

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

A. 510(k) Number:

k030477

B. Analyte:

Lipoprotein-associated phospholipase A2 (Lp-PLA2)

C. Type of Test:

Quantitative

D. Applicant:

diaDexus, Inc.

E. Proprietary and Established Names:

diaDexus™ PLAC™ Test

F. Regulatory Information:

1. Regulation section:
21 CFR866.5600
2. Classification:
Class II
3. Product Code:
NOE
4. Panel:
82 (Immunological Test Systems)

G. Intended Use

1. 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 (CHD).
2. Special condition for use statement(s):
NA
3. 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

H. Device Description:

The *in vitro diagnostic* reagent kit contains mouse monoclonal antibody coated microtiter stripwells (96), calibration materials (6), buffers, sample diluent, conjugate, substrate and stopping solution.

I. Substantial Equivalence Information:

1. Predicate device name(s):
Dade Behring N Latex Lp(a) Reagent Kit
2. Predicate K number(s):
k013128
3. Comparison with predicate:

Item	diaDexus PLAC™ Test	Dade Behring N Latex Lp(a) Reagent
Intended use	quantitative determination of lipoprotein-associated phospholipase A2 (Lp-PLA2) in human EDTA plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease	quantitative determination of Lp(a) in human serum and heparin plasma as an aid in the identification of individuals at risk from cardiovascular disease in specific populations when used in conjunction with clinical evaluation
Type of assay	sandwich enzyme immunoassay	particle enhanced immunonephelometry
Calibrator and control materials	6 calibrator materials included with kit; control materials sold separately	calibrator material sold separately; control materials sold separately
Analytical range	analytical range is 1.2 – 2000 ng/mL	analytical range is 0.1 – 1.6 g/L
Type of samples to be assayed	for use with EDTA plasma	for use with serum and heparinized plasma
Dilution of samples	assay samples diluted x 10	assay samples diluted automatically x 400
Detection instrument	spectrophotometer at 450 nm	BN Systems Nephelometer

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

NCCLS Guideline C28A, (“How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline – second edition”).

K. Test Principle:

Sandwich enzyme immunoassay using two specific monoclonal antibodies

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Three human serum pools with Lp-PLA2 concentrations of 109 ng/mL, 336 ng/mL and 649 ng/mL were assayed in duplicate using a single lot of reagents on two separate stripwells per day, for twenty days. With N=80, the intra-assay %CVs were 6.6, 5.3, 4.9, respectively and the inter-assay %CVs were 8.6, 8.9 and 8.4, respectively.

b. *Linearity/assay reportable range:*

The calibration materials range in concentration from 0 to 200 ng/mL. Using a times10 dilution of the sample, allows for detection of Lp-PLA2 of up to 2000 ng/mL. Further dilutions of samples are recommend up to a times 100 for detection up to 20000 ng/mL.

Four EDTA plasma samples containing different levels of endogenous Lp-PLA2 were diluted with sample diluent and assayed (dilution range: 1:5 to 1:20). Percent recovery was

determined as the observed value divided by the expected value, multiplied by 100. The average recovery of the diluted samples over a range of 133 to 1310 ng/mL Lp-PLA2 was 104%.

c. *Traceability (controls, calibrators, or method):*

NA

d. *Detection limit (analytical sensitivity):*

The zero calibrator material was assayed 24 times. The mean plus 2 standard deviation value was calculated as 1.2 mg/dL.

e. *Analytical specificity:*

Five endogenous substances, hemoglobin, triglycerides, cholesterol, bilirubin and albumin, found in blood were evaluated for interference in the assay. Five Lp-PLA2 plasma samples, ranging in concentration from 92 to 664 ng/mL were spiked with the substances above. Values with spiked samples were compared to the controls for each interfering substance. The acceptance criterion for no interference was recovery of the spiked sample within 15% of the control sample. No interference is claimed, i.e., recovery within the range of 85 – 115% was obtained for the following spiked concentrations: 500 mg/dL hemoglobin, 3000 mg/dL triglycerides, 500 mg/dL cholesterol, 20 mg/dL bilirubin and 6.2 g/dL albumin.

f. *Assay cut-off:*

NA

2. Comparison studies:

a. *Method comparison with predicate device:*

See results of clinical study. There was no quantitative comparison study performed with the predicate device.

b. *Matrix comparison:*

NA

3. Clinical studies:

A study was conducted by the manufacturer using 1348 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 at the start of the study and followed for the development of coronary heart disease for nine years. This was a case-cohort study where samples from all the CHD cases (608) were tested together with 740 appropriated matched participants without CHD (controls).

