November 11, 2017
Progenika Biopharma S.A., a Grifols Company
Diego Tejedor
Technical Director
Ibaizabal bidea, Edificio 504, Parque Tecnologico de Bizkaia
Derio, 48160 Es

Re: K171868
Trade/Device Name: A1AT Genotyping Test
Regulation Number: 21 CFR 866.5130
Regulation Name: Alpha-1-antitrypsin immunological test system
Regulatory Class: Class II
Product Code: PZH
Dated: June 20, 2017
Received: June 22, 2017

Dear Diego Tejedor:

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. 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 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and Part 809), please contact the Division of Industry and Consumer Education (DICE) at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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 the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education (DICE) at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely,

Kelly Oliner

For,
Lea Carrington
Director
Division of Immunology
and Hematology Devices
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)*
K171868

Device Name
A1AT Genotyping Test

Indications for Use *(Describe)*
The Progenika A1AT genotyping kit is a qualitative, polymerase chain reaction (PCR) and hybridization-based in vitro diagnostic test to be used with the Luminex 200TM instrument (with xPONENT® software) for the simultaneous detection and identification of 14 allelic variants and their associated alleles found in the Alpha-1 antitrypsin (A1AT) codifying gene SERPINA1. The test is intended for use with genomic DNA extracted from human whole blood samples collected as dry blood spots (DBS) or in K2-EDTA. The A1AT allelic variant genotypes and associated allele results, when used in conjunction with clinical findings and other laboratory tests, are intended as an aid in the diagnosis of individuals with A1AT deficiency (A1ATD).

The kit is indicated for prescription use only.

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."

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
CIF: ESA95091799
www.progenika.com - www.grifols.com

510(k) Summary

A. Name of the device: A1AT Genotyping Test

B. Common name: Test for SERPINA1 gene genotyping

C. Classification name: Class II

D. Applicant: Progenika Biopharma S.A.

Address: Parque Tecnológico de Bizkaia

Ibaizabal bidea, Edificio 504

C.P. 48160, Derio – Bizkaia (Spain)

Telephone number: +34 94 406 45 25

Fax number: +34 94 406 45 26

Contact person: Diego Tejedor, Technical Director

e-mail: diego.tejedor@grifols.com

E. Intended Use:

The Progenika A1AT genotyping kit is a qualitative, polymerase chain reaction (PCR) and hybridization-based in vitro diagnostic test to be used with the Luminex 200™ instrument (with xPONENT® software) for the simultaneous detection and identification of 14 allelic variants and their associated alleles found in the Alpha-1 antitrypsin (A1AT) codifying gene SERPINA1. The test is intended for use with genomic DNA extracted from human whole blood samples collected as dry blood spots (DBS) or in K2-EDTA. The A1AT allelic variant genotypes and associated allele results, when used in conjunction with clinical findings and other laboratory tests, are intended as an aid in the diagnosis of individuals with A1AT deficiency (A1ATD).

The kit is indicated for prescription use only.

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
CIF: ESA95091799
www.progenika.com - www.grifols.com

F. Device Description:

Alpha 1 antitrypsin (A1AT) Genotyping Test utilizes Luminex xMAP technology. Genomic DNA is extracted from DBS or from human K2-EDTA anticoagulated whole blood. Extracted DNA is amplified and biotinylated by multiplex PCR and PCR products are denatured and hybridized to oligonucleotide probes coupled to color-coded beads. Hybridized DNA is labeled with a fluorescent conjugate and the resulting signal is detected with a Luminex® 200 system. Raw data obtained is processed with the A1AT Genotyping Test ANALYSIS SOFTWARE in order to obtain the final report. The A1AT Genotyping Test ANALYSIS SOFTWARE algorithm converts the allelic variant genotypes into associated alleles, based on the current literature.

The A1AT Genotyping Test Kit is composed of 4 reagent components (A1AT PCR Master Mix, A1AT Beads Master Mix, SAPE, SAPE Dilution Buffer) required to perform all the above mentioned processing steps, and a CD containing the A1AT Genotyping Test ANALYSIS SOFTWARE and other necessary files. Two kit configurations are available: for 48 or for 192 tests (different amounts of the same reagent components are provided in each case).

G. Substantial Equivalence Information:

Predicate Device: HYDRAGEL 18 A1AT ISOFOCUSING Kit

510(k) number: k063498

Applicant: SEBIA, Inc.

Main conclusion: Although technologically different (isoelectrofocusing vs. PCR/hybridization based genotyping), the intended use of the HYDRAGEL 18 A1AT ISOFOCUSING kit and the A1AT Genotyping Test can be considered equivalent, since both aim at identifying variant forms of the A1AT protein. In addition based on the performance data, it can be considered that the differences in the technological characteristics do not raise different questions of safety and effectiveness.

