510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K181777

B. Purpose for Submission:

Clearance of a new device

C. Measurand:

Platelet activity index (PAI)

D. Type of Test:

Platelet aggregation

E. Applicant:

Aggredyne, Inc.

F. Proprietary and Established Names:

AggreGuide A-100 ADP Assay

G. Regulatory Information:

1. Regulation section:

   21 CFR 864.5700, Automated platelet aggregation system

2. Classification:

   Class II

3. Product code:

   JOZ, System, Automated Platelet Aggregation

4. Panel:

Hematology (81)

H. Intended Use:

1. Intended use(s):

   The AggreGuide A-100 ADP Assay is used with the AggreGuide A-100 instrument in non-CLIA waived physician's office or clinical laboratory for the detection of platelet dysfunction in patients age 22 or older receiving P2Y12 antiplatelet drugs, prasugrel and ticagrelor, using 3.2% sodium citrated whole blood. The AggreGuide A-100 ADP Assay is a semi-quantitative assay. The level of platelet aggregation is determined by the platelet activity index (PAI) where values < 4.7 PAI suggest that platelet dysfunction is due to the presence of P2Y12 antiplatelet drugs, prasugrel and ticagrelor. The test results should be interpreted in conjunction with all other clinical and laboratory data available to the clinician.

2. Indication(s) for use:

   Same as Intended Use above

3. Special conditions for use statement(s):

   - For prescription use only
   - Evaluation of residual platelet activity for patients on ticagrelor therapy should be made within 3–6 hours of the most recent dose.
   - Test results should be interpreted in conjunction with other clinical and laboratory data available to the clinician.

4. Special instrument requirements:

   AggreGuide A-100 instrument

I. Device Description:

The AggreGuide A-100 ADP Assay is used with the AggreGuide A-100 instrument and consists of disposable single-use cartridges with preloaded freeze dried adenosine-5-diphosphate (ADP). The AggreGuide A-100 instrument is a tabletop instrument that contains a touch screen for entering information and a detection chamber on the top surface that contains a laser diode and photodector to detect light scatter. The disposable single-use cartridges contain a sample well (reaction chamber) with preloaded freeze dried ADP reagent and a rotor to mix the whole blood sample with the ADP reagent.

J. Substantial Equivalence Information:

1. Predicate device name(s):

VerifyNow PRUTest

2. Predicate 510(k) number(s):

   K141427

3. Comparison with predicate:

Similarities		
Item	Device AggreGuide A-100 ADP Assay K181777	Predicate VerifyNow PRUTest K141427
Intended Use	The AggreGuide A-100 ADP Assay is used with the AggreGuide A-100 instrument in non-CLIA waived physician's office or clinical laboratory for the detection of platelet dysfunction in patients age 22 or older receiving P2Y12 antiplatelet drugs, prasugrel and ticagrelor, using 3.2% sodium citrated whole blood. The AggreGuide A-100-ADP Assay is a semi-quantitative assay. The level of platelet aggregation is determined by the platelet activity index (PAI) where values < 4.7 PAI suggest that platelet dysfunction is due to the presence of P2Y12 antiplatelet drugs, prasugrel and ticagrelor. The test results should be interpreted in conjunction with all other clinical and laboratory data available to the clinician.	The VerifyNow PRUTest is a whole blood test used in the laboratory or point of care setting to measure the level of platelet P2Y12 receptor blockade. For *in vitro* diagnostic use. For professional use only.
Cartridge Type	Disposable single-use cartridge	Same
Specimen Type	Whole blood collected in 3.2% sodium citrate collection tubes	Same
Platelet Activation Agonist	Adenosine-5-diphosphate (ADP)	Same
Testing Condition	37°C, approximately 5 minutes duration	Same
Specimen Collection-to-Test Time	Between 30 minutes and 4 hours	Same