Cox regression models were used to evaluate the association of Lp-PLA2 and CHD, using a univariate analysis (Model 1), a univariate analysis adjusted for demographics (Model 2), and a multivariate model adjusted for demographics and other prognostics factors (Model 3). Using high and low cutpoints of Lp-PLA2, generated from the study (420 and 310 ng/mL, the 67th and 33rd percentiles, respectively), the hazard ratios of the Cox regression analyses demonstrated that Lp-PLA2 may be used as a predictor of risk for CHD, for the highest and intermediate levels when compared to the lowest level of Lp-

PLA2, (see Table 1). It is noted that 5.5% (86) results were excluded from data analysis because they were outside the assay acceptance criteria. The labeling notes that different cut-points may be appropriate for different clinical populations.

Table 1. Risk Ratios of CHD for Subjects Across All LDL Levels

Lp-PLA2 (ng/mL)	Lp-PLA2 Risk Ratio (95% CI, p-value)		
	<310	310-420	>420
Model 1	1.0*	1.49 (1.11-1.99, p=0.008)	2.50 (1.89-3.31, p<0.001)
Model 2	1.0	1.24 (0.92-1.66, p=0.154**)	1.76 (1.32=2.36, p<0.001)
Model 3	1.0	1.71 (1.06-2.75, p=0.029)	2.12 (1.29-3.48, p=0.003)

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

**p-value is not significant

Model 1: univariate analysis

Model 2: adjusted for age, race, gender

Model 3: adjusted for age, race, gender, current smoking status, blood pressure, diabetes, HDL, LDL, CRP and Lp-PLA2 - LDL interaction

The interaction between Lp-PLA2 and LDL was evaluated as risk ratios in low LDL subgroups of <130 mg/dL and high LDL subgroups of \geq 130 mg/dL. The median value of LDL for the cohort population was 130 mg/dL. This defined the high and low LDL subgroups. Tables 2a and 2b represent the univariate analysis of the risk ratios in the high and low LDL subgroups. The risk ratios are calculated from Cox regression employing weighted case-cohort method with Barlow adjustment, n=1348.

Table 2a. Risk Ratios of CHD for Subjects with LDL <130 mg/dL

Lp-PLA2 (ng/mL)†	Lp-PLA2 Risk Ratio (95% CI)*		
	<310	310-420	>420
Risk Ratio	1.0	2.17 (1.41-3.36)	3.52 (2.25-5.49)
#CHD cases/total subjects in category	51/215 (23.7%)	75/195 (38.5%)	77/163 (47.2%)

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

†Lp-PLA2 cutpoints based on the Study Population across all LDL levels

Table 2b. Risk Ratios of CHD for Subjects with LDL >130 mg/dL

Lp-PLA2 (ng/mL)†	Lp-PLA2 Risk Ratio (95% CI)*		
	<350	350-460	>460
Risk Ratio	3.15 (2.08 – 4.77)	3.66 (2.43-5.51)	5.10 (3.43-7.57)
#CHD cases/total subjects in category	110/234 (47.0%)	126/247 (51.0%)	169/294 (57.5%)

*The lowest tertile for LDL <130 subgroup, with Lp-PLA2 values <310 ng/mL is used as the reference group

†Lp-PLA2 cutpoints based on the ARIC Study population with LDL >130 mg/dL

4. Clinical cut-off:

See the clinical study results in tables 2a and 2b above for Lp-PLA2 cut-points and LDL subgroups.

5. Expected values/Reference range:

Samples from apparently healthy males (n = 251) and females (n = 174) in the clinically relevant age range of 40 to 70 years were analyzed for Lp-PLA2.

The ethnic backgrounds were as follows: African-American n=26, Caucasian n=390, Hispanic n=8, and not specified n=1. The resulting central 90% was 120-342 ng/mL for females and 131-376 ng/mL for males.

M. Conclusion:

Based upon the information provided and the reviews from the statistician and medical officer, I recommend that this device is substantially equivalent to the predicate device, regulated by 21 CFR866.5600.