510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number

K191364

B Applicant

Fujimori Kogyo Co., Ltd.

C Proprietary and Established Names

Total Thrombus-formation Analysis (T-TAS) 01 System

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JOZ	Class II	21 CFR 864.5700 - Automated Platelet Aggregation System	HE - Hematology

II Submission/Device Overview:

A Purpose for Submission:

Clearance of a new device

B Measurand:

Platelet function

C Type of Test:

Platelet aggregation

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The T-TAS 01 Instrument is intended for use with T-TAS reagent chips in the clinical laboratory.

The T-TAS 01 PL chip is intended for use in the clinical laboratory for the analysis of the platelet thrombus formation process (primary hemostatic function) in patients age 21 and older with a history of conditions associated with impaired primary hemostatic function or use of antiplatelet therapy. The test uses BAPA-anticoagulated whole blood specimens to measure platelet adhesion to a thrombogenic collagen-coated surface and aggregation, which causes an increase in flow pressure inside the PL chip. The test measures primary hemostatic function as the area under the pressure-time curve (AUC), with AUC < 260 suggesting abnormal primary hemostatic function. Additional testing may be necessary to identify the cause(s) of abnormal primary hemostatic function. The test has been evaluated in patients taking antiplatelet therapy, in patients with von Willebrand disease, and in patients with Glanzmann's thrombasthenia. Other primary hemostasis disorders have not been evaluated.

The BAPA tube for T-TAS 01 is intended to be used for the collection, transport, and storage of blood specimens for use with the T-TAS 01 system.

C Special Conditions for Use Statement(s):

- Rx - For Prescription Use Only
- Additional testing may be necessary to identify the cause(s) of a primary hemostasis defect.
- The BAPA tube is used for the collection, transport, and storage of blood specimens for use with the T-TAS 01 system.

D Special Instrument Requirements:

IV Device/System Characteristics:

A Device Description:

The T-TAS 01 system is an automated platelet function system. It consists of a tabletop instrument controlled by a dedicated PC, a disposable, single-use flow chamber microchip, and anticoagulant collection tubes with benzylsulfonyl-D-Arg-Pro-4-amidinobenzylamide (BAPA). The PL Chip for T-TAS 01 contains a collagen-coated analytical path consisting of 26 microcapillary channels.

B Principle of Operation:

The assay is performed using BAPA-anticoagulated whole blood samples. BAPA inhibits thrombin and factor Xa. During the assay, the blood sample is exposed to arterial shear stresses at 1500 s^{-1} in the presence of a collagen-coated surface, which causes platelet attachment to collagen mediated by von Willebrand factor (vWF) and platelet activation. Platelet activation causes the release of endogenous factors that recruit and activate other platelets and cause aggregation, or platelet thrombus formation (PTF) and growth.

PTF causes occlusion of the microcapillary channels, which increases the flow pressure within the assay chip. The process of PTF in the flow chamber is continuously monitored by a pressure sensor that tracks pressure changes in the flow path. After the start button is pressed, the blood sample is injected into the chip at a high flow rate for the purpose of moving blood samples into the chip and past the microcapillaries without creating air bubbles. After the initial step, the assay begins, using a set flow rate. The flow pressure readings subtract the base pressure and are plotted in the pressure waveform graph. The assay is completed at 10 minutes or when the occlusion pressure reaches 60 kPa, whichever occurs first. The area under the flow pressure curve (AUC) over 10 minutes is automatically calculated. The end users will see the pressure waveform graph and the AUC results.

AUC results less than 260 are associated with abnormal primary hemostasis.

C Instrument Description Information:

Modes of Operation	Yes	No
Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?	☒	☐
Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?	☐	☒
Software		
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types.	☒	☐

1. Instrument Name:

   T-TAS 01 Instrument

2. Specimen Identification:

   Specimen identification is performed by use of a barcode scanner or manually typing the specimen information.

3. Specimen Sampling and Handling:

   - The T-TAS 01 system uses BAPA-anticoagulated whole blood freshly collected with a 21 gauge or larger-bore needle.
   - The whole blood is mixed with anticoagulant by gently inverting the tube 5 times.
   - The whole blood sample should be incubated upright at room temperature for 30 minutes prior to testing.
   - Blood samples should be measured between 30 minutes to 6 hours after collection.
   - Specimens should be transported at room temperature and extreme temperatures should be avoided
   - Use of pneumatic tube transport systems may cause platelet activation. Such transport systems will need to be validated by the laboratory for suitability
   - Avoid using hemolyzed specimens

4. Calibration:

   All calibration is performed by the manufacturer. There are no calibration activities performed by the end-user.

