United States

PL Chip Package Insert

for measurement of primary hemostatic ability

INTENDED USE:

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.

SUMMARY AND TEST PRINCIPLE:

Primary hemostasis describes the physiological mechanism of platelet plug (thrombus) formation following vascular injury. Primary hemostasis precedes secondary hemostasis, which involves activation of the coagulation cascade and stabilization of the platelet thrombus. Defects and disorders in primary hemostasis can be attributed to inherited or acquired causes (including platelet dysfunction induced by antiplatelet therapy) and may be suspected because the patient exhibits bruising, spontaneous bleeding from mucous membranes, and excessive bleeding during menstruation or following trauma. These defects and disorders can interfere with platelet adhesion to collagen, or they can interfere with platelet activation and aggregation (platelet dysfunction). The most common causes of impaired primary hemostatic function are von Willebrand disease (vWD) and use of antiplatelet therapy.

The T-TAS 01 system is an in vitro diagnostic device that is comprised of tabletop instrument controlled by a dedicated PC and a disposable, single-use flow chamber. The PL Chip is designed to specifically measure platelet thrombus formation (PTF) under physiological conditions on a collagen-coated analytical path consisting of 26 microcapillary channels[1-10]. Platelet thrombus formation is a direct indicator of the patient's primary hemostatic function. The assay is performed under arterial flow conditions using benzylsulfonyl-D-Arg-Pro-4-amidinobenzylamide (BAPA)-anticoagulated whole blood samples. BAPA is an anticoagulant that inhibits thrombin and factor Xa, blocking the coagulation cascade and allowing the PL assay to specifically measure only the platelet thrombus formation process (primary hemostasis). During the assay, the blood sample is exposed to arterial shear stresses at 1,500 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 contained within the platelets that recruit and activate other platelets and cause aggregation, and platelet thrombus formation. The growing platelet thrombus causes occlusion of the microcapillary channels, which increases the flow pressure within the assay chip. The process of platelet thrombus formation in the flow chamber is continuously monitored by a pressure sensor that tracks pressure changes in the flow path. Results are calculated automatically within 10 minutes or when the pressure a reading reaches 60 kPa above the baseline pressure, whichever occurs first. Results are displayed as AUC, which is the area under the flow pressure curve over 10 minutes.

REAGENTS AND MATERIALS PROVIDED:

The PL Chip is a ready-to-use, single use assay chip. All reagents necessary to run the test are contained within the assay chip. The PL Chip analytical path contains Type I collagen isolated from pig tendon immobilized on the chip surface. Each PL chip has two analytical paths, so it is possible to perform measurements of two blood samples with one assay chip.

Item	Contents	Catalog Number
PL Chip	20 chips	18002

MATERIALS REQUIRED BUT NOT PROVIDED:

Item	Catalog Number
T-TAS 01 Total Thrombus Formation Analysis System Instrument	18001
PL Chip Reservoir Set	18003
BAPA Tube	18004
Mineral Oil (Sigma-Aldrich catalog number 330779)	N/A
Pipettor capable of pipetting 320 µL and disposable pipette tips	N/A
Kimwipes or other dust-free tissue	N/A

*Warning; Use designated mineral oils. Otherwise the device may be damaged.

WARNINGS AND PRECAUTIONS:

- Caution: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.
- For in vitro diagnostic use only.
- For professional use only.
- Blood specimens, used assay chips, used reservoirs, and pipette tips are potentially infectious. Proper handling and disposal methods should be followed in accordance with local, state and federal regulations.
- Results should be interpreted in conjunction with other clinical findings and laboratory test results.
- Carefully follow the instructions and procedures described in this package insert.
- Do not use products beyond the expiration date printed on the label.
- Do not use the PL chip if the protective pouch is torn or punctured prior to opening.
- Do not use chips that are bent or deformed.

STORAGE AND HANDLING REQUIREMENTS:

Do not remove the assay chip from the pouch until ready for use.

The unopened assay chip is stable when stored at 2-8 °C until the expiration date on the package label. Assay chips must be used within 8 hours after removal from the sealed pouch.

Before using refrigerated assay chips, allow individual pouched assay chips to reach room temperature for at least 15 minutes before use. If a kit box containing multiple assay chips is being removed from refrigeration, allow the box to reach room temperature for at least 1 hour before use. Unused assay chips still in the sealed pouch should be returned to refrigeration.

