (Olivieri and Brittenham 1997). • Threshold above which deferasirox dose should be increased (to a maximum of 20 mg/kg/day) above the starting dose of 10 mg/kg /day in patients with NTDT (FDA 2013).	92 (90 - 95)	97 (95 - 98)
15.0	• Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload (Olivieri and Brittenham 1997) • Baseline LIC above which increase of	89 (85 - 93)	98 (98 - 99)

	deferasirox dose to 20 mg/kg/day should be considered after first 4 weeks of therapy for NTDT patients (FDA 2013).

Bias: The bias between the FerriSmart and FerriScan is negligible below 3 mg Fe/g dry tissue, and clinically acceptable above that threshold. However it is to be noted that FerriSmart and FerriScan should not be considered interchangeable.

Reproducibility: A validation study of the predicate demonstrated no statistical significant biases in calibration among 5 MRI scanners of different makes and models. As such, the measure of the limits of agreement between FerriSmart and the predicate includes any components of bias between sites.

While there is an overall bias between FerriSmart and FerriScan, the bias together with the random errors on the measurements do not result in unacceptable sensitivities and specificities of FerriSmart for predicting FerriScan results above the clinically relevant LIC thresholds. Most of the sensitivities and specificities are above 90% with exceptions being a specificity of 80 % (95% CI 73 – 87 %) for detecting FerriScan LIC values above 1.8 mg Fe/g dry tissue and a sensitivity of 89 % (95% CI 85 – 93 %) for detecting FerriScan LIC values above 15.0 mg Fe/g dry tissue. The threshold of 1.8 mg Fe/g dry tissue has more relevance to scientific population studies rather than clinical management of iron overload and therefore the low specificity at this threshold does not preclude the use of FerriSmart for monitoring iron loaded patients. The threshold of 15.0 mg Fe/g dry tissue is a key threshold used in management of iron overload. The sensitivity of 89% is likely acceptable for clinical use and is comparable with the sensitivity of FerriScan for predicting biopsy LIC above 15 mg Fe /g dry tissue (85%, 95% CI 70 – 94%) (St. Pierre et al. 2005).

RISK ANALYSES

Risk Analyses were performed through the development of the device in accordance with EN ISO 14971:2012 – *Medical Devices – Application of Risk Management to Medical Devices*.

Remaining risks have been identified and mitigated.

FerriSmart sensitivity and specificity are suitable for clinical decision making. This has been presented and discussed in the submitted documentation.

Report result is overseen by the radiologist and the final decision for clinical management of the patient is made by their treating clinician.

The overall risks for FerriSmart are considered acceptable. Post-marketing surveillance processes are in place and any events will be monitored closely. The Risk Analyses will be updated as deemed necessary.

The overall benefit of providing a cost-effective, quick, reliable, and accurate liver iron measuring test surpasses the risks.

LABELLING

FerriSmart labelling is in the form of a User Manual. This Manual presents in particular:

- The instructions for acceptance testing of images prior to processing: this includes verification that the data acquisition settings of the scanner are within a specified tolerance by performing a test scan prior to any patient scan, and use of an in-built

Input Quality Control Module in the FerriSmart system that verifies adherence to the correct scanning protocol and rejects any non-conforming images.

- The data processing quality assurance protocols: pre-analysis check of the images with the in-built Input Quality Control Module in the FerriSmart system that verifies adherence to scanning protocol and rejects any non-conforming images, and post-analysis aid for the radiologist to verify the relevance of the results with the display of the analysed images.
- The sensitivity and specificity of liver iron concentration measurements.

CONCLUSION

The 510(k) premarket notification for FerriSmart contains adequate information and data to enable the FDA-CDRH to determine substantial equivalence to the predicate device. Differences have been explained and justified, and where necessary, additional data has been presented to support the claims. Resonance Health Analysis Services Pty Ltd believes that sufficient evidence has been presented in this Dossier to conclude that FerriSmart is safe, effective and performs as well as the predicate.