5. Quality Control:

   The following three types of System Checks (SCs) are automatically performed but focus primarily on the functionality of the instrument:

SC Type	Frequency	Function
Simple SC	Automatically performed during each test	Check for pressure leaks inside the pumps. Check the solenoid valve, pump and tubing.
Automatic SC	Automatically performed every time the system is powered on or the PL chip is selected from the measurement screen.	Check for pressure leaks inside the pumps. Check the solenoid valve, pump and tubing.
Manual SC	Monthly (recommended)	Check for pressure leaks within the overall system, including the tubing from the pumps to the nozzles.

Testing of blood samples from a normal healthy donor is needed to confirm reagent integrity and performance of the PL chip. It is recommended to test a control donor blood sample in duplicate with each new shipment of PL chips received or to verify the performance of the system.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Dade PFA-100 Platelet Function Analyzer and Dade PFA-100 Reagents

B Predicate 510(k) Number(s):

K060489

C Comparison with Predicate(s):

Device & Predicate Device(s):	K191364	K060489
Device Trade Name	Total Thrombus-formation Analysis (T-TAS) 01 System	Dade® PFA-100® Platelet Function Analyzer Dade® PFA-100® Reagents

Device & Predicate Device(s):	K191364	K060489
General Device Characteristic Similarities		
Intended Use/Indications For Use	The T-TAS 01 Instrument is intended for use with T-TAS reagent chips in the clinical laboratory. The T-TAS 01 PL chip is intended for use in the clinical laboratory for the analysis of the platelet thrombus formation process (primary hemostatic function) in patients age 21 and older with a history of conditions associated with impaired primary hemostatic function or use of antiplatelet therapy. The test uses BAPA-anticoagulated whole blood specimens to measure platelet adhesion to a thrombogenic collagen-coated surface and aggregation, which causes an increase in flow pressure inside the PL chip. The test measures primary hemostatic function as the area under the pressure-time curve (AUC), with AUC < 260 suggesting abnormal primary hemostatic function. Additional testing may be necessary to identify the cause(s) of abnormal primary hemostatic function.	The Dade® PFA-100® Platelet Function Analyzer and Dade® PFA-100® Reagents are in vitro diagnostic devices intended to aid in the detection of platelet dysfunction in citrated human whole blood.

Device & Predicate Device(s):	K191364	K060489
	The test has been evaluated in patients taking antiplatelet therapy, in patients with von Willebrand disease, and in patients with Glanzmann's thrombasthenia. Other primary hemostasis disorders have not been evaluated. The BAPA tube for T-TAS 01 is intended to be used for the collection, transport, and storage of blood specimens for use with the T-TAS 01 system.	
Platelet Adhesion Matrix	Collagen	Same
Calibration	Factory calibrated	Same
Internal Quality Control	Self-test performed at least once per shift at the start of each shift	Same
External Quality Control	External quality control uses known control donor blood samples	Same
Assay Temperature	36˚C	37.9 ± 1˚C
Chip/Cartridge Warm-up Time in Instrument Prior to Assay	Same	< 2.5 minutes
Recommended Operating Temperature	68˚F to 86˚F (20˚C to 30˚C)	64˚F to 90˚F (18˚C to 29˚C)
General Device Characteristic Differences		
Specimen Type	BAPA-anticoagulated whole blood	Buffered sodium citrate-anticoagulated whole blood
Detection Principle	Measures integrated area under the curve of pressure over time as platelets adhere to a thrombogenic surface under high shear flow	Measures time required for platelets to adhere and aggregate, resulting in occlusion of an aperture under high shear flow conditions.

Device & Predicate Device(s):	K191364	K060489
	conditions.	
Mechanism of Platelet Activation	vWF-mediated binding to collagen at high shear rate	Soluble exogenous agonist (epinephrine) + vWF-mediated binding to collagen at high shear rate
Shear Rate During Assay	1500 s^{-1}	5000 s^{-1}
Other Reagents Necessary for Assay	Mineral oil	Trigger solution
Sample Volume	300–330 µL (320 µL recommended)	800 µL
Sample Incubation Time Prior to Assay	30 minutes at room temperature	15 minutes at room temperature
Maximum Allowable Sample Stability Time Prior to Assay	6 hours at room temperature	4 hours at room temperature
Assay Units	AUC	Closure time (seconds)
Recommended Cutoff	AUC < 260	> 170 seconds
Interpretation of Result	AUC ≥ 260 indicates the overall primary hemostatic function is normal. AUC < 260 is considered abnormal and indicates impaired primary hemostatic function (reduced platelet thrombus formation).	Closure time > 170 seconds is considered abnormal and indicates platelet dysfunction