SPECIMEN COLLECTION AND PREPARATION:

Measurements with the T-TAS 01 system involve assessment of biological activity and is dependent on proper collection of blood specimens. Blood specimens collected for analysis with the PL chip should be collected using only the specified BAPA Tube. Other anticoagulants are not suitable for use with the PL assay and should be avoided.

- Collect fresh BAPA-anticoagulated venous whole blood using a 21 gauge or larger-bore needle (18-20 gauge).
- Mix the anticoagulant with the sample by gently inverting the tube 5 times.
- Store the blood sample upright at room temperature for at least 30 minutes prior to testing with the PL chip. Do not use a rocker platform.
- Blood samples should be measured between 30 minutes to 6 hours after collection.

- Transport specimens upright at room temperature and avoid extreme temperatures. 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. If a specimen appears to be hemolyzed, another specimen should be obtained and tested.
- If the test needs to be repeated, ensure that the blood sample has been maintained according to the conditions described above, or collect a new sample.

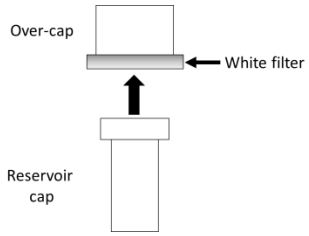
TEST PROCEDURE:

Procedural Notes:

- Do not remove the assay chip from the pouch until ready for use.
- Ensure that assay chips have reached room temperature prior to performing the assay.
- Assemble reservoir cap and over-cap.
- Care should be taken to avoid air gaps and bubbles. Blood samples should be carefully dispensed down the wall of the reservoir to avoid introducing bubbles.
- It is important to ensure a tight connection between the reservoir and nozzle, and between the reservoir cap and reservoir. A loose connection may be compressed when attaching the reservoir to the assay chip sample port, which may cause the blood sample to enter the analytical path prematurely. If the blood sample enters the analytical path before the assay is started, it is recommended to cancel the assay and repeat the procedure using another analytical path or assay chip.
- The reservoir should be inserted into the assay chip sample port vertically. Avoid holding the nozzle during this step and avoid connecting the reservoir to the assay chip sample port at an angle.
- Use designated mineral oils. Otherwise the device may be damaged.

Assay Preparation:

- Do not remove the assay chip from the pouch until ready for use.
- Assay chips may be placed on the pre-heater for at least 1 min before the assay, to allow stabilization of the temperature. This step is optional but can reduce the time required to heat the chip to the operating temperature.
- Assemble the reservoir cap and over-cap prior to performing the assay by firmly pressing the wide part of the reservoir cap to the white filter on the over-cap.



Testing Blood Samples:

The PL assay is performed at 36 °C, which is controlled by a heated stage on the instrument. The T-TAS 01 assay procedure is summarized below, and the user is guided through each of the steps via on-screen instructions.

1. Remove the assay chip from the sealed pouch and insert the assay chip into the stage on the T-TAS 01 instrument.
2. Wipe any excess mineral oil from the nozzle using a Kimwipe or dust-free tissue and connect the reservoir to the nozzle firmly.
3. Mix the blood sample by gently inverting 5 times, and pipette 320 µL of BAPA-anticoagulated whole blood into the reservoir. The allowable pipette volume can be between 300-330 µL.

4. While holding the reservoir, insert the reservoir cap firmly with a slight twisting motion, and then lift to remove its over-cap.
5. While holding the reservoir, invert the reservoir and connect it vertically to the sample port on the assay chip with a slight twisting motion until resistance is felt. Avoid making the connection at an angle.
6. Push the start button on the computer touchscreen. Results are generated automatically.

After the assay has been completed, gently remove the reservoir from the sample port on the assay chip. Hold the reservoir horizontally to avoid leakage of its contents, and twist to remove the used reservoir from the nozzle. Place the nozzle in its holder and discard used reservoirs, pipette tips, and assay chips in a suitable biohazard waste container.

RESULTS:

Results are expressed as AUC, which is the area under the flow pressure curve over a 10-minute period.

Interpretation:

AUC ≥ 260 indicates that primary hemostatic defects are not identified.

AUC < 260 is considered abnormal and indicates impaired primary hemostatic function (reduced platelet thrombus formation).

EXPECTED VALUES:

Reference Interval:

The AUC reference interval for the T-TAS 01 PL assay is 270.0 – 447.7.

