DE NOVO CLASSIFICATION REQUEST FOR
FERRISCAN R2-MRI ANALYSIS SYSTEM
DECISION SUMMARY

A. Regulatory Information

1. Identification

FDA identifies this generic type of device as:

Liver iron concentration imaging companion diagnostic for deferasirox

The liver iron concentration imaging companion diagnostic for deferasirox is an image processing device intended to aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox. The device calculates a numeric value for liver iron concentration based on magnetic resonance images acquired under controlled conditions. The calculated numeric value is used to assess the need for deferasirox treatment and for monitoring treatment in patients with non-transfusion-dependent thalassemia. The liver iron concentration imaging companion diagnostic for deferasirox is essential to the safe and effective use of deferasirox in patients with non-transfusion-dependent thalassemia.

2. **New Regulation Number**: 21 CFR 892.1001

3. **Classification**: Class II

4. **Product Code**: PCS

B. Background

1. **Device name**: FerriScan R2-MRI Analysis System

2. **Submission number**: K124065

3. **Date of De Novo**: December 21, 2012

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6. **Requester's Recommended Classification**: Class II

C. Indications for use

The FerriScan R2-MRI Analysis System is intended to measure liver iron concentration to aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox.

1. **Limitations**

   For prescription use only.

   Please refer to the labeling for a more complete list of warnings, precautions and contraindications.

D. Device Description

The FerriScan R2-MRI Analysis System is a post-processing software tool that measures liver iron concentration based on the proton transverse relaxation rate (R2) of MRI images. R2 values are converted to liver iron concentration measurements using a calibration curve.

The information provided to clinicians is essential to the identification of non-transfusion-dependent thalassemia (NTDT) patients that may benefit from deferasirox therapy and the ongoing management of NTDT patients on deferasirox therapy.

The key components for the FerriScan R2-MRI Analysis System for liver iron concentration measurement are:

1. Magnetic Resonance Imaging Protocol: Specific magnetic resonance imaging protocols are used for the acquisition of the raw image data. The FerriScan Phantom Pack is used to verify the MRI protocol set up.

2. R2 analysis Software: The image analysis software embodies an analysis methodology for performing the R2 measurement and imaging of the liver.

3. Liver Iron Measurement: An additional software module incorporates a calibration curve relating R2 to liver iron concentration to produce a liver iron concentration report.

FerriScan Phantom Pack

The FerriScan Phantom Pack provides a reference standard for use in the verification of MRI scanners for use with the FerriScan R2-MRI Analysis System and to assist in the verification of individual patient scans. The phantoms consist of vials of known concentrations of aqueous manganese chloride ($MnCl_2$), provided to MRI centers in a sealed box (the FerriScan Phantom Pack). The concentrations of $MnCl_2$ in the FerriScan Phantom Pack are designed to cover the R2 values typically found in normal individuals and patients with liver iron overload (0.2 mM-3.2 mM $MnCl_2$).

E. Summary of Nonclinical/Bench Studies

Nonclinical performance data were provided to address the following areas:

1. Biocompatibility/Materials

Not applicable

2. Shelf Life/Sterility

Not applicable

3. Electromagnetic Compatibility and Electrical Safety

Not applicable

4. Magnetic Resonance (MR) Compatibility

Not applicable

5. **Software**

Software documentation included in the 510k for the R2-MRI Analysis System (K043271) was adequate. There are no software changes related to this de novo and the additional indication for use as an imaging companion diagnostic for deferasirox for patients with NTDT.

6. **Performance Testing – Bench**

Reproducibility

Reproducibility is defined as measurement precision under different locations, operators, measuring systems, and replicate measurements on the same or similar objects. Unlike repeatability, reproducibility requires the same measurement procedure and the same operating conditions. It is only location, operator, and/or measuring system that may differ.

Phantom testing was used to demonstrate reproducibility in K043271. The phantom testing included an assessment of spatial variation of R2 measurements in a uniform phantom and $MnCl_2$ solutions of varying concentrations. The coefficient of variability across 13 different scanners was less than 2.1%.

7. **Performance Testing – Animal &/or Cadaver**

Not applicable.

F. Summary of Clinical Information

1. **Companion diagnostic study demonstrating the use of the device in NTDT patient identification and monitoring for use with deferasirox**

The device was used as part of the inclusion criteria and as the primary endpoint in the clinical studies for the use of deferasirox (Exjade) in the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia syndromes (NTDT) (beta-thalassemia intermedia, hemoglobin E beta-thalassemia, and alpha-thalassemia) and a liver iron concentration (LIC) >5 mg Fe/g dry weight (dw).

