November 5, 2019

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

Re: K192858
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: October 1, 2019
Received: October 4, 2019

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. 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 and Part 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 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 https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, 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).

Sincerely,

Douglas Jeffery, Ph.D.
Chief
Division of Immunology
and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
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)*
K192858

Device Name
A1AT Genotyping Test

Indications for Use *(Describe)*
The Progenika A1AT genotyping kit is a quantitative, 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 intended for use with genomic DNA extracted from human whole blood samples collected as dry blood spot (DBS) or in K2-EDTA or from human saliva samples collected as buccal swabs using ORAcollect Dx model OCD-100. 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.

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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

Special 510(k) Summary

A. Name of the device: A1AT Genotyping Test

B. Common name: Test for SERPINA1 gene genotyping

C. Regulatory information:

a. **Classification**: Class II
b. **Regulation Section:** 21 CFR 866.5130, Alpha-1-antitrypsin immunological test system
c. **Classification Product Code:** PZH, *SERPINA1* Variant Detection System
d. **Review panel:** Immunology (82)

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 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 or from human saliva samples collected as buccal swabs using ORAcollect·Dx model OCD-100. The A1AT allelic variant

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

F. Device Description:

Alpha 1 antitrypsin (A1AT) Genotyping Test utilizes Luminex xMAP technology. Genomic DNA is extracted from DBS or from human EDTA anticoagulated whole blood or from human saliva samples collected as buccal swabs using ORAcollect·Dx model OCD-100. 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: A1AT Genotyping Test

510(k) number: K171868

Applicant: Progenika Biopharma S.A.

Main conclusion: The similarities among the candidate device and the predicate device show that A1AT Genotyping Test for use with human saliva samples

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Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
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www.progenika.com - www.grifols.com

collected as buccal swabs using ORAcollect·Dx model OCD-100 is substantially equivalent to the predicate.

Based on the risk assessment and performance data, it can be considered that the differences due to new sample matrix do not raise different questions of safety and effectiveness.

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Fax: +34 94 406 45 26
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Comparison table:

Item	Candidate Device Modified A1AT Genotyping Test	Predicate Device A1AT Genotyping Test (K171868)
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 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 or from human saliva samples collected as buccal swabs using ORAcollect·Dx model OCD-100. 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.	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.
Specimen Type	Genomic DNA extracted from human whole blood samples collected as DBS or in K2-EDTA and human saliva samples collected as buccal swabs using ORAcollect·Dx model OCD-100.	Genomic DNA extracted from human whole blood samples collected as DBS or in K2-EDTA.
Target	Same.	Qualitative identification of A1AT alleles (which represent the phenotypes) causing A1ATD.

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48160 Derio - Bizkaia - SPAIN
Phone: +34 94 406 45 25
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CIF: ESA95091799
www.progenika.com - www.grifols.com

Item	Candidate Device Modified A1AT Genotyping Test	Predicate Device A1AT Genotyping Test (K171868)
Device components	Same.	The test is composed of four reagent components (A1AT PCR Master Mix, A1AT Beads Master Mix, SAPE and SAPE Dilution Buffer) in sufficient quantity for either 48 or 192 tests and a CD containing the A1AT Genotyping Test ANALYSIS SOFTWARE.
Technology	Polymerase chain reaction (PCR) and hybridization-based in vitro diagnostic test to be used with the Luminex 200TM instrument (with xPONENT® software). DNA is extracted from human whole blood samples collected as dry blood spots (DBS) or in K2-EDTA or from human saliva samples collected as buccal swabs using ORAcollect·Dx model OCD-100, 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 resulting signal is detected with a Luminex 200TM system. The raw data obtained is finally processed with the A1AT Genotyping Test ANALYSIS SOFTWARE in order to obtain the final report.	Polymerase chain reaction (PCR) and hybridization-based in vitro diagnostic test to be used with the Luminex 200TM instrument (with xPONENT® software). DNA is extracted from human whole blood samples collected as dry blood spots (DBS) or in K2-EDTA, 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 resulting signal is detected with a Luminex 200TM system. The raw data obtained is finally processed with the A1AT Genotyping Test ANALYSIS SOFTWARE in order to obtain the final report.
Performance specifications	– Lower Limit of Detection: same. – Interferences: α-amylase, hemoglobin, immunoglobin A, total protein, microbes, eating food without beef, eating food with beef, drinking, smoking, chewing gum, mouth washing and brushing teeth.	– Lower Limit of Detection: 0.0310 ng/µl DNA. – Interferences: hemoglobin, bilirubin, triglycerides and short blood draw.