The reference interval was determined from the 5th to 95th percentile (central 90%) of AUC results obtained from PL assay measurements at three clinical sites using a population of 142 individuals (96 females, 46 males, age 38.0 ± 11.3 years) without a history of inherited or acquired platelet dysfunction, and without laboratory evidence of von Willebrand disease. PL assay AUC results were not influenced by age, gender, ethnicity, or race.

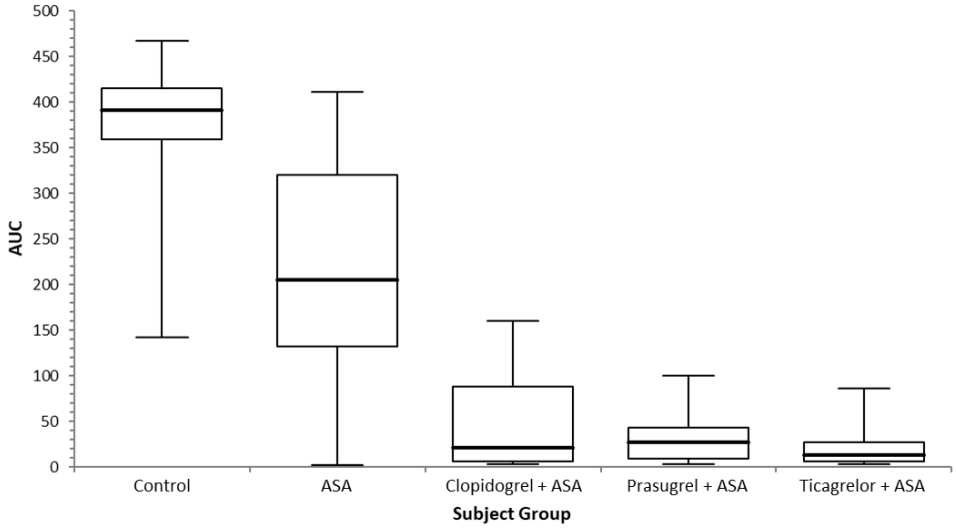
CLINICAL PERFORMANCE:

Sensitivity and negative agreement of the PL assay for detecting conditions associated with associated with abnormal primary hemostatic function were calculated from data obtained from a total of 274 subjects enrolled at a total of 6 investigational sites. Negative agreement was calculated using PL assay results from healthy donors confirmed to have normal primary hemostatic function because they did not have laboratory evidence or prior diagnosis of disorders affecting primary hemostatic function, nor were they taking medications that affect primary hemostatic function. Sensitivity was calculated using PL assay results from the following patient groups with conditions associated with impaired primary hemostatic function: subjects taking antiplatelet therapy (81 mg aspirin monotherapy and dual antiplatelet therapy), subjects diagnosed with von Willebrand disease, and subjects diagnosed with Glanzmann's thrombasthenia. Within the vWD patient group, 12 patients had vWD type 1, 10 patients had vWD type 2, and 3 patients had vWD type 3.

A summary of T-TAS 01 PL assay AUC results for the various subject groups is provided below.

Group	N	Mean	SD	Median	Range
Healthy Donors	142	381.5	55.5	390.9	142.5 – 467.7
Aspirin Monotherapy	57	218.4	114.4	205.7	2.7 – 410.9
Clopidogrel + ASA	18	46.2	47.3	21.7	3.6 – 159.8
Prasugrel + ASA	15	31.1	26.7	27.1	3.6 – 100.2
Ticagrelor + ASA	14	23.1	25.1	13.6	3.2 – 86.6
von Willebrand Disease	25	149.3	152.7	64.1	7.2 – 422.3
Glanzmann's Thrombasthenia	3	7.1	10.7	1.6	0.3 – 19.5

The distribution of AUC results from healthy controls and subjects taking antiplatelet therapy is shown below.



A summary of negative agreement and sensitivity of the AUC < 260 cutoff for aspirin monotherapy (ASA), dual antiplatelet therapy (DAPT, separated by DAPT type), von Willebrand disease (vWD), and Glanzmann's thrombasthenia (GT) is provided in the table below.