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
CIF: ESA95091799
www.progenika.com - www.grifols.com

Comparison table:

Item	Predicate Device: HYDRAGEL 18 A1AT isofocusing kit (k063498)	Candidate Device: A1AT Genotyping Test kit	Similarity/Difference
Intended Use	The HYDRAGEL 18 A1AT ISOFOCUSING kit is designed for the qualitative detection and identification of the different phenotypes of Alpha-1 antitrypsin (A1AT). Phenotyping results in conjunction with clinical findings and other laboratory assays aid in the diagnosis of Alpha-1 antitrypsin deficiency. The analysis is performed on human sera separated into electrophoretic patterns ready for qualitative analysis. The procedure includes isoelectrofocusing on agarose gel, performed on the semi-automatic HYDRASYS system, followed by immunofixation with anti-Alpha-1 antitrypsin antiserum. The use of enzyme labeled anti-Alpha-1 antitrypsin antiserum enhanced the detection and identification of the different phenotypes.	The Progenika A1AT genotyping kit is a qualitative, polymerase chain reaction (PCR) and hybridization-based in vitro diagnostic test to be used with the Luminex 200TM instrument (with xPONENT® software) for the simultaneous detection and identification of 14 allelic variants and their associated alleles found in the Alpha-1 antitrypsin (A1AT) codifying gene SERPINA1. The test is intended for use with genomic DNA extracted from human whole blood samples collected as dry blood spots (DBS) or in K2-EDTA. The A1AT allelic variant genotypes and associated allele results, when used in conjunction with clinical findings and other laboratory tests, are intended as an aid in the diagnosis of individuals with A1AT deficiency (A1ATD). The kit is indicated for prescription use only.	Similarity: Both are intended as an aid in the diagnosis of individuals with A1ATD. Difference: Phenotyping techniques vs genotyping techniques.
Specimen Type	Human serum from whole blood samples.	Human whole blood samples (DBS or K2-EDTA tubes).	Similarity: Blood samples. Difference: serum vs whole blood.
Target	Qualitative identification of A1AT phenotypes (directly linked to the genotype alleles) indicative of A1ATD.	Qualitative identification of A1AT alleles (which represent the phenotypes) causing A1ATD.	Similarity: Qualitative tests for A1ATD detection. Difference: Phenotype vs Genotype.

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
CIF: ESA95091799
www.progenika.com - www.grifols.com

Item	Predicate Device: HYDRAGEL 18 A1AT isofocusing kit (k063498)	Candidate Device: A1AT Genotyping Test kit	Similarity/Difference
Technology	Isoelectrofocusing on agarose gel, performed on the semi-automatic HYDRASYS system, followed by immunofixation with anti-Alpha-1 antitrypsin antiserum.	DNA extracted from DBS or from human K2-EDTA anticoagulated whole blood amplified and biotinylated by multiplex PCR and PCR products denatured and hybridized to oligonucleotide probes coupled to color-coded beads. Hybridized DNA is labeled with a fluorescent conjugate and resulting signal is detected with a Luminex® 200 system. The Raw data obtained is finally processed with the A1AT Genotyping Test ANALYSIS SOFTWARE in order to obtain the final report.	Similarity: NA. Difference: Isoelectrofocusing and immunofixation vs PCR-hybridization based genotyping.
Performance specifications	- Lowest detectable limit: 5 mg/dL - Interferences: Hemoglobin, bilirubin, triglycerides and cholesterol. Four concentrations per interferent. - Within-run and between run reproducibility. - Accuracy: 68 samples, comparator: polyacrylamide gels.	- Lower Limit of Detection: 0.0310 ng/µl DNA - Interferences: hemoglobin, bilirubin, triglycerides and short blood draw. - Lot-to-Lot and external reproducibility studies. - Accuracy: 116 samples, comparator: Bi-directional Sanger sequencing - Further specific studies (cross-contamination, DNA extraction…).	Similarity: Adequate performance results to ensure safety and effectiveness. Difference: general study designs.

NA: non applicable.

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
CIF: ESA95091799
www.progenika.com - www.grifols.com

H. Performance Data:

Analytical Data:

a) Precision:

Lot-to-lot repeatability: The lot-to-lot repeatability was determined by testing the "Sample Panel" (five DNA samples covering Z/Z, M/Z, S/S, M/S, and S/Z Sample Results) in triplicate with three different reagent lots, by two operators, on six non-consecutive days, alternating between two Luminex instruments. An overall repeatability of 99.7% was obtained for Sample Results.

