SYNOPSIS

Name of Sponsor/Company	Janssen-Cilag Australia Pty Ltd
Name of Finished Product	Prograf®
Name of Active Ingredient	Tacrolimus

Status: Draft

Date: 10 May 2013

Prepared by: Janssen-Cilag Pty Ltd.

Protocol No.: OTH/506-TRA-4004

Title of Study: PRIDE – Prograf Investigation of Diet and Exercise

Study Name: A pilot trial of the effect of dietary and exercise intervention on insulin resistance and metabolic parameters in de novo renal transplant recipients on Prograf® (tacrolimus)

NCT No.: NCT00492661

Clinical Registry No.: CR013702

Coordinating Investigator: Professor Steve Chadban, Royal Prince Alfred Hospital, Missenden Rd, Camperdown NSW 2050 Australia.

Study Centers: The study was conducted at 4 transplant centers in Australia, including the following: RPA Hospital, QEH, Monash Medical Center and Royal Perth Hospital.

Publications (References): Chadban S., Clayton P., Whitman G., Wyburn G., Butcher B., Rees T., Russ G., Mulley W., Irish A., Dunstan D., Eris J. (2010) A prospective trial of diet and exercise to improve glucose metabolism and cardiovascular risk for de novo kidney transplant recipients treated with tacrolimus-based immunosuppression (an interim analysis). TTS 2010 XXIII International Congress.

Chadban S., Clayton P., Whitman G., Wyburn G., Butcher B., Rees T., Russ G., Mulley W., Irish A., Dunstan D., Eris J. (2009) A prospective trial of diet and exercise to improve glucose metabolism and cardiovascular risk for de novo kidney transplant recipients treated with tacrolimus-based immunosuppression (an interim analysis). Abstract 132. TSANZ 28th Annual Scientific Meeting.

Study Period: First study-related procedure/observation for enrolled subjects: 27 July 2007. Last observation for last subject: 9 June 2010. Database lock: 11 October 2010.

Phase of Development: Phase IV

Objectives: The principal objective of this trial was to examine, in an exploratory manner, whether a combined dietary and exercise intervention, added to standard care, reduces the expected prevalence of insulin resistance in *de novo* renal transplant recipients taking tacrolimus. The primary endpoint was the proportion of subjects with insulin resistance, as defined by a homeostasis model assessment (HOMA-IR) of >1 at 6 months.

The secondary objectives of this study were to:

- examine the prevalence of impaired fasting glycemia (impaired fasting glucose [IFG]/impaired glucose tolerance [IGT]/diabetes mellitus [DM]) in renal transplant subjects on tacrolimus who receive a dietary and exercise intervention.
- assess the effect of the combined dietary and exercise intervention on risk factors for cardiovascular disease, such as hypertension, dyslipidemia and obesity.
- assess the effect of the combined dietary and exercise intervention on specific renal transplant outcomes, such as the estimated glomerular filtration rate (eGFR), the incidence of acute rejection, and subject and graft survival.
- understand the feasibility of implementing a dietary and exercise program for the wider population of renal transplant recipients, and the impact that such a program may have on health-related quality-of-life (QoL) and participation in physical exercise.
- assess drug utilization during the study period, including use of induction therapy mean doses and trough levels of tacrolimus, mean doses of other immunosuppressive therapies, and utilization of other medications, such as antihypertensives and lipid lowering agents.
- assess safety issues related to the implementation of a dietary and exercise intervention in renal transplant recipients.

Methodology: This study was an open-label, single-arm, multi-center, prospective pilot study conducted to evaluate the effects of a combined dietary and exercise intervention on glucose metabolism. The subject population was comprised of *de novo* renal transplant recipients (cadaveric or living renal allograft) who were given an oral tacrolimus-based immunosuppression regimen. The intervention included both intensive dietary advice and supervised progressive resistance training (PRT) over a period of 6 months. Efficacy and safety evaluations were performed at Baseline, Months 1 (Week 4), 3 (Week 12), and 6 (Week 24). An interim analysis was added in the Statistical Analysis Plan (SAP) to allow earlier presentation of the data. Data from the interim analysis were presented at TZANZ 2010. The use of insulin was prohibited in this trial. Inhibitors of P450 3A4 (e.g. cimetidine, ciprofloxacin, erythromycin and fluconazole) and inducers of P450 3A4 (e.g. barbiturates and carbamazepine) may alter the metabolism of tacrolimus and were prohibited. Amendments to the study protocol, with respect to study design, included changes to the inclusion criteria in the second and third protocol amendments to allow for inclusion of ABO incompatible subjects in the study; and additions to the exclusion criteria to clarify the subject population and timeframes.