Differences		
Item	Device AggreGuide A-100 ADP Assay K181777	Predicate VerifyNow PRUTest K141427
Test Principle	Whole blood is mixed with ADP. ADP activates platelets by binding	Fibrinogen-coated microparticles are used in the VerifyNow

Differences		
Item	Device AggreGuide A-100 ADP Assay K181777	Predicate VerifyNow PRUTest K141427
	to the ADP receptors on the platelet surface resulting in platelet aggregation. P2Y12 inhibitors inhibit ADP-induced platelet aggregation by blocking the P2Y12 ADP receptor on the platelet surface.	PRUTest device to bind activated platelet GP IIb/IIIa receptors. ADP is incorporated into the assay to activate platelets, and the reagent is formulated to specifically measure P2Y12-mediated platelet aggregation. When the activated platelets are exposed to the fibrinogen-coated microparticles, aggregation occurs in proportion to the number of activated platelet receptors. The VerifyNow PRUTest reports results in P2Y12 Reaction Units (PRU).
Reagent Composition	Adenosine-5-diphosphate (ADP)	Adenosine-5-diphosphate (ADP), Prostaglandin E1, human fibrinogen coated beads, peptide, fatty acid, buffer and preservative.
Detection Method	Optical, light scatter	Optical, light transmittance
Measurement Unit	PAI, platelet activity index Dimensionless scalar	PRU, P2Y12 reaction units Dimensionless scalar
Expected Values/ Reference Range	4.7–9.6 PAI	170–272 PRU
Reportable Range	2.1–12.0 PAI PAI < 2.1: the result is reported as "LOW" accompanied by a message "No Detectable Aggregation" PAI > 12: the result is reported as "HIGH", accompanied by a message "Aggregation is High, reliability of a PAI greater than 12 has not been established."	
Energy Source	Optical: laser at 785 nm Mechanical: rotating motor with magnet	Optical: near-infrared light source Mechanical: reciprocating magnet

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition, 2014

CLSI EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline – Second Edition, 2009

CLSI EP28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition, 2010

CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition, 2012

ISO 14971:2007, Medical devices – Application of risk management to medical devices – Second Edition, 2007

L. Test Principle:

The AggreGuide A-100 instrument uses a laser diode and photodetector to measure light scatter. A whole blood sample is added to the reaction chamber of the AggreGuide A-100 ADP Assay cartridge. The reaction chamber contains a preloaded freeze-dried agonist, ADP, as well as a magnetically activated rotor that mixes the agonist with the whole blood sample. ADP activates platelets by binding to the ADP receptors on the platelet surface resulting in platelet aggregation. P2Y12 inhibitors inhibit ADP-induced platelet aggregation by blocking the P2Y12 ADP receptor on the platelet surface. The laser in the AggreGuide A-100 instrument emits light into the sample and platelet aggregates are detected by the observation of light scatter. The amount of platelet aggregation is proportional to the amount of platelet aggregates detected in the sample. Test results are reported as a Platelet Activity Index (PAI), where higher values are associated with more platelet activity/aggregation and lower values are associated with less platelet activity/aggregation.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The repeatability study was conducted using one instrument, with three donor samples across the reportable range including a high level sample (> 6.5 PAI), a sample near the cut-off (3.7–5.7 PAI) and a low level sample (< 3.7 PAI). For each donor, five to ten whole blood sample tubes were collected and three replicates were performed per tube on three different days, for a total of minimum of 60 measurements per donor. The SD results for the levels below 4.7 PAI and the %CV results for the levels above 4.7 PAI were found to be acceptable.