Parameter	N	Value	95% CI
Negative Agreement	142	95.8%	91.1-98.0%
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%	50.6-87.9%
Sensitivity (GT)	3	100.0%	43.9-100.0%

Von Willebrand disease severity can be highly variable, particularly in Type 1 vWD, and patients with mild vWD may not present with clinically significant bleeding. Within the vWD patient group, abnormal PFA-100 Col/EPI and Col/ADP demonstrated sensitivity that was similar to the PL assay Col/EPI and Col/ADP demonstrated sensitivity that was similar to the PL assay (80%, [95% CI 61-90%]) and there was excellent overall agreement between the PL assay and PFA-100 assay (overall 88% [69-97%], percent positive agreement 72% [51-88%], percent negative agreement 100% [40-100%]). All 7 of the vWD patients with AUC results above 260 had either normal PFA-100 results or vWF antigen, vWF activity, and FVIII:C results that were all higher than levels considered to be strongly associated with vWD (30%)[11].

The effect of antiplatelet therapy on primary hemostatic ability is influenced by the potency (i.e. dosage and/or number of antiplatelet agents taken), duration that the patient has been taking antiplatelet therapy, and the time elapsed since the last dose. Results that are inconsistent with the clinical presentation should be evaluated in the context of potency, duration, and time elapsed since last dose.

ANALYTICAL PERFORMANCE:

Reportable Range:

The reportable range is established from the lowest to the highest value recorded in the clinical studies. The reportable range for the T-TAS 01 PL assay AUC is 0.3 – 467.7.

Precision:

Assay precision was evaluated using three operators, three T-TAS 01 instruments, and three PL chip lots. BAPA-anticoagulated whole blood specimens collected from one control donor and two donors taking aspirin were tested. The blood specimens had AUC results representing specimens with normal primary hemostatic ability (High), abnormal primary hemostatic ability (Low), and hemostatic ability near the assay cutoff (Middle). The results were within the specification of CV ≤ 15% or SD ≤ 39 and are summarized below.

Sample	N	Mean	Repeatability 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

Between-site reproducibility was also studied by performing 5 replicate PL assay measurements per day over 5 days at each of three different locations using BAPA-anticoagulated whole blood samples from four donors. The donors included a healthy control donor and three donors taking aspirin therapy that had high, middle, and low AUC results similar to the precision study. All results within each day of tested were within the specification of CV ≤ 15% or SD ≤ 39.

Assay Interference:

T-TAS 01 PL assay measurements do not involve the use of external reagents or enzymes. Pharmaceutical agents and their metabolites, and dietary substances would exert their influences by affecting actual biological primary hemostatic ability, not the PL assay. Blood samples from patients that have ingested substances known to affect primary hemostatic function (such as antiplatelet medications or non-steroidal anti-inflammatory drugs) may exhibit reduced primary hemostatic function. Similarly, certain fatty acids and lipids found in various diets are known to affect primary hemostatic function.

The following substances were tested for their ability to interfere with the PL assay AUC result and did not significantly affect the AUC results when present at the plasma concentrations indicated.

Compound	Class	Concentration	Compound	Class	Concentration
Acetaminophen	Analgesic	7.8 mg/dL	Heparin	Anticoagulant	525 U/L
Bilirubin	Blood component	40 mg/dL	L-Thyroxine	Hormone	0.0858 mg/dL
Caffeine	Stimulant	21.6 mg/dL	Metformin	Antihyperglycemic	2.4 mg/dL
Captopril	ACE inhibitor	0.528 mg/dL	Omeprazole	Proton pump inhibitor	1.68 mg/dL
Catechin	Flavinol/antioxidant	5 mg/dL	Pravastatin	Statin	0.414 mg/dL
Cilostazol	Vasodilator/antiplatelet	1.25 mg/dL	Propranolol	Beta-blocker	0.202 mg/dL
Dabigatran	Anticoagulant	0.047 mg/dL	Rivaroxaban	Anticoagulant	0.044 mg/dL
Dextran 40	Plasma expander	2400 mg/dL	Streptokinase	Fibrinolytic	50,000 U/dL
Diltiazem	Calcium channel blocker	0.18 mg/dL	Theophylline	Bronchodilator	6 mg/dL
Dipyridamole	Vasodilator/antiplatelet	0.25 mg/dL	Tirofiban	Antiplatelet	N/A
Fish Oil	Dietary supplement	25.6 mg/dL	Triglycerides	Blood component	750 mg/dL
Ibuprofen	NSAID	0.438 mg/dL	Warfarin	Anticoagulant	7.5 mg/dL

Cilostazol, dipyridamole, ibuprofen, and tirofiban are all known to inhibit platelet activity, and reduced the AUC result in a dose-dependent manner. The maximum tirofiban concentration without interference was not determined.