Number of Subjects (planned and analyzed): The planned total sample size was 60 subjects; however, due to a slow recruitment rate, a total of 55 subjects were enrolledand considered sufficient for this exploratory pilot study. All subjects were included in the intent-to-treat (ITT) and safety analysis populations. Of the 55 subjects enrolled in this study, 46 subjects were included in the per protocol (PP) population.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria: Male and female *de novo* kidney transplant recipients (aged ≥18 years) receiving tacrolimus-based immunosuppression were considered for this study. Subjects had sufficiently recovered from surgery to tolerate an intensive exercise evaluation and had initiated tacrolimus as first-line immunosuppression. All subjects provided written informed consent.

Exclusion Criteria: Subjects who met any of the following criteria were excluded from the study:

- Subjects with significant disease or disability that would have prevented adherence to the study protocol (e.g. cardiac instability, including unstable angina and/or other unstable disease, severe cognitive impairment).

- Subjects with significant post-surgical complications that would have prevented participation in the exercise component of the study (e.g. wound dehiscence or infection).

- Non-ambulatory subjects and subjects with contraindications to maximal exercise testing or high-intensity PRT.

- Subjects who had received multiple-organ transplantation.

- Subjects requiring ongoing systemic immunosuppressive therapy for an indication other than renal transplant, and if this therapy was in excess of that required for normal transplant immunoprophylaxis.

- Subjects who were >12 weeks post-renal transplant or who had diabetes mellitus (DM) requiring insulin.

Test Product, Dose and Mode of Administration, Batch No.: This was a study of a diet and exercise regimen, in addition to standard care, and hence, there was no investigational product. Tacrolimus capsules were administered orally.

Reference Therapy, Dose and Mode of Administration, Batch No.: This was a single-arm study with no reference therapy.

Duration of Treatment: The treatment period was 6 months.

A subject was withdrawn from the study for any of the following reasons:

- withdrawal of consent;

- the investigator considered that, for safety reasons, it was in the best interest of the subject to be withdrawn;

- the subject developed a medical or mobility condition that prevented their ongoing participation in the exercise component of the study, e.g. acute myocardial infarction, unstable cardiac arrhythmia, significant exacerbation of musculoskeletal pain in association with resistance training, acute inflammatory joint disease;

- lost to follow-up.

Criteria for Evaluation:

Primary Efficacy Evaluation: Proportion of subjects with insulin resistance, as defined by a homeostasis model assessment (HOMA-IR) of >1 at 6 months.

Secondary Efficacy Evaluation: The secondary efficacy evaluations included:

- Proportion of subjects with composite endpoint of IFG/IGT/DM at 6 months.

- β-cell function, evaluated using HOMA-β

- Body mass index (BMI), waist-hip-ratio (WHR), bone mineral density (BMD) and body composition

- Blood pressure (BP)
- Lipid profile and glycated hemoglobin (HbA_{1c})
- eGFR, measured using the abbreviated Modification of Diet in Renal Disease (MDRD) equation
- Incidence of acute rejection, and subject and graft survival
- Health-related quality-of-life (HRQoL) as measured by SF-36; and participation in physical activity, as measured by the Active Australia Survey
- Rate of dietary and exercise compliance, evaluated with a 3-day weighed food record and exercise log presented to the coordinator at the end of each month, respectively. Weekly telephone conversations were also used in both assessments.

Safety Evaluations: Safety and tolerability assessments included the regular monitoring and recording of all adverse events (AEs) and serious AEs (SAEs), discontinuations, exposure to study treatments, and concomitant and prior medications. Safety assessments also included physical examinations, electrocardiogram (ECG) measurements and laboratory investigations, including hematology, biochemistry, fasting lipid profile, tacrolimus trough level and glucose metabolism.

