Proteomics International
LABORATORIES LTD

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Study shows PromarkerD ability to also predict late-stage kidney decline in type-2 diabetes patients

- **Collaborative study with Janssen demonstrates the potential of PromarkerD to predict late-stage, as well as early-stage, renal decline**
- **Result adds to strong existing evidence for PromarkerD as a tool for predicting the onset of diabetic kidney disease**
- **Preliminary findings show the potential for PromarkerD to evaluate people with existing kidney damage and the seriousness of their kidney disease**
- **Predicting late-stage diabetic kidney disease (DKD) can assist in the application of treatment programs aimed at increasing the time to dialysis and renal failure for patients**
- **Findings have the potential to further broaden the Company's target market, encompassing 32m adults with diabetes in the United States**
- **Results presented at the American Diabetes Association's 82nd Scientific Sessions being held 3-7 June 2022 in New Orleans, Louisiana, USA**

Proteomics International Laboratories Ltd (Proteomics International; ASX: PIQ) is pleased to announce the results of a study demonstrating the potential ability of the PromarkerD test to predict late-stage renal decline.

PromarkerD is already a proven diagnostic test for diabetic kidney disease, predicting the onset of the condition up to four years in advance. This study extends the potential use of PromarkerD to predict a further decline in renal function among people who already have kidney disease.

The results were presented overnight at the American Diabetes Association's 82nd Scientific Sessions.

The finding comes from analysis of the completed CANagliflozin cardioVascular Assessment Study (CANVAS), as part of the ongoing collaboration between Proteomics International and Janssen Research & Development, LLC [ASX: 31 Mar 2020; 15 June 2020].

Proteomics International managing director Dr Richard Lipscombe said this research is preliminary but shows PromarkerD has the potential to warn of late-stage outcomes, such as progression to macroalbuminuria[1], in patients both with and without existing kidney damage. (Macroalbuminuria is widely considered a measure of severe kidney disease. Once a patient is defined as having macroalbuminuria, the patient, in the absence of renal protective treatments, can quickly progress to dialysis and end stage renal failure).

"This exploratory data is promising and indicates the use of PromarkerD may be expanded to include people with existing kidney disease. However, the current PromarkerD algorithm has been optimised

[1] *Macroalbuminuria is defined as albumin-to-creatinine ratio of >30mg/mmol*

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for the prediction of early onset of DKD and the test algorithm would need further optimisation for this new use. The results also suggested further studies were warranted to explore whether PromarkerD could predict additional cardiovascular outcomes, such as heart failure and stroke."

The study was based on a post-hoc analysis of 3,525 people with type 2 diabetes, followed for three years in the completed CANVAS trial. The key findings were that moderate and high-risk PromarkerD scores were increasingly prognostic for adverse renal and cardio outcomes (versus low-risk scores), and PromarkerD remained a significant independent predictor of late-stage outcomes even after adjusting for other clinical risk factors, including existing kidney function, age, diabetes duration, and blood pressure.

The American Diabetes Association's annual Scientific Sessions is the world's largest diabetes conference, typically attracting more than 10,000 delegates. This year's event runs from 3-7 June, both virtually and in New Orleans, United States.

American Diabetes Association Scientific sessions poster presentation (ID: 855-P); [copy attached]

Titled: *PromarkerD Predicts Late-Stage Renal Function Decline in Type 2 Diabetes in the Canagliflozin Cardiovascular Assessment Study (CANVAS)*

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PromarkerD is also being showcased at the event (booth 1402) as part of the Company's US roll-out strategy and its ongoing engagement with Key Opinion Leaders (KOLs) and end users of the test, who could include primary care physicians, specialists nephrologists and diabetologists, diagnostic laboratories and pharmaceutical companies.

Authorised by the Board of Proteomics International Laboratories Ltd (ASX.PIQ).

ENDS

About PromarkerD (www.PromarkerD.com)

Diabetic kidney disease (DKD) is a serious complication arising from diabetes which if unchecked can lead to dialysis or kidney transplant. PromarkerD is a prognostic test that can predict future kidney function decline in patients with type 2 diabetes and no existing DKD. The patented PromarkerD test system uses a simple blood test to detect a unique 'fingerprint' of the early onset of the disease by measuring three serum protein biomarkers, combined with three routinely available conventional clinical variables (age, HDL-cholesterol and estimated glomerular filtration rate (eGFR)). A cloud based algorithm integrates the results into a patient risk report. In clinical studies published in leading journals PromarkerD correctly predicted up to 86% of otherwise healthy diabetics who went on to develop diabetic kidney disease within four years. The PromarkerD test is CE Mark registered in the European Union.

Further information is available through the PromarkerD web portal.

To visit the PromarkerD virtual booth please see: www.PromarkerD.com/product

About Proteomics International Laboratories (PILL) (www.proteomicsinternational.com)

Proteomics International (Perth, Western Australia) is a wholly owned subsidiary and trading name of PILL (ASX: PIQ), a medical technology company at the forefront of predictive diagnostics and bio-analytical services. The Company specialises in the area of proteomics – the industrial scale study of the structure and function of proteins. Proteomics International's mission is to improve the quality of lives by the creation and application of innovative tools that enable the improved treatment of disease.

