

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k050523

B. Purpose for Submission:

Clearance of new intended use for previously cleared device

C. Measurand:

Lipoprotein-Associated Phospholipase A₂ (Lp-PLA₂)

D. Type of Test:

Quantitative Enzyme Immunoassay

E. Applicant:

diaDexus, Inc.

F. Proprietary and Established Names:

diaDexus PLAC™ Test

G. Regulatory Information:

1. Regulation section:

21 CFR §866.5600, Low-density lipoprotein immunological test system

2. Classification:

Class II

3. Product code:

NOE, test, system, immunoassay, lipoprotein-associated phospholipase A₂

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The diaDexus PLAC™ Test is an enzyme immunoassay for the quantitative determination of Lp-PLA2 (Lipoprotein-Associated Phospholipase A₂) in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease and ischemic stroke associated with atherosclerosis.

3. Special conditions for use statement(s):

For professional use only

To be used in conjunction with clinical evaluation and patient risk assessment.

4. Special instrument requirements:

Microtiter plate reader with a bandwidth of 10 nm or less and an optical density range of 3 or greater at 450nm

I. Device Description:

The diaDexus PLAC™ Test contains mouse monoclonal antibody coated microtiter stripwells (96), calibration materials (6), buffers, sample diluent, conjugate, substrate and stopping solution.

J. Substantial Equivalence Information:

1. Predicate device name(s):

diaDexus PLAC™ Test

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

k030477, k040101

3. Comparison with predicate:

The device is exactly the same as the predicate device except that a new intended use has been included (prediction of the risk for ischemic stroke associated with atherosclerosis).

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

None were referenced.

L. Test Principle:

The diaDexus PLAC™ Test is a sandwich-type enzyme immunoassay that uses two anti-Lp-PLA₂ monoclonal antibodies. One antibody is immobilized on the bottom of microtiter wells. Sample and buffer are incubated in the wells and the unbound fractions are washed off. The second antibody (labeled with horseradish peroxidase) is added and incubated to bind with the Lp-PLA₂ bound to the surface of the well. The excess is washed away, and a colorimetric substrate is added and allowed to react with the peroxidase to form a blue color. A stop solution converts the resulting color from blue to yellow which is measure spectrophotometrically at 450 nm. The measured absorbance is directly proportional to the amount of Lp-PLA₂ in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Analytical performance was established under k030477.

b. *Linearity/assay reportable range:*

Analytical performance was established under k030477.

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

Analytical performance was established under k030477.

d. *Detection limit:*

Analytical performance was established under k030477.

e. *Analytical specificity:*

Analytical performance was established under k030477.

f. *Assay cut-off:*

See clinical studies in 3 c. below.

2. Comparison studies:

a. *Method comparison with predicate device:*

Not applicable.

b. *Matrix comparison:*

Not applicable.

3. Clinical studies:

a. *Clinical Sensitivity:*

Not applicable. See clinical information below.

b. *Clinical specificity:*

Not applicable. See clinical information below.

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

A study was conducted by the manufacturer using 956 samples from patients who were part of a large multi-center epidemiologic study, sponsored by the National Heart, Lung and Blood Institute. Patients, 47 to 69 years of age, were free from coronary heart disease or stroke at the start of the study and followed for the development of coronary heart disease (CHD) or stroke for ~9 years. This was a case-cohort study where samples from all the ischemic stroke cases associated with atherosclerosis (194) were tested together with 762 appropriately matched participants without CHD or stroke (controls).

Cox regression models were used to evaluate the association of Lp-PLA2 and ischemic stroke associated with atherosclerosis, using a univariate analysis (Model 1), a univariate analysis adjusted for demographics (Model 2), and a multivariate model adjusted for demographics and other prognostic factors (Model 3). The same cutpoints of Lp-PLA2 as were used in the original CHD risk indication were investigated in this study (420 and 310 ng/mL, the 67th and 33rd percentiles, respectively) to divide study participants into tertiles. The hazard ratios of the Cox regression analyses demonstrated that Lp-PLA2 may be used as a predictor of risk for ischemic stroke associated with atherosclerosis for the highest tertile when compared to the lowest tertile of Lp-PLA2. See tables below for additional information.