Sample Level	Mean	Within-Run		Between-Run		Total	
		SD	%CV	SD	%CV	SD	%CV
High Level	8.5	0.46	5.4	0.15	1.8	0.48	5.6
Mid-Level	4.6	0.47	10.2	0.00	0.0	0.47	10.2
Low Level	0.62	0.27	43.5	0.12	19.4	0.30	48.4

The reproducibility study was conducted with three normal donors, three lots of cartridges and three instruments where a single cartridge lot was used on each instrument. For each donor, seven to ten whole blood sample tubes were collected three observations

per tube, for multiple days with a minimum of 3 days to 20 days. Four runs were performed with five replicates per run on each instrument per tube. To demonstrate precision performance for each sample/donor, the %CV and SD for each component of variability were calculated; including, within-run, between-run, between-lot and between-instrument. Due to biological variation of platelet function, between-donor and between-day variability was not calculated.

Donor #	N	Mean	Within-Run		Between-Lot		Between-Instrument		Between-Run		Total Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
022	560	8.89	0.63	7.4%	0.19	2.2%	0.03	0.4%	0.66	7.7%	0.94	11.0%
023	140	8.69	0.62	7.1%	0.0	0.0%	0.22	2.6%	0.66	7.6%	1.08	12.4%
033	220	9.17	0.64	7.0%	0.38	4.1%	0.75	8.1%	0.68	7.4%	0.75	8.1%

b. Linearity/assay reportable range:

Linearity is not applicable.

Assay Reportable Range:

The numerical values of PAI are reported between the values of 2.1 and 12.0. When levels of aggregation are less than 2.1, the PAI is reported as “LOW” accompanied by a message “No Detectable Aggregation.” When levels of aggregation are greater than 12.0, the PAI is reported as “HIGH”, accompanied by a message “Aggregation is High, reliability of a PAI greater than 12 has not been established.”

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability is not applicable.

Shelf Life Stability:

In accordance with CLSI EP25-A, the shelf-life stability study was conducted for the AggreGuide A-100 ADP Assay cartridges using an isochronous study design with four different time points including baseline. Six donors representing high (normal), medium (normal) and low (dysfunctional due to P2Y12 inhibitor) were used to test shelf-life stability. Donor samples were tested on three different lots of aged cartridges (previously manufactured production lots) compared to one freshly manufactured lot that was less than one week old. Each donor was tested with each cartridge lot in five replicates per time point using a single instrument. Shelf-life stability was assessed in terms of measurand drift for each donor and lot. The data provided were found to be acceptable to support the 18-month shelf-life stability claim at room temperature.

Transportation Stability:

The transportation (shipping) stability study was conducted with one cartridge lot,

one instrument and a single donor sample. The donor sample was collected in sodium citrate anticoagulant and tested under stressed (-20°C and 55°C) and unstressed (room temperature) conditions, for five runs and two replicates per run. To simulate a stressed condition, the assay cartridge was placed in a temperature control test compartment under different temperature cycles. The compartment temperature was lowered to -20°C and raised to 55°C. At each temperature, the cartridges were maintained for 60 minutes. The transition time from -20°C to 55°C was 15 minutes. The transition time from 55°C to -20°C was 25 minutes. The data provided for the transportation stability study was assessed with a linear regression analysis and was found to be acceptable.

Shipping temperature is monitored by an indicator attached to the box label which will change color if the temperature of the box exceeds 54°C.

Sample Stability:

Sample stability was determined using whole blood samples collected from donors. The samples were stored at room temperature (20–25°C) and subsequently analyzed using one assay cartridge lot on one instrument at a minimum of eight different time points (ranging from 2 minutes to more than 6 hours from collection). The data supported a sample stability claim at room temperature for 30 minutes to 4 hours post-collection.

Open-pouch Stability:

The AggreGuide A-100 ADP Assay cartridges are packaged in Mylar pouches. An open-pouch stability study was conducted to demonstrate stability of the cartridges after removal from the Mylar pouch. The study was conducted by testing three normal donor samples at four different time points (ranging from 1 minute to 60 minutes). Each time point consisted of one test and one control observation on the same instrument which was operated by the same user. For each time point, test results were compared to the respective baseline results. The data demonstrate that the AggreGuide A-100 ADP Assay cartridges should be used within 12 minutes of opening the Mylar pouch.