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PromarkerD Predicts Late-Stage Renal Function Decline in Type 2 Diabetes in the Canagliflozin Cardiovascular Assessment Study (CANVAS)

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Presented at the ADA 82nd Scientific Sessions
12-G Clinical Therapeutics/New Technology – SGLT Inhibitors
Poster 855-P

Background & Aim

- A third of people with type 2 diabetes (T2D) have chronic kidney disease (CKD), the leading cause of end-stage renal disease (ESRD).
- Current standard of care tests (urinary albumin-to-creatinine ratio (uACR), and estimated glomerular filtration rate (eGFR)) have limited ability to predict CKD progression.
- PromarkerD is a novel blood test that has been shown to predict early-stage renal function decline (incident CKD or eGFR <60 mL/min/1.73m^2) in T2D[1,2,3]
- The aim of this study was to assess the ability of PromarkerD to predict later-stage renal decline in participants with T2D from CANVAS, a randomized controlled trial of canagliflozin vs. placebo (NCT01032629)[4].

Methods

- PromarkerD scores were measured at baseline in 3,525 CANVAS participants (mean age 62.7 years, 67% males, median diabetes duration 12.5 years, mean eGFR 77 mL/min/1.73m^2 and median uACR 11.6 mg/g).
- PromarkerD is a biomarker-based test that combines the concentration of three proteins (CD5L, ApoA4, IGFBP3) measured by immuno-affinity mass spectrometry, with clinical data (age, serum HDL-cholesterol, eGFR) to provide test scores categorized as low-, moderate- or high-risk for adverse renal outcomes.
- The ability of PromarkerD (modeled as both risk categories and a continuous risk score) to predict three composite cardio-renal outcomes was assessed using Cox proportional hazards (time-to-event) modeling:
  - **Outcome 1)** ≥40% eGFR decline, ESRD, or renal death
  - **Outcome 2)** cardiovascular disease (CVD) death or outcome 1
  - **Outcome 3)** progression to macroalbuminuria (uACR >300 mg/g) or outcome 1
- Adjustment for canagliflozin treatment, as well as a range of clinically relevant risk factors was performed.
- Follow-up was from baseline to date of first outcome or censoring due to exit from study.

Participant Characteristics

- During 5.4-5.7 years (mean range) of follow-up, 138 (3.9%), 380 (10.8%) and 427 (12.1%) participants experienced outcomes 1 to 3, respectively. Total follow-up time for all participants ranged from 19.1 thousand person years for outcome 3 to 19.9 thousand person years for outcome 1.
- With the exception of gender, significant baseline differences were observed for all demographic characteristics when comparing participants with at least 1 outcome to those without (Table 1).

Table 1. Participant characteristics at baseline	Total cohort N=3,525	No cardio-renal outcome N=2,873	≥1 cardio-renal outcome N=652	P-value
Participants in treatment arm (N, %)	2,346 (66.6)	1,947 (67.8)	399 (61.2)	0.001
Age (years)	62.7±7.8	62.4±7.8	64.0±7.9	<0.001
Male gender (N, %)	2,364 (67.1)	1,909 (66.4)	455 (69.8)	0.10
Diabetes duration (years)	12.5 [8.0-18.0]	12.0 [8.0-17.2]	13.0 [9.7-19.0]	<0.001
HbA_{1C} (%)	8.0 [7.5-8.7]	8.0 [7.4-8.7]	8.2 [7.6-8.9]	<0.001
Supine systolic blood pressure (mm Hg)	137±16	136±16	139±16	0.001
Urinary ACR (mg/g)*	11.6 [6.4-35.2]	10.0 [6.0-23.2]	43.6 [12.4-159.0]	<0.001
eGFR (mL/min/1.73m^2)	77.0±18.7	77.9±18.3	72.9±19.9	<0.001

All values are mean±standard deviation, proportions or median [interquartile range]; *17 participants excluded as missing baseline uACR values.

Table 2. Outcomes experienced by baseline PromarkerD risk category (N, %)	Total cohort N=3,525	Outcome 1 N=138	Outcome 2 N=380	Outcome 3 N=427
Low (<30%)	1,336 (37.9)	30 (21.7)	93 (24.5)	123 (28.8)
Moderate (30% - <60%)	2,067 (58.6)	103 (74.6)	276 (70.3)	285 (66.7)
High (≥60%)	122 (3.5)	5 (3.6)	20 (5.3)	19 (4.5)

Results – PromarkerD Predicts Late-Stage Renal Outcomes

PromarkerD Risk Categories:

- Participants with PromarkerD moderate- or high-risk scores were more likely to experience cardio-renal outcomes than low-risk participants (Table 2).
- Significantly higher rates of cardio-renal outcomes were experienced in participants with PromarkerD moderate-risk scores compared to those classified as low-risk (unadjusted, p<0.001) (Figure 1, Table 3). A similar trend was observed for high-risk versus low-risk, but likely due to small numbers, this result was not statistically significant.
- The hazard rates for experiencing any of the cardio-renal outcomes remained significantly elevated (p≤0.001) for participants with moderate-risk compared to low-risk scores after adjustment for canagliflozin treatment, baseline eGFR and uACR (Table 3), as well as further adjustment for other baseline confounders including age, diabetes duration, HbA_{1c} and systolic blood pressure (p≤0.003, data not shown).