Statistical Methods:

Sample Size Calculation: This study was a single-arm exploratory pilot study and, as such, a formal sample size calculation was not performed. The proportion of subjects expected to experience insulin resistance in the absence of the diet and exercise intervention was estimated to be 75% at 6 months, based on data reported by Armstrong and colleagues, 2005. Based upon the assumption that the intervention will reduce the insulin resistance at 6 months to 60%, with a precision of 15%, an analyzed 41 subjects were required at the 95% confidence level (CI). However, allowing for a 40% dropout rate, 60 subjects needed to be enrolled to yield interpretable data after 6 months of treatment.

Statistical Methods: The primary endpoint was the proportion (and 95% CI) of subjects with insulin resistance (as measured by the proportion of individuals with HOMA-IR>1 at 6 months). HOMA-IR was calculated using the original equation described by Matthews et al, 1985:

$$\text{HOMA-IR}=\frac{\text{FPI}\times\text{FPG}}{22.5}$$

Where, FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose concentration (mmol/L). Insulin resistance was defined as HOMA-IR scores >1. HOMA-IR scores were assessed at each visit and changes from Baseline were summarized. HOMA-IR scores were tabulated and compared against the benchmark expected proportion of 75%.

The secondary endpoint analyses included:

- Proportion of subjects with IFG/IGT/DM at 6 months.
    - IFG was defined as a fasting venous plasma glucose concentration of ≥6.1 mmol/L but <7.0 mmol/L, together with a 2-hour plasma glucose concentration of <7.8 mmol/L.
    - IGT was defined as a fasting venous plasma glucose of <7.0 mmol/L, together with a 2-hour plasma glucose of ≥7.8 mmol/L but <11.1 mmol/L.
    - DM was defined as a fasting plasma glucose concentration of ≥7.0 mmol/L *or* a 2-hour plasma glucose ≥11.1 mmol/L.

- Assessment of β-cell function at each visit and change from Baseline via calculation of HOMA-β:

$$HOMA-\beta = \frac{20 \times FPI}{FPG - 3.5}$$

  Where FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose concentration (mmol/L). Visit results and change from Baseline were summarized as for continuous variables.

- Calculation of BMI, WHR, BMD, BP and laboratory evaluations at each visit, and change from Baseline were summarized as for continuous variables.

- HbA_{1c} was measured at Baseline and Visits 3 and 4.

- Tabulation of the incidence of acute rejection, graft loss and death. Acute rejections were classified and tabulated as spontaneously resolving, corticosteroid sensitive, corticosteroid resistant, or other (as per the protocol). Acute rejections were tabulated according to Banff Criteria.

- The SF-36 was scored according to the method of Ware and colleagues. The Active Australia Survey was analyzed as per the Australian Institute of Health and Welfare (AIHW) guidelines. Data and changes from Baseline were summarized and tabulated.

- Compliance with dietary advice was measured on a categorical scale from 0 (no compliance) to 10 (full compliance) and summarized with frequency tabulations (n[%]). Compliance with the exercise program was measured as completion of 3 exercise sessions per week for the 6-month period. Compliance was categorized as <50%, 50-80% or >80% compliant with the program.

Analysis Population: The ITT population included all subjects who were enrolled and who proceeded to the initial dietary and exercise intervention. The primary analysis was based upon ITT principles. The PP analysis included those subjects who completed all 6months of the study according to the protocol. The safety population included all 55 subjects enrolled in the study.

RESULTS:

STUDY POPULATION: A total of 55 subjects were enrolled in the study and allocated to the intervention; of these, 46 subjects (83.6%) completed the study and 9 subjects (16.4%) were withdrawn. The 9 subjects were withdrawn for the following reasons: non-compliance (1 subject), withdrawal of consent (2 subjects), AE (5 subjects), and death (1 subject).

The age of enrolled subjects ranged from 19.5 to 70.3 years (mean age 48.6 years). The majority of subjects were male (31 [56.4%]) and Caucasian (43 [78.2%]).