Results of Cox Regression Models – Ischemic Stroke Associated with Atherosclerosis Analysis Population

Lp-PLA ₂ (ng/mL)	Lp-PLA ₂ Risk Ratio (95 % CI, p-value)*		
	< 310	310 - 420	> 420
# ischemic stroke cases associated with atherosclerosis / total subjects	47 / 283 (16.6 %)	44 / 305 (14.4 %)	103 / 368 (28 %)
Model 1	1.0	0.85 (0.57 – 1.29, p=0.45)	1.79 (1.27 – 2.52, p=0.0010)
Model 2	1.0	0.89 (0.59 – 1.35, p=0.58)	2.09 (1.46 – 3.01, p=0.0001)
Model 3	1.0	0.89 (0.58 – 1.36, p=0.59)	1.81 (1.22 – 2.69, p=0.0034)

*the lowest tertile with Lp-PLA₂ values <310 ng/mL is used as a reference group

Model 1: univariate analysis

Model 2: adjusted for age, race, and gender

Model 3: adjusted for age, race, gender, diabetes, LDL, HDL, blood pressure, smoking, BMI, and CRP

Further analyses were performed to determine if Lp-PLA₂ was predictive of ischemic stroke associated with atherosclerosis across the complete range of systolic blood pressure (SBP) in the population, and to determine whether blood pressure and Lp-PLA₂ were additive in assessing risk for ischemic stroke. Systolic blood pressure tertile cutpoints were assigned by the 33rd and 67th percentiles of the population (113 and 130 mm Hg, respectively). The study population was divided into the low, mid, and high range (1st, 2nd, and 3rd tertile) of SBP and the low, mid, and high range of Lp-PLA₂. The relative risk of each group was compared to the risk of events associated with the group in the 1st tertile of the two variables.

Risk Ratios of Ischemic Stroke Associated with Atherosclerosis: Additive Effects of Lp-PLA₂ and Systolic Blood Pressure

		Lp-PLA ₂ (ng/mL)		
		<310	310-420	>420
SBP (mm Hg)	# ischemic stroke cases associated with atherosclerosis/total subjects in category	47/283 (16.6%)	44/305 (14.4%)	103/368 (28.0%)
<113	29/270 (10.7%)	1.00	1.00 (0.34-2.99, p=0.99)	2.45 (0.96-6.25, p=0.06)
113-130	60/337 (17.8%)	2.49 (0.98-6.31, p=0.05)	1.42 (0.53-3.84, p=0.49)	3.72 (1.56-8.91, p=0.003)
>130	105/349 (30.1%)	3.67 (1.50-8.99, p=0.004)	3.99 (1.64-9.69, p=0.002)	6.40 (2.75-14.86, p<0.0001)

CHD was a strong predictor of ischemic stroke associated with atherosclerosis in all three models (see Tables below). However, the third tertile of Lp-PLA₂ remained a predictor even when CHD was incorporated in all three models with risk ratios decreasing by less than 0.2 units in all cases.

Results of Cox Regression Models – Ischemic Stroke Associated with Atherosclerosis Analysis Population (additional adjustment for CHD included in all 3 models)

Lp-PLA ₂ (ng/mL)	Lp-PLA ₂ Risk Ratio (95% CI, p-value)*		
	<310	310-420	>420
# ischemic stroke cases associated with atherosclerosis / total subjects	47/283 (16.6%)	44/305 (14.4%)	103/368 (28.0%)
Model 1	1.0	0.82 (0.55-1.24, p=0.36)	1.62 (1.14-2.29, p=0.0069)
Model 2	1.0	0.89 (0.59-1.34, p=0.57)	2.03 (1.41-2.93, p=0.0001)
Model 3	1.0	0.86 (0.56-1.31, p=0.48)	1.75 (1.18-2.60, p=0.0057)

* The lowest tertile with Lp-PLA₂ values <310 ng/mL is used as the reference group

Model 1: adjusted for CHD

Model 2: adjusted for age, race, gender, CHD

Model 3: adjusted for age, race, gender, diabetes, LDL, HDL, blood pressure, smoking, BMI, CRP, CHD

Results of Cox Regression Models –Ischemic Stroke Associated with Atherosclerosis Analysis Population Predictive power of CHD diagnosis

CHD Status	CHD Risk Ratio (95% CI, p-value)*	
	No CHD	CHD
# ischemic stroke cases associated with atherosclerosis / total subjects	146/849 (17.2%)	48/107 (44.9%)
Model 1	1.0	2.94 (2.11-4.09, p<0.0001)
Model 2	1.0	2.90 (2.07-4.06, p<0.0001)
Model 3	1.0	2.26 (1.58-3.23, p<0.0001)

* “No CHD” is used as the reference group

Model 1: adjusted for Lp-PLA₂

Model 2: adjusted for age, race, gender, Lp-PLA₂

Model 3: adjusted for age, race, gender, diabetes, LDL, HDL, blood pressure, smoking, BMI, CRP, Lp-PLA₂

4. Clinical cut-off:

The hazard ratios of the Cox regression analyses demonstrated that Lp-PLA2 may be used as a predictor of risk for ischemic stroke associated with atherosclerosis for the highest tertile (>420 ng/mL) when compared to the lowest tertile (<310 ng/mL) of Lp-PLA2. See tables above for additional information.

5. Expected values/Reference range:

See k030477.

N. Proposed Labeling:

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

O. Conclusion:

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