Expected Values for Controls:

The labeling for the AggreGuide A-100 ADP Assay requires the quality control cartridge (QC2) test to be performed on the AggreGuide A-100 instrument every 30 days, or every 200 assays, whichever occurs first. The QC2 cartridge serves as a method of detecting gross failure of the AggreGuide A-100 instrument. The AggreGuide A-100 ADP Assay cannot be performed on the AggreGuide A-100 instrument unless a QC2 test has been successfully performed within the defined interval (30 days or 200 assays).

There are no manufactured external controls for AggreGuide A-100 ADP Assay. The

manufacturer recommends that laboratories establish their own donor reagent controls and may consider the following when establishing control donor groups:

- Normal PAI: In accordance with the specimen collection and handling instructions provided in the labeling, collect whole blood from healthy adult donors. The donor must not have taken any medication that is known to affect platelet function for at least seven days and should have prior platelet aggregation tests with results within the normal range established by the laboratory. The manufacturer recommends using donors whose PAI value is > 4.7.
- Abnormal PAI: In accordance with the specimen collection and handling instructions provided in the labeling, collect whole blood from a donor under chronic aspirin treatment. The manufacturer recommends using donors whose PAI value is < 4.7.

The manufacturer recommends performing quality control (normal and abnormal) for each new lot of AggreGuide A-100 ADP Assay cartridges. Quality control may be performed more frequently in accordance with laboratory procedures.

Expected Values for Calibrators:

The AggreGuide A-100 ADP Assay is factory calibrated, as such, calibration is not performed by the user of the device.

d. Detection limit:

In accordance with CLSI EP17-A2, the Limit of Blank (LoB) study was conducted by testing five K_2EDTA whole blood samples over 30 days, 30 runs per day, 2 replicates per run. Twenty-eight cartridge lots were run on one AggreGuide A-100 instrument. The LoB was determined to be 0.8 PAI.

e. Analytical specificity:

Analytical specificity for the AggreGuide A-100 ADP Assay was determined by spiking normal whole blood samples collected in sodium citrate anticoagulant with various concentrations of interferents. The following endogenous and exogenous interfering substances were evaluated and showed no significant interference up to the specified concentration in whole blood samples collected in 3.2% sodium citrate anticoagulant tubes.

Endogenous Substances	
Interferent	Concentration
Hemolysis	600 mg/dL
Bilirubin	10 mg/dL
Triglycerides	361 mg/dL
Exogenous Substances	
Acetaminophen	15.7 mg/dL
Aminocaproic acid	0.90 mg/dL
Caffeine	11.0 mg/dL
Captopril	0.276 mg/dL
Catechin	2.54 mg/dL
Chlorpromazine	0.303 mg/dL
Cilostazol	2.22 mg/dL
Cimetidine	2.99 mg/dL
Dextran 40	2,425 mg/dL
Diltiazem	0.0090 mg/dL
Dipyridamole	1.01 mg/dL
Fish Oil	32.0 mg/dL
Gabapentin	2.7 mg/dL
Glipizide	0.30 mg/dL
Glucosamine HCl	0.203 mg/dL
Heparin	340.5 U/dL
Ibuprofen	21.8 mg/dL
Insulin	0.00053 mg/dL
Liraglutide	0.0168 mg/dL
L-Thyroxine	5.00 mg/dL
Metformin	1.20 mg/dL
Norfluoxitine	0.0695 mg/dL
Norverapamil	0.056 mg/dL
Omeprazole	0.755 mg/dL
Oxypurinol	1.36 mg/dL
Pravastatin	0.0207 mg/dL
Prednisone	0.121 mg/dL
Propranolol	0.102 mg/dL
Salicylic Acid	2.87 mg/dL
Sitagliptin	0.12 mg/dL
Streptokinase	40200 U/dL
Theophylline	5.70 mg/dL
Valsartan	1.17 mg/dL
Warfarin sodium	7.50 mg/dL

f. Assay cut-off:

The cut-off for the AggreGuide A-100 ADP Assay was determined to be 4.7 PAI.