External Reproducibility*:* The reproducibility of the device was determined by testing 17 samples covering all the heterozygous genotype of the 14 allelic variants (5 collected in DBS, 11 archived genomic DNA samples and 1 synthetic sample) tested by two operators per each of the three external sites (LifeShare Blood Center and Progenika Inc. in the USA, and the University of Pavia in Italy) over at least a 20-day period. Each operator tested those samples in duplicate on three non-consecutive days. A 100% of correct Sample Results was obtained in the study.

b) Stability*:*

Real-time Stability: a Real-time Stability study has been performed with kits of three different lots stored at 2-8ºC. There were eight test points: 3, 6, 9, 10, 12, 13, 15 and 16 months after manufacturing. At each test point 20 replicates of the "Sample Panel" were analyzed per reagent lot. All the samples provided correct Sample Results at every time point, and as such, 15 months product stability when stored at 2-8ºC has been demonstrated (one month before the last time point at which acceptance criteria were met).

Open Vial Stability: With the purpose of determining the stability of the product after it has been opened for the first time, 20 replicates of the "Sample Panel" were tested at six test points (6, 9, 12, 13, 15, and 16 months after manufacturing, equivalent to 0, 3, 6, 7, 9, and 10 months after opening for the first time). All the Sample Results obtained at every time point was correct and as such, the product has proved up to 9 months stability after the vials were first opened.

c) Lower Limit of Detection (LoD):

The DNA concentration at which 95% of sample replicates resulted in correct Sample Results was determined by testing 20 replicates of nine DNA dilutions of the "Sample Panel" (from 0.16 to 0.0033 ng/μl) using two reagent lots. It was shown that the highest LoD among the two lots used was 0.0310 ng/μl.

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
CIF: ESA95091799
www.progenika.com - www.grifols.com

d) DNA Extraction Validation:

With the aim of testing the possible impact of different extraction methods on assay performance, twelve blood samples (covering >95% of cases worldwide where allelic variants have been identified in the A1AT coding gene) collected in DBS (two types) and in K2-EDTA tubes were extracted three times by two operators on three different days. All the Sample Results obtained were correct with every extraction method.

e) Cross-contamination:

With the purpose of evaluating that the test does not show detectable cross-contamination or carryover between samples or between samples and Negative Controls during processing. No cross-contamination that could result in an incorrect Sample Results was detected.

f) Interfering Substances:

The effect of the presence of hemoglobin (555 mg/dL), bilirubin (36.8 mg/dL), triglicerides (4260 mg/dL), and K2-EDTA short drawn (5X K2-EDTA concentration) on product performance was evaluated by spiking five blood samples collected both, in DBS and in K2-EDTA tubes, with mentioned potential interfering substances. Correct Sample Results were obtained in every case.

Comparison Data:

g) Method Comparison:

The results obtained with the A1AT Genotyping Test were compared with the results obtained from bi-directional Sanger sequencing. A total of 116 DNA samples, representing as many variants interrogated by the assay as possible, were included in the study, distributed as follows: 66 clinical samples, 46 genomic DNAs extracted from cell lines and 4 synthetic DNA samples.

The sample panel covered all heterozygous and homozygous genotypes of each allelic variant and 15 compound heterozygous genotypes.

The comparison showed 100 % concordance between A1AT Genotyping Test and bidirectional Sanger sequencing results, as it is shown in the table below.

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
CIF: ESA95091799
www.progenika.com - www.grifols.com

Allelic variant	Most frequently associated Allele	Genomic DNA, n			Synthetic DNA, n		Concordance (%)
		-/-	+/-	+/+	+/-	+/+	
c.187C>T	**PI* I**	105	7	0	1	1	100%
c.194T>C	**PI* M procida**	104	8	0	1	1	100%
c.226_228delTTC	**PI* M malton**	103	9	0	1	1	100%
c.230C>T	**PI* S iiyama**	112	0	0	1	1	100%
c.552delC	**PI* Q0 granite falls**	111	1	0	2	2	100%
c.646+1G>T	**PI* Q0 west**	111	1	0	2	2	100%
c.721A>T	**PI* Q0 bellingham**	109	3	0	2	2	100%
c.739C>T	**PI* F**	106	6	0	2	2	100%
c.839A>T	**PI* P lowell**	107	5	0	2	2	100%
c.863A>T	**PI* S**	64	40	8	2	2	100%
c.1096G>A	**PI* Z**	70	35	7	2	2	100%
c.1130dupT	**PI* Q0 mattawa**	109	2	1	2	2	100%
c.1158dupC	**PI* Q0 clayton**	110	2	0	2	2	100%
c.1178C>T	**PI* M heerlen**	109	2	1	2	2	100%

I. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

J. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

K. Date of summary preparation:

November 8, 2017