EFFICACY RESULTS:

Primary Endpoint: In the ITT population, 92.7% (95% CI: 85.6% to 99.8%) of subjects were defined as having insulin resistance (HOMA-IR>1) at Baseline. Following the dietary and exercise intervention, this number had reduced to 82.6% (95% CI: 71.2% to 94.0%) of subjects (Table 1). Similar results were observed in PP population. The results for change from baseline in HOMA-IR are shown in Figure 1.

Table 1 HOMA-IR ITT population

	Baseline (n=53)	Visit 2 (n=53)	Visit 3 (n=48)	Visit 4 (n=45)
HOMA-IR	2.00 ± 1.18 1.70 [0.93 to 4.67] 0.84 – 7.20	2.37 ± 3.40 1.75 [0.92 to 4.23] 0.77– 24.3	1.80 ± 0.90 1.53 [0.83 to 3.36] 0.47 – 5.08	2.39 ± 2.79 1.68 [0.71 to 5.96] 0.18 – 14.4
Change in HOMA-IR from baseline	–	0.53 ± 3.11 -0.02 [-2.16 to 2.85] -2.31 – 19.4	-0.05 ± 0.90 -0.18 [-1.55 to 1.35] -2.12 – 3.04	0.52 ± 2.48 0.08 [-1.76 to 2.81] -2.39 – 11.3
Insulin resistant (HOMA-IR >1)				
No	4 (7.3%)	5 (9.4%)	8 (16.7%)	8 (17.4%)
Yes	51 (92.7%)	48 (90.6%)	40 (83.3%)	38 (82.6%)

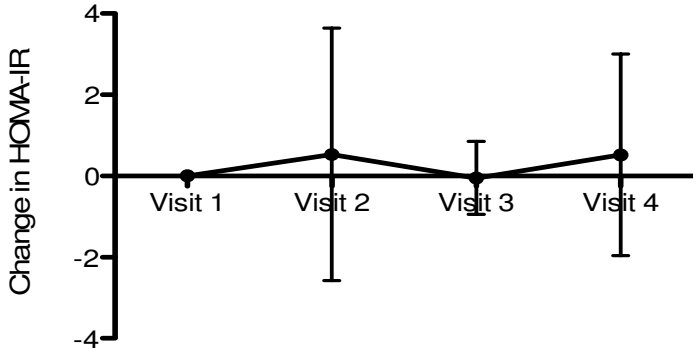

Figure 1 Change in HOMA-IR score from baseline (ITT population)

Secondary Endpoints: The percentage of subjects with IFG decreased from 4.1% (2 subjects) at Baseline to 0 at 6 months. At Baseline, 24.5% of subjects (12 subjects) had IGT and at 6 months, 25% of subjects (11 subjects) had IGT. The number of subjects with DM decreased from 24.5% (12 subjects) at Baseline to 11.4% (5 subjects) at 6 months. The mean β-cell function increased during the study, as shown by the change from Baseline in HOMA-β score (Figure 2). However, there was a wide variation in results.

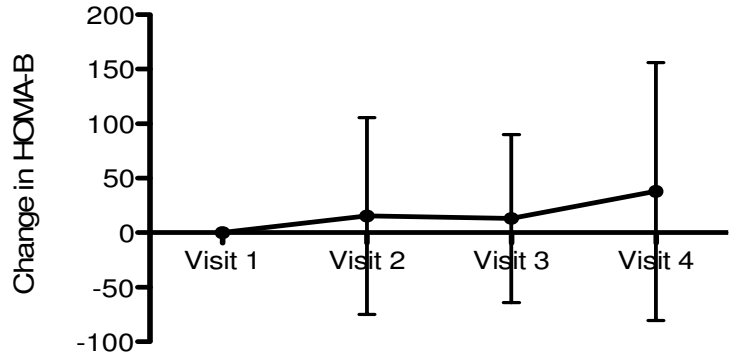

Figure 2 Change in HOMA-β score from Baseline (ITT population)

The changes in BMI and WHR were small and with large standard deviations. Changes in BMD were also negligible.

The mean systolic BP decreased from 132 ± 14 mmHg at Baseline to 125 ± 15 mmHg at 6 months. The mean diastolic blood pressure decreased slightly.