The safety and effectiveness of Exjade to treat chronic iron overload in NTDT patients were established in two clinical trials designed to measure the change in liver iron concentration (LIC) after 52 weeks of treatment. In the first trial, 166 patients were randomly assigned to receive 5 milligrams per kilogram of Exjade, 10 mg/kg of Exjade, or a placebo daily. Results showed Exjade-treated patients achieved the target LIC within 52 weeks of treatment in 15% and 27%, respectively, compared with 4% in placebo-treated patients. The second trial consisted of 133 patients previously enrolled in the first study, either getting an additional year of treatment or crossing

over from the placebo arm. All patients received 5 mg/kg, 10 mg/kg or 20 mg/kg of Exjade daily. Results showed that 35% of the evaluable patients achieved the target LIC.

2. <u>Precision and bias</u>

Bias is defined as estimate of a systematic measurement error and describes the difference between the average (expected value) of measurements made on the same object and its true value.

Precision is defined as the closeness of agreement between measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions.

A calibration study is defined as a study used to define an empirically-derived relationship.

A validation study is defined as a study that provides objective evidence that the implementation of the relationship defined in the calibration study can consistently provide the expected measurement results.

Precision and bias were determined from two clinical studies: a calibration study and a validation study. Atomic absorption spectrometry from liver biopsy was used as the reference measurement of LIC in both studies.

A 105-patient calibration study with patients (LIC from 0.3 to 42.7 mg Fe/g dw) found an average standard error of LIC by FerriScan of approximately 15% and reported a Bland-Altman 95% limits of agreement with liver biopsy of -56 – 50% with bias of -3%.

A validation study was performed with a 233-patient subgroup from the ESCALATOR (Efficacy and Safety of long-term treatment with ICL670 in β-thALAssemia patients with Transfusional hemOsideRosis) trial with LIC from 0.7 mg Fe/g dw to 50.1 mg Fe/g dw. The Bland-Altman 95% limits of agreement between R2-MRI and biopsy LIC measurements are 74 and -71% with a bias of 1.9%. Five MRI systems were used in the study with no statistical difference observed in bias or precision between MRI systems.

Inhomogeneity of iron within the liver leads to variability in LIC by liver biopsy and the FerriScan R2-MRI Analysis System. The coefficient of variation for needle biopsy LIC for non-disease liver is approximately 19% and may increase for cirrhotic livers to more than 40% (Emond et al. Quantitative study of the variability of hepatic iron concentrations. Clin Chem, 1999. 45(3):340-6. Kreeftenberg, et al. Measurement of iron in liver biopsies—a comparison of three analytical methods. Clin Chem Acta,

1984. 144(2-3):255-62.). Unlike biopsy information, the FerriScan R2-MRI Analysis System provides an image of the distribution of iron throughout the liver.

The mean percentage difference values for LIC between FerriScan R2-MRI and liver biopsy-derived values by atomic absorption spectrometry were not significantly different than zero in either study. The average standard error of LIC by FerriScan on a single LIC measurement is approximately 15% and the coefficient of variation for needle biopsy is at least 19%. These results confirm the robustness of FerriScan MRI-R2 Analysis System in comparison to liver biopsy.

3. Repeatability

Repeatability is defined as the measurement precision under the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time.

Sixty individuals were tested twice on separate occasions and R2 repeatability was assessed. Each subject was scanned twice on two separate visits. A standard deviation in the R2 measurement of 8.1% was observed, which is consistent with the 7.7% random error in the ten-patient repeatability study included in the initial calibration study.

4. Sensitivity and specificity

The sensitivity and specificity of FerriScan R2-MRI Analysis System were determined in the calibration study included in the original 510(k) (K043271).

Table 1 - FerriScan R2-MRI Analysis System Sensitivity and Specificity reproduced from K043271.

LIC threshold (mg Fe/g dw)	*Sensitivity (95% confidence limits) %*	*Specificity (95% confidence limits) %*
1.8	94 (86 – 97)	100 (88 – 100)
3.2	94 (85 – 98)	100 (91 – 100)
7.0	89 (79 – 95)	96 (86 – 99)
15	85 (70 – 94)	82 (83 – 96)

G. Labeling

The labeling is sufficient and satisfies the requirements of 21 CFR § 801.109 Prescription devices.

1. **Labeling must specify instructions for acceptance testing of images prior to processing.**

   The labeling includes a detailed verification process for assessing whether or not a given MRI site can be used to perform patient scans for FerriScan Analysis. The FerriScan Phantom Pack is scanned at the MR site. Input quality control, output quality control, and quality assurance of the phantom testing must pass the acceptance testing prior to performing patient scanning.

   The labeling describes a detailed process for acceptance testing of phantom and patient images prior to processing. The acceptance testing includes both pass/fail criteria and protocols to assess the images. If a phantom or patient dataset fails to pass the acceptance testing, the MRI dataset is rejected and the phantom or patient may need to be rescanned. Acceptance testing includes verification that acquisition settings are within specified tolerances, assessment of the phantom images, visual inspection of image quality, assessment of patient movement (for example, breathing artifacts), and verification that the scanner used passed the site verification process.