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Item	Candidate Device Modified A1AT Genotyping Test	Predicate Device A1AT Genotyping Test (K171868)
	– Lot-to-Lot and External Reproducibility studies: same. – Accuracy: 147 samples, comparator: Bi-directional Sanger sequencing.	– Lot-to-Lot and external reproducibility studies. – Accuracy: 116 samples, comparator: Bi-directional Sanger sequencing.
Intended population	Same.	Prescription use only.
DNA extraction method	Whole blood samples collected as DBS or in K2-EDTA: same. Saliva samples collected as buccal swabs using ORAcollect·Dx model OCD-100: – QIAamp DNA Blood Mini Kit (Qiagen) – Commercial lysis and neutralization solutions (Sigma) – QIAsymphony DNA Mini Kit (Qiagen)	Whole blood samples collected in K2-EDTA: QIAamp DNA Blood Mini Kit (Qiagen) Whole blood samples collected as DBS: – Commercial lysis and neutralization solutions (Sigma) – Home-made buffer
Specimen Stability	– Whole blood samples collected in K2-EDTA: same. – Whole blood samples collected as DBS: same. – Saliva samples collected as buccal swabs using ORAcollect·Dx model OCD-100 (DNA Genotek): up to 60 days when stored at ambient temperature.	– Whole blood samples collected in K2-EDTA: up to 24 days before DNA extraction at 2-8ºC. – Whole blood samples collected as DBS: up to 6 months at ambient temperature.

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H. Performance Data:

Analytical Data:

a) Precision/Reproducibility:

See K171868 for Lot-to-Lot Variability and Site to Site Reproducibility information.

b) Reagent Stability*:*

See K171868 for Real-Time and Open-Vial Stabilities information.

Stability studies based on the same protocol, acceptance criteria and results as K171868 have proved up to 24 months reagent stability when stored at 2-8ºC and up to 9 months reagent stability after the vials were first opened.

c) Specimen Stability*:*

See K171868 for whole blood samples collected as DBS or in K2-EDTA stabilities.

Saliva samples are collected in ORAcollect·Dx model OCD-100. See K152464 for saliva samples stability information.

d) Lower Limit of Detection (LoD):

See K171868 for LoD information.

e) DNA Extraction Variability:

See K171868 for DNA Extraction Variability in whole blood samples collected as DBS or in K2-EDTA information.

With the aim of testing the possible impact of 3 different extraction methods on assay performance, twelve saliva samples (covering >95% of cases worldwide where allelic variants have been identified in the A1AT coding gene) collected as buccal swabs using ORAcollect·Dx model OCD-100 were extracted three

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

times by two operators on three different days and tested in duplicate. Results obtained for all samples tested with each extraction method were correct.

f) Cross-reactivity and Cross-contamination:

See K171868 for Cross-reactivity and Cross-contamination information.

g) Interfering Substances:

See K171868 for Interfering Substances information in whole blood samples collected as DBS or in K2-EDTA.

Saliva samples collected in ORAcollect·Dx model OCD-100 from five (5) random donors (M/M except one M/Z) were spiked with salivary α-amylase at 395 U/mL; hemoglobin at 226 mg/dL; immunoglobin A at 0.43 mg/mL and total protein at 3.18 mg/mL (composed of 0.185 mg/mL salivary α-amylase, 0.43 mg/mL IgA and 2.56 mg/mL human serum albumin). No inhibition of the assay was observed for any of the interfering substances tested.

Saliva samples from five (5) random donors (M/M except one M/F and one M/S) were collected in ORAcollect·Dx model OCD-100 prior to the activity (baseline/control sample), immediately after the activity and 30 minutes after the activity. Seven (7) activity groups were tested: eating food without beef, eating food with beef, drinking, smoking, chewing gum, mouth washing and brushing teeth. The results indicated that saliva samples collected in ORAcollect·Dx model OCD-100 should be collected at least 30 minutes after the activity which is compatible with the instructions for use of ORAcollect·Dx model OCD-100.