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition

CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition

CLSI EP28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition

CLSI EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

CLSI GP34-A, Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Approved Guidance

ISO 14971, Medical devices – Applications of Risk Management to Medical Devices

CLSI GP39-A6, Tubes and Additives for Venous and Capillary Blood Specimen Collection; Approved Standard – Sixth Edition

EN 61326-1, Electrical equipment for measurement, control, and laboratory use – EMC requirements – Part 1: General requirements

EN 61326-2-6, Electrical equipment for measurement, control, and laboratory use – EMC requirements – Part 2-6: Particular requirements for in vitro diagnostic (IVD) medical equipment

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision:

a. Repeatability Study

The repeatability study was performed at a single laboratory. Three unique venous blood samples representing different AUC levels (low, middle, high) were tested on either two of the three T-TAS 01 instruments. A normal donor provided the sample with normal primary hemostatic ability (high). Two donors taking aspirin provided specimens with primary hemostatic ability around the assay cutoff (middle) and abnormal primary hemostatic ability (low). Each sample was analyzed in duplicate on three PL chip lots and two T-TAS 01 instruments by three different trained operators. The results met the pre-defined acceptance criteria.

Operator	A						B						C					
T-TAS 01 instrument	4			5			5			6			4			6		
PL chip lot	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Replicate	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB	AB

Sample	N	Mean	Within-Run (SD, %CV)	Between-Operator (SD, %CV)	Between-Lot (SD, %CV)	Between-Instrument (SD, %CV)	Total (SD, %CV)
High	36	428.1	10.7, 2.5	2.0, 0.5	4.7, 1.1	1.6, 0.4	11.9, 2.8
Middle	36	237.3	31.7, 13.4	6.4, 2.7	10.5, 4.4	0.0, 0.0	34.0, 14.3
Low	36	130.7	18.4, 14.1	11.8, 9.0	13.5, 10.3	0.0, 0.0	25.7, 19.6

b. Reproducibility

The reproducibility study was conducted at three sites over five days. At each site, four unique whole blood samples were tested in five duplicate measurements with one PL

chip lot and one T-TAS 01 instrument. The four donor types used in the study are as follows, considering inter-individual variability in response to aspirin:

Donor	AUC Result Category (AUC < 260 = Abnormal)	Aspirin Use	Aspirin Response
1	Normal	No	N/A
2	Normal	Yes	Poor Response
3	High Abnormal	Yes	Medium Response
4	Low Abnormal	Yes	High Response

The study evaluated the within-run and between-day precision. Since different donors were recruited at each site for the precision study, results were not pooled across days or donors due to natural inter- and intra-individual variability in response to aspirin. The pre-defined acceptance criteria were. All results met the pre-defined acceptance criteria.

Site 1:

Donor	N	Mean	Within-Run (SD, %CV)	Between-Day (SD, %CV)	Total (SD, %CV)
1	25	413.4	12.8, 3.1	16.7, 4.0	21.1, 5.1
2	25	366.5	25.8, 7.7	0.0, 0.0	25.8, 7.7
3	25	140.8	23.9, 17.0	27.9, 19.8	36.7, 26.1
4	25	50.0	15.2, 30.3	12.9, 25.9	19.9, 39.9

Site 2:

Donor	N	Mean	Within-Run (SD, %CV)	Between-Day (SD, %CV)	Total (SD, %CV)
1	25	417.7	20.0, 4.8	13.1, 3.1	23.9, 5.7
2	25	347.5	27.5, 7.9	10.7, 3.1	29.5, 8.5
3	25	176.0	26.0, 14.8	21.9, 12.5	34.0, 19.3
4	25	78.4	22.7, 29.0	20.8, 26.5	30.8, 39.3

Site 3:

Donor	N	Mean	Within-Run (SD, %CV)	Between-Day (SD, %CV)	Total (SD, %CV)
1	25	411.1	11.9, 2.9	10.0, 2.4	15.5, 3.8
2	25	336.4	20.2, 6.0	23.2, 6.9	30.7, 9.1
3	25	162.6	28.9, 17.7	3.6, 2.2	29.1, 17.9
4	25	54.6	10.2, 18.7	13.6, 24.8	17.0, 31.1

2. Linearity:

   Not applicable

3. Analytical Specificity/Interference:

   The interference studies were conducted to determine whether various substances commonly encountered in the intended use population affect the T-TAS 01 PL assay results. The analytical specificity for the T-TAS 01 PL assay was determined by spiking venous whole

blood samples taken from a normal donor (AUC ≥ 260) and a donor taking aspirin (AUC < 260). There were at least four replicate measurements for each control and test blood sample. The following endogenous and exogenous interfering substances were evaluated and showed no significant interference up to the specified concentration in the venous whole blood samples collected in the BAPA tubes.