2. **Labeling must specify data processing quality assurance protocols.**

   The labeling describes a data processing quality assurance protocol for phantom image processing. The acceptance testing includes both pass/fail criteria and protocols for processing the phantom images and calculating R2 values. An acceptable range of calculated values for each vial of $MnCl_2$ is indicated.

   The labeling describes a data processing quality assurance protocol for patient image processing. The acceptance testing includes pass/fail criteria and protocols for processing the patient images and determining LIC. The quality assurance protocol includes processing elements such as region-of-interest selection, background noise assessment, and motion correction.

3. **Labeling must specify the sensitivity and specificity of Liver Iron Concentration measurements.**

   The labeling describes sensitivity and specificity of the device.

H. Risks to Health

The table below identifies the risks to health that may be associated with use of liver iron concentration imaging companion diagnostic for deferasirox and the measures necessary to mitigate these risks.

Table 1: Identified Risks to Health

Identified Risks to Health	Mitigation Measures
False positive result	Special controls (1), (2)(i), and (2)(ii)
False negative result	Special controls (1), (2)(i), and (2)(ii)
Sensitivity and specificity are not suitable for clinical decision making	Special controls (1) and (2)(iii)

I. Special Controls:

In combination with the general controls of the FD&C Act, the liver iron concentration imaging companion diagnostic for deferasirox is subject to the following special controls:

(1) Design verification and validation must include nonclinical and clinical performance testing demonstrating the bias, precision, repeatability, and reproducibility of liver iron concentration measurements.

(2) Labeling must include:
   (i) Instructions for acceptance testing of images prior to processing;
   (ii) Data processing quality assurance protocols; and
   (iii) The sensitivity and specificity of liver iron concentration measurements.

J. Benefit/Risk Determination

1. Risks

The risks of the device are based on data collected in a clinical study described above.

The risks of the FerriScan R2-MRI Analysis System are associated with the potential mismanagement of patients resulting from false results of the test. Patients with NTDT could be inappropriately started on or stopped from deferasirox or put on the wrong dose of the pharmaceutical if the companion diagnostic incorrectly estimates LIC.

- A false negative result may lead to deferasirox treatment being withheld from a patient who might have benefitted.
- A false positive result may lead to deferasirox treatment being administered to a patient who is not expected to benefit, and potentially any adverse side effects associated with treatment.
- If the sensitivity and specificity are not suitable for clinical decision making, the clinician may not be able to make a proper determination of treatment.

2. Benefits

The probable benefits of the device are also based on data collected in a clinical study as described above.

The imaging companion diagnostic is a non-invasive way to estimate liver iron concentration (LIC). The advantage of being able to non-invasively assess LIC is that the dose of the therapeutic pharmaceutical can be adjusted based on serial MRI-based LIC measurements in patients with non-transfusion-dependent thalassemia (NTDT) without requiring the patient to receive an invasive biopsy. This allows serial management of NTDT without requiring liver biopsies every six months. MRI based determination of LIC saves the patient the pain, inconvenience, and risk of liver biopsy every six months.

3. Other factors

Additional factors to be considered in determining probable risks and benefits for the FerriScan R2-MRI Analysis System include:

There is currently no FDA cleared or approved test for the selection of candidate NTDT patients for treatment with deferasirox.

The haematologist or gastroenterologist managing the patient always has the option to perform an invasive liver biopsy if they suspect the companion diagnostic does not accurately reflect the overall clinical condition of the patient. Therefore, the companion diagnostic is of relatively low risk. For a full discussion of the benefit/risk of the deferasirox in NTDT, see drug approval for Exjade from Novartis (NDA 021882).

4. Assessment of Benefits and Risks

In conclusion, given the available information above, the data support that for non-transfusion-dependent thalassemia (NTDT) patients, the FerriScan R2-MRI Analysis System is an aid in the assessment of NTDT patients for whom deferasirox therapy is being considered and for monitoring of NTDT patients receiving deferasirox therapy, the probable benefits outweigh the probable risks for the FerriScan R2-MRI Analysis System. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

K. Other comments

The concept of an imaging companion diagnostic device is similar to that of an in vitro companion diagnostic device: it provides information that is essential for the safe and effective use of a corresponding therapeutic product.

L. Conclusion

The de novo for the FerriScan R2-MRI Analysis System is granted and the device is classified under the following:

1. **Product Code**: PCS
2. **Device type**: Liver iron concentration imaging companion diagnostic for deferasirox.
3. **Class**: Class II
4. **Regulation**: 21 CFR 892.1001