Levels of serum cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol decreased slightly during the study, while low density lipoprotein (LDL) cholesterol levels increased slightly.

Small increases were also observed in HbA_{1c} and eGFR levels.

There were 8 (14.6%) subjects who experienced a rejection episode during the study. Five (9.1%) subjects experienced 1 rejection episode, 2 (3.6%) subjects experienced 2 rejection episodes and 1 (1.8%) subject experienced 3 rejection episodes.

Subject health status, as measured by the SF-36, increased during the study. The mean score increased for all 8 health domains measured: physical functioning, bodily pain, role limitations due to physical health problems, emotional well-being, social functioning, energy/fatigue, general health perceptions and perceived change in health. The Active Australia Survey showed vigorous physical activity increased by 50 ± 134 minutes per week and moderate physical activity increased by 16 ± 83 minutes per week from Baseline to 6 months, although with large variations between subjects.

Subjects were considered compliant with the diet program if their dietary compliance was 8 or above on the categorical scale. At Visits 2 and 3, 54.8% and 54.2% of subjects, respectively, were compliant with the dietary advice. At Visit 4, the compliance had decreased to 35.6%.

Subjects were considered compliant with the exercise program if their exercise compliance was categorized as >80%. At Visit 2, 30.2% of subjects were compliant with the exercise program. At Visits 3 and 4, 41.7% and 41.3% of subjects, respectively were compliant.

A total of 18.87%, 20.83% and 17.78% of subjects at Visits 2, 3 and 4, respectively were compliant with both the diet and exercise regime; while 33.96%, 25.0% and 40.0%, respectively were compliant with neither regime.

The PP secondary efficacy endpoint results were similar to those of the ITT population.

SAFETY RESULTS: A total of 508 AEs occurred during the study (Table 2). All subjects (n=55) experienced at least 1 AE. A total of 39 subjects experienced AEs that were considered possibly, probably or definitely related to the diet and exercise intervention; while 100 subjects reported AEs that were considered possibly, probably or definitely related to tacrolimus. One subject died during the study; the cause of death was pseudo-obstruction of the large bowel due to splenic flexure tumor. The investigator considered the event to be unrelated to tacrolimus or the study intervention.

Table 2 Adverse Events with an Incidence of ≥5% by MedDRA SOC and MedDRA Preferred Term

MedDRA SOC Term	MedDRA Preferred Term	Numberof Subjects	Proportion of Subjects (%)
Blood and lymphatic system disorders	Anaemia	4	7.3
	Neutropenia	5	9.1
Gastrointestinal disorders	Abdominal distension	3	5.5
	Abdominal pain	6	10.9
	Diarrhoea	16	29.1
	Dyspepsia	3	5.5
	Nausea	5	9.1
	Vomiting	6	10.9
General disorders and administration site conditions	Chest pain	6	10.9
	Influenza like illness	5	9.1
	Oedema peripheral	5	9.1
	Pyrexia	6	10.9
Infections and infestations	Gastroenteritis	3	5.5
	Nasopharyngitis	7	12.7
	Oral herpes	3	5.5
	Upper respiratory tract infection	3	5.5
	Urinary tract infection	7	12.7
Investigations	Biopsy kidney	5	9.1
	Blood alkaline phosphatase increased	5	9.1
	Blood calcium decreased	3	5.5
	Blood creatinine increased	12	21.8
	Liver function test abnormal	3	5.5
	White blood cell count decreased	12	21.8
Metabolism and nutrition disorders	Diabetes mellitus	5	9.1
	Glucose tolerance impaired	16	29.1
	Hypercalcaemia	5	9.1
	Hyperinsulinaemia	4	7.3
	Hypertriglyceridaemia	3	5.5
	Hypocalcaemia	3	5.5
Musculoskeletal and connective tissue disorders	Arthralgia	6	10.9
	Back pain	7	12.7
	Musculoskeletal pain	7	12.7
	Osteopenia	3	5.5
	Pain in extremity	4	7.3
Nervous system disorders	Headache	10	18.2
	Lethargy	3	5.5
	Tremor	4	7.3
Renal and urinary disorders	Haematuria	4	7.3
	Microalbuminuria	3	5.5
Reproductive system and breast disorders	Dysmenorrhoea	5	9.1
Respiratory, thoracic and mediastinal disorders	Cough	8	14.5
	Dyspnoea	4	7.3
Skin and subcutaneous tissue disorders	Alopecia	5	9.1
Surgical and medical procedures	Stent removal	3	5.5
	Ureteral stent removal	3	5.5
Vascular disorders	Hypertension	4	7.3

There were 24 SAEs during the study. The most common of these were pyrexia (3 subjects) and urinary tract infection (2 subjects). SAEs by number of subjects experiencing the events are summarized in Table 3.