Compound	Concentration	Compound	Concentration
Acetaminophen	7.8 mg/dL	Heparin	525 U/mL
Bilirubin	40 mg/dL	L-Thyroxine	0.0858 mg/dL
Caffeine	21.6 mg/dL	Metformin	2.4 mg/dL
Captopril	0.528 mg/dL	Omeprazole	1.68 mg/dL
Catechin	5 mg/dL	Pravastatin	0.414 mg/dL
Cilostazol	1.25 mg/dL	Propranolol	0.202 mg/dL
Dabigatran	0.047 mg/dL	Rivaroxaban	0.044 mg/dL
Dextran 40	2400 mg/dL	Streptokinase	50,000 U/dL
Diltiazem	0.18 mg/dL	Theophylline	6 mg/dL
Dipyridamole	0.25 mg/dL	Triglycerides	750 mg/dL
Fish Oil	25.6 mg/dL	Warfarin	7.5 mg/dL
Ibuprofen	0.438 mg/dL		

Cilostazol, dipyridamole, ibuprofen and tirofiban are known to reduce platelet activity in a dose-dependent manner. The maximum tirofiban concentration without interference was not determined.

Hemolysis significantly affects assay AUC results due to shear-induced platelet activation and aggregation. Therefore, a statement is included in the package insert to alert the user not to use hemolyzed specimens when performing the T-TAS 01 PL assay.

There was no significant hemodilution effect on AUC results up to 20%.

There was no significant effect of under-filling the BAPA blood collection tube on AUC results up to 50%.

4. Assay Reportable Range:

The reportable range and the analytical measurement range for the T-TAS 01 assay were determined upon the range of clinical samples as 0.3–467.7. However, the numeric output of the PL assay has not been evaluated for correlation to disease severity.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

a. Shelf Life/Stability

i. Reagent stability for T-TAS 01 PL chip

Open-pouch stability studies were isochronously performed to characterize the stability of PL chips following removal from the sealed pouch and storage at ambient temperature. Venous whole blood samples were collected from a single healthy donor

with normal primary hemostatic ability into BAPA-anticoagulated tubes. Three PL chip lots were tested and two PL chips from each lot were removed from their pouches and stored at ambient temperature for the following durations prior to testing: <5 minutes, 4 hour, 6 hours, 8 hours and 10 hours. Each chip was tested with normal donor blood in quadruplicate. The "<5 minute" condition serves as the control condition for comparison. The data support a stability claim of up to 8 hours at ambient temperature after PL chip removal from the pouch.

Closed-pouch stability studies were isochronously performed to characterize the stability of PL chips when stored in sealed pouches under refrigeration (2–8˚C). Venous whole blood samples were collected into BAPA-anticoagulated tubes from two healthy donors with normal primary hemostatic ability and a native donor with abnormal AUC result. Three PL chip lots were tested. Two PL chips from each lot were tested following the tested storage condition at the following durations after their manufacture: 0–13 months. Each chip was tested with each blood sample in quadruplicate. The control condition was a fresh PL chip lot that was newly manufactured prior to the testing timepoint. The data support a stability claim of 12 months when stored at 2–8˚C.

ii. Blood sample stability

The stability of BAPA-anticoagulated blood specimens stored at room temperature was tested by collecting venous whole blood samples from two healthy normal donors and two subjects taking aspirin with abnormal primary hemostatic function. Blood samples were stored upright at room temperature for 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours prior to testing. Three T-TAS 01 instruments and one lot of PL chips were used in the test. Six replicate measurements were performed for each tested time point. The control condition was established as 30 minutes after sample collection. Results were averaged prior to analysis. Each condition was compared to the control condition by calculating the % of control for the average of the replicates. The results demonstrate that BAPA-anticoagulated venous blood samples are stable for up to 6 hours after collection.

6. Detection Limit:

Not applicable

7. Assay Cut-Off:

The T-TAS PL 01 assay cut off (AUC < 260) was established in a group of 122 apparently healthy adults (34 females, 88 males, ages 20–45). The recruited participants did not take antiplatelet or nonsteroidal anti-inflammatory drugs (NSAID). They did not have any history of significant bleeding or diagnosis of a primary hemostatic abnormality.