Figure 1. Cardio-renal outcomes by baseline PromarkerD risk category.

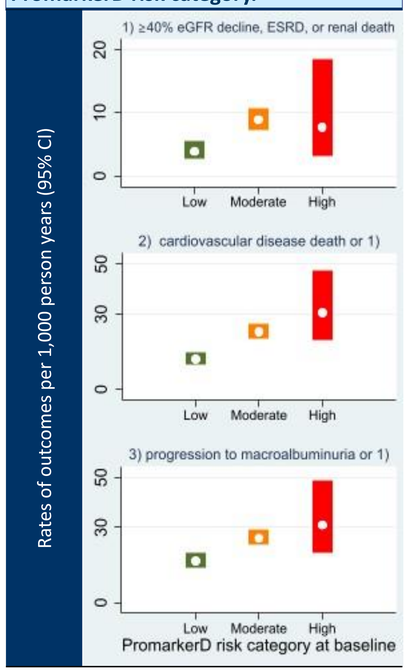

Table 3. Association of baseline PromarkerD risk categories with cardio-renal outcomes.	unadjusted	adjusted for treatment with Canagliflozin, eGFR and uACR
Outcome	PromarkerD moderate- vs low-risk [HR (95%CI), *P*)	
1) ≥40% eGFR decline, ESRD, or renal death	2.30 (1.53-3.45), <0.001	2.08 (1.38-3.14), 0.001
2) CVD death or (1)	1.91 (1.51-2.42), <0.001	1.71 (1.34-2.17), <0.001
3) progression to macroalbuminuria or (1)	1.56 (1.26-1.92), <0.001	1.43 (1.15-1.77), 0.001
Outcome	PromarkerD high- vs low-risk [HR (95%CI), *P*)	
1) ≥40% eGFR decline, ESRD, or renal death	2.01 (0.78-5.19), 0.15	1.67 (0.64-4.36), 0.30
2) CVD death or (1)	2.56 (1.58-4.15), <0.001	1.80 (1.08-2.97), 0.02
3) progression to macroalbuminuria or (1)	1.88 (1.16-3.04), 0.01	1.55 (0.95-2.53), 0.082

PromarkerD Risk Scores:

- When PromarkerD score was assessed as a continuous variable, it was observed that for each 10% increase in PromarkerD score, there was an average increase in the hazard rate of developing cardio-renal outcomes of between 12% (Outcome 3) and 27% (Outcome 2). These results were attenuated after adjustment, but remained consistent with unadjusted analyses (Table 4) (P≤0.041).

Table 4. Association of baseline PromarkerD score with cardio-renal outcomes.	unadjusted	adjusted for treatment with Canagliflozin, eGFR and uACR
Outcome	Per 10 point increase in PromarkerD [HR (95%CI), *P*)	
1) ≥40% eGFR decline, ESRD, or renal death	1.22 (1.08-1.38), 0.001	1.17 (1.03-1.33), 0.015
2) CVD death or (1)	1.27 (1.18-1.37), <0.001	1.20 (1.11-1.29), <0.001
3) progression to macroalbuminuria or (1)	1.12 (1.05-1.20), 0.001	1.08 (1.00-1.16), 0.041

Conclusions

- This post-hoc analysis of data from 3,525 CANVAS participants with T2D showed that PromarkerD can predict late-stage renal function decline:
  - Moderate- and high-risk scores were increasingly prognostic for outcomes versus low-risk scores by risk category;
  - Higher PromarkerD scores were significantly predictive of outcomes by continuous risk score; and
  - Following adjustment for canagliflozin treatment, eGFR and uACR, as well as other known conventional clinical risk factors including age, diabetes duration, HbA_{1c}, and systolic blood pressure, PromarkerD remained a significant independent predictor of outcomes.
- This study extends the clinical utility of PromarkerD from predicting not only early-stage kidney disease (incident CKD or eGFR <60 mL/min/1.73m^2) in people with T2D, but also later-stage outcomes (40% decline in eGFR or progression to macroalbuminuria) in people with and without existing kidney damage.
- Given the significant findings for the composite outcomes including cardiovascular death and progression to macroalbuminuria, further studies are warranted to explore the prognostic utility of PromarkerD for additional cardiovascular-specific outcomes.

Acknowledgements: This study was funded by Proteomics International (PI). PromarkerD biomarker concentrations and risk scores were measured using archived samples from the CANVAS study by PI using a patented test owned by the company. The CANVAS study was funded by Janssen Research & Development, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation. **References**: [1]Diab Care 2017;40:1548-1555, [2]J Diab Comp. 2019;33:107406, [3]J Clin Med. 2020;9(10):3212, [4]NEJM. 2017;377(7):644-657.