Supplementary Table 1: Trial registration data set

TITLE	WORTH: Randomised Crossover study of a DPP4 inhibitor, and thiazolidinedione as second or third line therapy in patients with type 2 diabetes who have suboptimal glycaemic control on metformin and/or sulphonylurea therapy
SHORT TITLE	WORTH
Protocol Version Number and Date	Version 1: date 01 December 2018 first version submitted for ethics approval Version 2: date 28 December 2018 removal of word "WORTH" Version 3: ddate 08 April 2019 - Minor amendment to inclusion criteria from 'metformin monotherapy or metformin plus sulfonylurea' to 'metformin and/or sulfonylurea', minor amendment of exclusion criteria from 'Currently treated with corticosteroids' to 'Currently treated with oral corticosteroids'. Additional minor operational clarifications are also included in the updated protocol and related study documents. Minor change of each study medication duration (vildagliptin or pioglitazone) from 16 weeks to 4 months Version 4: date 07 November 2019 – Minor amendment to increase recruitment beyond target of 300 participants, provided it is within the recruitment period, up to a maximum of 400 participants before the recruitment period ends on 30 March 2020 due to higher than expected number of protocol deviations.
Methodology	Two-period, two-treatment, randomised crossover study of a DPP4 inhibitor (vildagliptin), and thiazolidinedione (pioglitazone) as second or third line therapy in patients with type 2 diabetes who have suboptimal glycaemic control on metformin and/or sulphonylurea therapy
Study Duration	Estimated duration for the main study protocol from when the trial opens (after all ethics and locality approvals have been received) to when the last subject/patient recruited has completed all study processes is 2 years
Study Centre	Host site: University of Auckland

Objectives	The WORTH study aims to directly test potential stratification of a participant's glucose response to each test medication according to key baseline characteristics such as ethnicity, genetics, obesity and lipid levels. The primary objective is to test potential stratification of glycaemic response according to ethnicity: ie: whether those of Māori or Pacific ethnicity respond differently to two diabetes medications compared to non-Māori/non-Pacific people. We hypothesise that those of Māori or Pacific ethnicity will have greater fall in HbA1c after Pioglitazone than Vildagliptin The secondary objectives are (1) to test potential stratification of glycaemic response according to *CREBRF* and other genotypes, obesity and lipid profile (2) to develop a bioresource for the assessment of biomarkers (including other genetic markers) and diabetes medication response. We hypothesis that (a) Obese patients (BMI>30kg/m^2) and/or those with high Triglycerides (TG>2.3mmol/l) at baseline achieve a lower HbA1c when receiving Pioglitazone than Vildagliptin (b) Those with *CREBRF* variant genotype have greater fall in HbA1c after Vildagliptin than Pioglitazone
Phase of the Trial	IV
Number of Subjects/Patients	A target sample size of 300 participants (40:60 split between Māori or Pacific vs non-Māori, non-Pacific) will give 80% power at 5% significance level to detect an effect size of 0.35 SD between two patient groups on the difference in HbA1c between two test drugs. This sample size has allowed for 10% lost to follow up. The study may recruit beyond the target sample size of 300 (up to a maximum of 400 participants) as long as it is still within the recruitment period (01/02/2019 to 30/03/2020).
Treatment duration	2 x 4 months intervention
Follow up duration	Total duration 8 months
Planned Trial Period	24 months 01/02/2019 – 31/01/2021
Main Inclusion Criteria	Patients with a confirmed clinical diagnosis of Type 2 diabetes, age ≥18 and ≤80 years with capacity to give informed consent. Patients who have suboptimal glycaemic control on stable doses of metformin and/or sulphonylurea for 3 months, have an HbA1c >58mmol/mol but ≤110mmol/mol.
Statistical Methodology and Analysis	This is not a standard crossover study of comparative drug efficacy, but a study examining whether there is stratification in drug response by key baseline characteristics such as ethnicity, genotype, and BMI. The primary outcome variable is on treatment HbA1c after 4 months on each of the two drugs. The key primary analysis for each hypothesis is to assess whether the difference in achieved HbA1c for the two drugs is different by ethnicity grouping of patients. Generalised linear mixed model will be used to test the difference between patient groups using both fixed and random

	effects. The fixed effects will include the baseline outcome value, stratification factors, crossover period, drug class, patient group and its interaction with drug. The random effect will include patient as the cluster. Statistical analysis will be performed based on the intention-to-treat principle.
Investigational Medicinal Product(s)	- DPP4i (vildagliptin), recently Pharmac *funded T2D medication as of 1 October 2018* - Thiazolidinedione (pioglitazone), Pharmac *funded T2D medication since 2004.*

Supplementary Table 2: Trial sponsor and key personnel

Chief Investigator	Associate Professor Rinki Murphy R.Murphy@auckland.ac.nz Tel: 021 1428470
Sponsor	University of Auckland Department of Medicine
Funder(s)	Health Research Council (HRC)
Clinical Trials Unit	Middlemore Clinical Trials Unit
Statistician	Dr Yannan Jiang University of Auckland
Trials pharmacist	Dale Griffiths Clinical Trials Pharmacist
Committees	The WORTH Trial Management Committees will be defined as • Trial Steering Committee (TSC) • Data Monitoring Committee (DMC)