Table 3 Serious adverse events (ITT population)

MedDRA SOC	MedDRA Preferred Term	Number of Subjects	Proportion of Subjects (%)
Gastrointestinal disorders	Diarrhoea	1	1.8
	Large intestinal obstruction	1	1.8
	Nausea	1	1.8
General disorders and administration site conditions	Chest pain	1	1.8
	Pyrexia	3	5.5
Immune system disorders	Kidney transplant rejection	1	1.8
Infections and infestations	Cytomegalovirus infection	1	1.8
	Gastroenteritis	1	1.8
	Septic shock	1	1.8
	Urinary tract infection	2	3.6
	Viral tonsillitis	1	1.8
Investigations	Angiogram	1	1.8
	Blood creatinine increased	1	1.8
	Cystoscopy	1	1.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer	1	1.8
	Lymphoma	1	1.8
Renal and urinary disorders	Renal artery stenosis	1	1.8
	Ureteric obstruction	1	1.8
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	1.8
Surgical and medical procedures	Arterial therapeutic procedure	1	1.8
	Medical device change	1	1.8

Five subjects withdrew due to an AE: back injury (1 subject), back pain aggravated (1 subject), post-transplant lymphoproliferative disorder (1 subject), and depression (2 subjects). Back pain aggravated was considered possibly related to the diet and exercise intervention, and post-transplant lymphoproliferative disorder and depression (1 subject) were considered possibly related to tacrolimus.

Tacrolimus trough levels were within target in 50.9% (10 to 15 ng/mL), 69.2% (8 to 15 ng/mL), 53.5% (8 to 15 ng/mL) and 86.1% (5 to 12 ng/mL) of subjects at Visits 1, 2, 3 and 4, respectively.

STUDY LIMITATIONS: It was estimated that 60 subjects would be required in this study; however, only 55 subjects enrolled.

It was planned that all the primary and secondary objectives would be analyzed by dietary and exercise compliance. However, only the primary and major secondary objectives were analyzed by compliance; and for the secondary outcome analyses by exercise and dietary compliance, the results are presented on an ITT basis only.

The PRT results are not reported, as it was felt that summarizing this measure would be difficult to interpret and uninformative given that it is common practice to start at lighter loads and gradually build up to heavier resistances.

No other notable study limitations were identified by the Sponsor.

CONCLUSIONS: The implementation of a structured dietary and exercise intervention in the controlled environment of a clinical trial has allowed an initial evaluation of the effect that such an intervention has on glucose metabolism and other important cardiovascular parameters within the renal transplant group, and gives valuable information on endpoints such as biopsy-proven acute rejection and subject/graft survival. In addition, important initial data has been obtained regarding compliance and HRQoL.

This exploratory study found that a combined dietary and exercise intervention, in addition to standard care, reduced the prevalence of insulin resistance in *de novo* renal transplant recipients on tacrolimus from 92.7% (95% CI: 85.6% to99.8%) to 82.6% (95% CI: 71.2% to94.0) over a period of 6 months.

Although there was little change in the percentage of subjects with IFG and IGT, the percentage of subjects with diabetes decreased from 24.5% to 11.4%. At 6 months, there was an increase in mean β-cell function, although these results showed large variability between subjects. There were only small changes in other measures of cardiovascular health such as BMI, WHR and laboratory measures.

The findings indicate that the combined dietary and exercise intervention, added to standard care, can reduce the expected prevalence of insulin resistance in *de novo* renal transplant recipients on tacrolimus. HRQoL may also be increased with dietary and exercise intervention. There were no concerning safety signals associated with the intervention.

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