2. Comparison studies:

   a. Method comparison with predicate device:

   Not applicable

   b. Matrix comparison:

   Not applicable

3. Clinical studies:

   A clinical study was conducted at seven intended use sites in the U.S. using three instruments and six assay cartridge lots. For each study subject, whole blood was collected and tested at baseline and at each time point of the on-therapy state. Note: each study subject adhered to an aspirin regimen which included aspirin ingestion prior to the collection of the baseline sample and a daily 81 mg dose post-baseline.

   In addition to the baseline measurement, samples were collected from subjects on ticagrelor therapy at the following time points to represent the respective phase of the on-therapy state: 3–6 hours (post-loading, "full-effect"), 24 hours to represent the "not full-effect" and 7 days (post-maintenance, "full-effect"). In addition to the baseline measurement, samples were collected from subjects on prasugrel at the following time points to represent the respective phase of the on-therapy state: 24 hours and 7 days (post-maintenance) which represent the "full-effect" states. All study samples were tested with the AggreGuide A-100 ADP Assay and the VerifyNow PRUTest.

   Note: Although the clinical study included three study arms in which patients receiving ticagrelor, prasugrel, or clopidogrel were evaluated, the AggreGuide A-100 ADP Assay is intended to detect platelet dysfunction in patients receiving ticagrelor and patients receiving prasugrel. The data provided in the tables below represent the performance of ticagrelor and prasugrel as claimed in the Intended Use.

   a. Clinical Sensitivity:

Sensitivity Stratified by On-Therapy Status with 95% Confidence Intervals					
Drug Therapy	N	Status	On-therapy Status (time from dose)	AggreGuide A-100 ADP Assay (95% CI)	VerifyNow PRUTest (95% CI)
Prasugrel	43	Full-Effect	Post-Loading (24 hours)	1.000 (0.918, 1.000)	0.977 (0.877, 0.996)
	43		Post-Maintenance (7 days)	0.907 (0.784, 0.963)	0.977 (0.877, 0.996)
Ticagrelor	85	Full-Effect	Post-Loading (3–6 hours)	0.906 (0.825, 0.952)	1.000 (0. 957, 1.000)

Sensitivity Stratified by On-Therapy Status with 95% Confidence Intervals					
Drug Therapy	N	Status	On-therapy Status (time from dose)	AggreGuide A-100 ADP Assay (95% CI)	VerifyNow PRUTest (95% CI)
	143		Post-Maintenance (7 days)	0.839 (0.770, 0.890)	0.986 (0.951, 0.998)
	143	Not Full-Effect	Post-Loading (24 hours)	0.571 (0.491, 0.652)	0.860 (0.794, 0.908)

b. Clinical specificity:

Specificity at Baseline/Prior to Administration of Study Drug			
Baseline Observation	N	AggreGuide A-100 ADP Assay (95% CI)	VerifyNow PRUTest (95% CI)
Prasugrel	43	0.907 (0.774, 0.973)	0.974 (0.874, 0.999)
Ticagrelor	143	0.924 (0.867, 0.961)	0.965 (0.921, 0.989)
Prasugrel and Ticagrelor	186	0.919 (0.871, 0.951)	0.968 (0.931, 0.985)

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The reference range for the AggreGuide A-100 ADP Assay was established in a study involving 129 healthy adult subjects (22–75 years of age) who were not receiving anti-platelet medication. The study cohort consisted of a diverse population of males and females with different ethnic backgrounds representative of the U.S. population. The reference range was determined by the one-sided lower bound of the 95% confidence interval. The lower limit is 4.54 PAI.

N. Proposed Labeling:

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

O. Conclusion:

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