Hemodilution up to 20% did not significantly affect PL assay AUC results.

Underfilling of the BAPA blood collection tube by up to 50% did not significantly affect PL assay AUC results.

TEST LIMITATIONS:

- Microthrombi, particulates, or air bubbles in the sample could adversely affect the test results and should be avoided. Care should be taken to ensure proper sample collection and avoidance of air bubbles during sample transfer into the reservoir.
- The test has been evaluated with BAPA-anticoagulated whole blood samples. Other sample types and anticoagulants have not been evaluated and should not be used.
- The clinical history and medication history of the patient should be reviewed if results are inconsistent with the clinical presentation. Many medications are known to affect platelet function.
- Low platelet count or low hematocrit may produce low AUC results. Blood specimens with hematocrit levels less than 25% or platelet counts less than $114x10^3/\mu L$ have not been evaluated.
- Certain fatty acids and lipids found in various human diets are known to affect platelet function. Physicians may wish to advise patients to refrain from fatty foods prior to testing.
- Primary hemostatic function can be impaired by congenital platelet abnormalities or use of medications that affect platelet function, which may be observed as abnormal AUC results. PL chip assay performance has not been established for platelet inhibiting agents or congenital platelet abnormalities other than those described in this document.
- The PL assay measures overall primary hemostatic function, which represents the totality of platelet activation pathways that may be stimulated under arterial shear conditions across a collagen-coated surface. Accordingly, patients with evidence by other agonist-based assays of an effect of a particular antiplatelet therapy may have primary hemostatic function within normal values with the PL assay.
- Patients with vWD type 2N have not been evaluated with the PL assay. vWD type 2N is not associated with impaired platelet thrombus formation, so patients with vWD type 2N may have normal PL AUC levels.
- The numeric output of the PL assay has not been evaluated for correlation to disease severity.
- Abnormal PL assay results alone do not constitute diagnostic evidence for the presence of antiplatelet therapy or the presence of vWD or Glanzmann's thrombasthenia. PL assay results should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

QUALITY CONTROL:

Three types of System Checks (SC) can be performed to assess the performance of the T-TAS 01 instrument: Simple SC, Automatic SC, and Manual SC. Please refer to the T-TAS 01 User's Manual for instructions on performing instrument quality control.

As part of the T-TAS 01 PL assay system quality control (QC) it is recommended to test in duplicate a control donor blood sample with each new shipment of PL chips received or whenever the institution wishes to verify the performance of the system. The system will be considered under control if the mean AUC falls within the established reference range. If the mean AUC is outside the reference range, repeat this procedure with a second individual from the laboratory's established control donor group.

If the mean AUC from both individuals is outside the reference range, contact Technical Support. If the mean AUC from the second individual is within the reference range, the platelet function status and medication history of the first individual should be considered.

For the purpose of QC testing, a control donor group should be established. The qualified QC donors should have an AUC result near the middle of the reference range and acceptable replicate results.

The following procedure is an example of how to establish the control donor group:

1. Individuals who are potential donors must be free from any medication or condition known to affect platelet function.
2. Test each potential donor by performing two replicate PL chip measurements.
3. Qualify the donor if the duplicate mean is within the reference range and the duplicate coefficient of variation (CV) is less than or equal to 15 %.

Note: The acceptable range may need to be modified depending on the mean AUC established by individual laboratories for normal adults.

It is recommended that the laboratory run the quality control procedure in a manner consistent with its established quality control program and in conformance with local, state, and/or federal regulations or accreditation requirements.

ASSISTANCE:

For assistance, please contact your local distributor.

REFERENCES:

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DEFINITION OF SYMBOLS:

Symbol	Definition
	Do Not Re-use
 YYYY-MM-DD	Use-by date

Symbol	Definition
CE	CE Mark
	Consult Instructions for use
LOT	Batch code
REF	Catalogue number
IVD	*In Vitro* diagnostic medical device
	Temperature limit
	Manufacturer
EC REP	Authorized representative In the European Community
Σ	Contains sufficient for <*n*> tests
CONTENT	Number of contents
	Do not use if package is damaged
Rx only	This product is restricted to sale by or on the order of a licensed healthcare practitioner

ZACROS Corporation
1-1-1 Koishikawa, Bunkyo-ku,
Tokyo 112-0002 Japan

EC REP
Medical Device Safety Service GmbH
Schiffgraben 41
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CE