January 21, 2022

PreventionGenetics, LLC
% Joanne Totosy De Zepetnek
Vice President, Regulatory Affairs and Quality
Rhythm Pharmaceuticals, Inc.
222 Berkeley Street
Boston, MA 02116

Re: DEN200059
Trade/Device Name: POMC/PCSK1/LEPR CDx Panel
Regulation Number: 21 CFR 862.1164
Regulation Name: Setmelanotide eligibility gene variant detection system
Regulatory Class: Class II
Product Code: QRV
Dated: September 3, 2021
Received: September 7, 2021

Dear Joanne Totosy De Zepetnek:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the POMC/PCSK1/LEPR CDx Panel, a prescription device with the following indications for use:

> The POMC/PCSK1/LEPR CDx Panel is a next generation sequencing (NGS)-based in vitro diagnostic test that analyzes genomic DNA isolated from blood or saliva. Specimens used with the test are K_2EDTA blood collected using certain indicated K_2EDTA blood collection devices and saliva collected using ORAcollect-Dx™ OCD-100 devices. The test detects germline nucleotide substitutions, short insertions and deletions, and copy number variants (CNVs) within the following 3 genes:
> - Pro-opiomelanocortin (*POMC*)
> - Proprotein Convertase Subtilisin/Kexin type 1 (*PCSK1*)
> - Leptin Receptor (*LEPR*)
>
> The test is a companion diagnostic device intended to select adult and pediatric patients 6 years of age and older who have obesity and certain variants in *POMC, PCSK1* or *LEPR* genes for treatment with IMCIVREE® (setmelanotide) in accordance with the approved therapeutic product labeling. The POMC/PCSK1/LEPR CDx Panel is a single-site assay performed at PreventionGenetics, LLC (Marshfield, WI).

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the POMC/PCSK1/LEPR CDx Panel, and substantially equivalent devices of this generic type, into Class II under the generic name setmelanotide eligibility gene variant detection system.

FDA identifies this generic type of device as:

> **Setmelanotide eligibility gene variant detection system**. A setmelanotide eligibility gene variant detection system is a qualitative in vitro diagnostic device intended to detect germline variants within genes isolated from human specimens for the purpose of identifying patients with obesity who may benefit from treatment with setmelanotide in accordance with the approved therapeutic product labeling.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On September 18, 2020, FDA received your De Novo requesting classification of the POMC/PCSK1/LEPR CDx Panel. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the POMC/PCSK1/LEPR CDx Panel into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, in response to our request for additional information letter dated December 2, 2020, and during interactive review, FDA has determined that, for the previously stated indications for use, the POMC/PCSK1/LEPR CDx Panel can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks to health are risks associated with incorrect performance of the test and incorrect interpretation of genetic data leading to false positive or false negative results. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Identified Risks to Health	Mitigation Measures
Incorrect performance of the test leading to false positive results (causing patients to receive drug treatment inappropriately) or false negative results (causing patients to miss an opportunity for drug treatment)	• Certain design verification and validation activities, including documentation of certain studies. • Certain labeling information, including certain limiting statements and performance information.

Identified Risks to Health	Mitigation Measures
Incorrect interpretation of genetic data leading to false positive results (causing patients to receive drug treatment inappropriately) or false negative results (causing patients to miss an opportunity for drug treatment)	• Certain design verification and validation activities, including documentation of certain studies and variant interpretation and classification procedures. • Certain labeling information, including certain limiting statements and performance information.

In combination with the general controls of the FD&C Act, the setmelanotide eligibility gene variant detection system is subject to the following special controls:

(1) Design verification and validation must include:
   (i) Detailed documentation of studies that provide data bridging the efficacy of setmelanotide in the clinical trial patient population identified by the clinical trial assay(s) to the efficacy of setmelanotide in the device intended use population identified by the device using the clinical trial samples, or through an alternative approach determined to be appropriate by FDA.
   (ii) Detailed documentation of studies that provide data demonstrating the accuracy of the device using clinical specimens representing the intended use specimen type(s) and intended use variant type(s) from the intended use population, including the clinical trial samples, or through an alternative approach determined to be appropriate by FDA. Accuracy of the device must be evaluated at the variant level and sample level, through evaluation of variant and non-variant sequences at the nucleotide level as well as variant interpretation, by comparison to validated bidirectional Sanger sequencing methods or through other methods determined to be appropriate by FDA. If the device will be used at more than one site, the data must demonstrate accuracy across multiple intended use sites.
   (iii) Detailed documentation of studies that provide data demonstrating the precision of the device for the intended use specimen type(s) and intended use variant type(s) from the intended use population. Precision must be evaluated at the variant level and sample level, through evaluation of variant and non-variant sequences at the nucleotide level as well as variant interpretation, using multiple reagent lots, operators, and instruments over multiple days, or through an alternative precision study design determined to be appropriate by FDA. If the device will be used at more than one site, data must demonstrate adequate, as determined by FDA, reproducibility across multiple intended use sites.
   (iv) Detailed documentation of studies that provide data demonstrating the analytical specificity of the device for the intended use specimen type(s), including an evaluation of cross-reactivity and cross contamination.
   (a) Cross-reactivity (e.g., from homologous regions, paralogs, pseudogenes, repeated sequences, high GC content regions, segmental duplications, and other types of cross-reactive sequences) must be evaluated to assess the detection of unintended alleles or incorrect calls in the target regions covered by the device.
   (b) Cross-contamination must be evaluated to detect carryover and co-mingling of input specimens throughout the process (e.g., from sample collection and library preparation to variant interpretation).

(v) Detailed documentation of studies that provide data demonstrating adequate, as determined by FDA, stability of the specimens used in the design validation studies in paragraphs (1)(i)-(iv), as applicable.
(vi) Detailed documentation of information demonstrating adequate, as determined by FDA, analytical quality metrics and thresholds.
(vii) Detailed documentation of information demonstrating adequate, as determined by FDA, procedures that will be performed for variant interpretation and classification, including the procedures that will be performed for variant interpretation and classification changes that may occur as new scientific information becomes available. The information must indicate how the personnel performing such interpretation and classification are trained.

(2) The labeling required under 21 CFR 809.10(b) and any test report generated must include:
(i) Limiting statements that:
(a) Explain that the classification and interpretation of variants identified reflects the current state of scientific understanding at the time the results are issued.
(b) Explain variants could change classification as new scientific information becomes available, which may impact patient eligibility for therapeutic treatment.
(c) If applicable, explain sufficient scientific information is not available to assign pathogenicity to variants of uncertain significance (VUS).
(ii) A detailed summary of the performance testing, including results, required under paragraphs 1(i)-(1)(iv).

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Setmelanotide eligibility gene variant detection system they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); 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/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); 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 FD&C Act; 21 CFR 1000-1050).

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Jessica Chu at 301-796-9056.

Sincerely,

Kellie B. Kelm -S

Kellie B. Kelm, Ph.D.
Director
Division of Chemistry
and Toxicology Devices
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