8. Accuracy (Instrument):

Not applicable

9. Carry-Over:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

The method comparison study was performed to compare the performance of T-TAS 01 PL assay to the predicate device PFA-100 assay. Both assays evaluated 25 patients with vWD and three patients with GT. The predicate device involves the measurement of the collagen/epinephrine (Col/Epi) cartridge and collagen/ADP (Col/ADP) cartridge. The result interpretation was according to the PFA-100 test cartridge package insert. The following table demonstrates the percent positive, percent negative and overall agreement between the T-TAS 01 PL assay and the PFA-100 assay for the vWD and GT patients.

Subject Type	N	Percent Positive Agreement (95% CI)	Percent Negative Agreement (95% CI)	Overall Agreement (95% CI)
vWD	25	72% (51–88%)	100.0% (40–100%)	88% (69– 97%)
GT	3	100% (43.9–100.0%)	N/A	100% (43.9–100.0%)

2. Matrix Comparison:

Not applicable

C Clinical Studies:

1. Clinical Sensitivity:

Six investigational sites recruited 142 healthy subjects, 57 patients on aspirin (81-mg ASA) monotherapy, 47 subjects taking dual antiplatelet therapy (18 subjects on clopidogrel and ASA, 15 subjects on prasugrel and ASA, and 14 subjects on ticagrelor and ASA), 25 vWD patients and three GT patients. Among vWD patients, there were 12 patients with Type 1, 10 patients with Type 2 and three patients with Type 3. The study was to evaluate the sensitivity and specificity of the T-TAS 01 PL assay to detect conditions associated with the abnormal primary hemostatic function. At each investigational site, blood samples were tested in duplicate using BAPA-anticoagulated whole blood samples. Measurements were performed within four hours of sample collection. The first measurement was used for the data analysis. The following table provides a summary for each subject group.

Parameter	N	Value	95% CI
Sensitivity (ASA)	57	68.4%	55.5-79.0%
Sensitivity (clopidogrel + ASA DAPT)	18	100.0%	81.5-100.0%
Sensitivity (prasugrel + ASA DAPT)	15	100.0%	78.2-100.0%
Sensitivity (ticagrelor + ASA DAPT)	14	100.0%	76.8-100.0%
Sensitivity (vWD)	25	72.0%	51–88%

Parameter	N	Value	95% CI
Sensitivity (GT)	3	100.0%	43.9-100%
Negative agreement (healthy)	142	95.8%	91.1–98.0 %

2. Clinical Specificity:

   See Clinical Sensitivity above.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

Three clinical sites recruited 142 healthy adult subjects to establish the reference range for the T-TAS 01 PL assay. At each testing site, blood samples were tested in duplicate using BAPA-anticoagulated whole blood samples. Measurements were performed within four hours of sample collection. The first measurement was used for the data analysis. The central 90% reference interval is 270.0–447.7. Measurements from a separate group of 20 healthy subjects validated the established reference interval (302.5–429.1).

F Other Supportive Instrument Performance Characteristics Data:

1. BAPA blood collection tube validation

   a. BAPA tube vacuum performance

      The BAPA tube vacuum performance was conducted to demonstrate the stability of the tube vacuum at ambient temperature. BAPA tubes from three production lots were stored at room temperature. The tube vacuum was measured by allowing the tube to fill with water, measuring the weight of the water inside the tube and converting the weight (gram) to volume (mL). Five replicate measurements were performed for each condition. The study is on-going. Current results support the vacuum present in the BAPA tube for T-TAS 01 is stable for 10 months.

   b. BAPA tube anticoagulant fill

      The BAPA tube anticoagulant fill study was conducted to determine the consistency of BAPA anticoagulant added to the BAPA tube for the T-TAS 01 system. Three lots of the BAPA tubes were used and ten replicate measurements were performed for each lot. The results demonstrated that the amount of BAPA anticoagulant added to the BAPA tube for the T-TAS 01 system is consistent.

   c. Sterilization

The BAPA tube was sterilized by gamma irradiation. Sterilization validation was conducted and concluded that there is a 1 in 1,000,000 possibility that the product is not sterile.

d. Transportation stress test

Transport stress test was conducted to demonstrate the stability of BAPA tubes after transportation. The randomly selected samples were put on the oscillation device for three days (frequency at 150 times/min) to simulate the bumping situation in transportation. The device was also exposed to high temperature (40˚C) and high humidity (80% relative humidity) for 30 days. The test results support the stability of BAPA tubes after transportation.

2. Restriction of Hazardous Substances Directive (RoHS)

The following substances in the T-TAS 01 do not exceed any threshold as set forth by the RoHS directive: cadmium, hexavalent chromium, lead, mercury, polybrominated biphenyls, polybrominated diphenyl ethers

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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