DNAs from human cell lines (MS, MZ, SZ, SS and MZ) were spiked with DNA of the following microbes: Staphylococcus epidermis, Streptococcus mutans, Lactobacillus casei, Actinomyces viscosus and Candida albicans. No inhibition of the assay was observed for any of the microbial interfering substances tested.

Potentially interfering variants identified for the allelic variants detected by the A1AT Genotyping Test are listed in the table below. None of the listed potentially interfering variants was tested.

Progenika Biopharma, S.A.
Ibaizabal bidea, Edificio 504
Parque Tecnológico de Bizkaia
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Allelic Variant RefSeq: NM_001127701.1	Reported Associated Alleles	Interfering variants
c.187C>T	**PI* I**	rs199422213
c.194T>C	**PI* M procida**	rs199422213
c.226_228delTTC	**PI* M malton**	rs199422213
c.230C>T	**PI* S iiyama**	rs199422213
c.552delC	**PI* Q0 granite falls**	rs148207011
c.646+1G>T	**PI* Q0 west**	rs148207011
c.721A>T	**PI* Q0 bellingham**	rs200634040, rs72552401
c.739C>T	**PI* F**	rs544632177, rs577164283
c.839A>T	**PI* P lowell**	rs1049800
c.863A>T	**PI* S**	rs149537225
c.1096G>A	**PI* Z**	rs143370956, rs201774333, rs551595739, rs372571769
c.1130dupT	**PI* Q0 mattawa**	rs148362959, rs372571769
c.1158dupC	**PI* Q0 clayton**	rs143329723, rs121912712, rs372571769
c.1178C>T	**PI* M heerlen**	rs61761869, rs372571769

One sample homozygous for PI* Q0 amersfoort (c.552C>G) was tested and detected as homozygous for PI* Q0 granite falls (c.552delC). The information related to this interfering variant has been included in the assay limitations section of the package insert.

Comparison Data:

h) Method Comparison:

See K171868 for Method Comparison information in whole blood samples.

Progenika Biopharma, S.A.
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The results obtained with the A1AT Genotyping Test were compared with the results obtained from bi-directional Sanger sequencing. A total of 147 DNA samples, representing all variants interrogated by the assay, were included in the study, distributed as follows: 140 archived left-over clinical genomic DNA samples obtained from human saliva collected as buccal swabs (ORAcollect·Dx model OCD-100), 3 genomic DNA samples extracted from cell lines and 4 synthetic DNA samples.

The sample panel covered all heterozygous and homozygous genotypes of each allelic variant and 12 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.

Allelic Variant	Most frequently associated Allele	Genomic DNA, n			Synthetic DNA, n		Concordance (%)
		-/-	+/-	+/+	+/-	+/+	
c.187C>T	**PI* I**	130	13	0	1	1	100%
c.194T>C	**PI* M procida**	138	5	0	1	1	100%
c.226_228delTTC	**PI* M malton**	120	21	2	1	1	100%
c.230C>T	**PI* S iiyama**	143	0	0	1	1	100%
c.552delC	**PI* Q0 granite falls**	143	0	0	2	2	100%
c.646+1G>T	**PI* Q0 west**	143	0	0	2	2	100%
c.721A>T	**PI* Q0 bellingham**	143	0	0	2	2	100%
c.739C>T	**PI* F**	139	4	0	2	2	100%
c.839A>T	**PI* P lowell**	128	14	1	2	2	100%
c.863A>T	**PI* S**	93	35	15	2	2	100%
c.1096G>A	**PI* Z**	93	35	15	2	2	100%
c.1130dupT	**PI* Q0 mattawa**	137	5	1	2	2	100%
c.1158dupC	**PI* Q0 clayton**	143	0	0	2	2	100%
c.1178C>T	**PI* M heerlen**	138	5	0	2	2	100%

I. Proposed Labeling:

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

J. Conclusion:

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

K. Date of summary preparation:

September 30, 2019.