CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:
Acute Metabolic Effects of Fenofibrate Administration in Patients with Diabetic Nephropathy

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Protocol Title: Acute Metabolic Effects of Fenofibrate Administration in Patients with Diabetic Nephropathy

Protocol Number: SGHDN01

Protocol Version/ Date: Version 2.0 dated  6 May 2019

Sponsor Name: National Medical Research Council (LCG16May001)

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP)

Principal Investigator Name: TAN HONG CHANG

Principal Investigator Signature: ________________________________

Date: ________________________________
1 BACKGROUND AND RATIONALE

Diabetic nephropathy (DN) is a common cause of end-stage renal disease (ESRD) and accounts for nearly half of all new patients starting dialysis in Singapore, the country with the highest rates of DN in the Asia-Pacific region. Despite the scale of the problem, little progress has been made in our understanding of the pathogenesis of the disorder and no new therapies have been offered. We have conducted a metabolomics study of human diabetic nephropathy that revealed evidence for alterations in mitochondrial fuel metabolism in patients with the disease, a finding also reported in other recent studies of human DN. Based on this finding we believe that dysregulated mitochondrial fuel oxidation is a major driver of diabetic nephropathy.

In collaboration with clinician-scientists at Khoo Tech Puat Hospital (KTPH) in Singapore, we have recently conducted a comprehensive metabolic profiling study of over 300 human diabetic nephropathy patients using our tandem MS-based metabolomics platforms. The study used serum from patients with diabetic nephropathy and matched controls with diabetes but without nephropathy. The patients with diabetic nephropathy showed a metabolite pattern suggesting alterations in fatty acid oxidation (Figure 1).

![Figure 1: Acyl-carnitine species in human subjects with diabetic nephropathy are elevated.](image)

The metabolomics profiling study showed that patients with DN have elevated levels of several short chain acyl-carnitines (Figure 1, top right) including C3 (propionyl-), C4 (butyryl-) and C5 (isovaleryl-carnitine). This pattern of elevated short-chain acyl-carnitines resembles what is observed in several inherited metabolic disorders including short-chain acyl-coA dehydrogenase (SCAD). Based on this we hypothesize that dysregulated mitochondrial fuel oxidation is a major driver of diabetic nephropathy. The goal of the current study is to investigate in greater detail mitochondrial fuel metabolism in patients with diabetic kidney disease.
1.1 General Introduction

Fenofibrate is an agonist of peroxisome-proliferator activating receptor (ppar)-alpha that is approved for the treatment of hypercholesterolaemia and hypertriglyceridemia alone or combined in patients unresponsive to dietary and other non-drug therapeutic measures. Fenofibrate is also indicated for the reduction in the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy. Presently fenofibrate is not indicated for the treatment of diabetic nephropathy.

1.2 Rationale and Justification for the Study

We hypothesize that treatment with fenofibrate, taken orally at 300 mg per day or 100 mg per day (adjusted for renal impairment) for 30 days will lead to significant changes in the circulating metabolomics pattern in patients with DN.

Since we are interested in understanding the metabolic effects of the drug, we propose to administer the drug for a period of 30 days. We will perform a comprehensive analysis of the state of fuel metabolism in these patients before, and after the administration of fenofibrate using targeted metabolomics and other approaches. Our goal is to discover key changes in fuel metabolism in DN patients receiving fenofibrate.

1.2.1 Rationale for the Study Purpose

Several clinical studies have demonstrated the effectiveness of fenofibrate, a clinically approved drug, in reducing the rate of microvascular complications in patients with DN. Although the mechanism for fenofibrate’s beneficial effect in DN is unknown the major physiologic action of fenofibrate is to stimulate mitochondrial fuel oxidation pathways. Thus, we now propose to study the effects of fenofibrate on fuel metabolism patterns in patients with DN.

Fenofibrate is known to cause an elevation of serum creatinine, likely by inhibiting renal tubular creatinine secretion. Use of fenofibrate is also limited by several important drug interactions. However, completion of the study will provide us with a better understanding of the relationship between mitochondrial fuel oxidation, fenofibrate and the biochemical changes surrounding the development of DN. The study may also point the way to more targeted therapies with fewer potential deleterious side effects.

1.2.2 Rationale for Doses Selected

The dose of fenofibrate in this study is selected based on the study subject’s estimated creatinine clearance based on Cockcroft-Gault equation. The dose selection is similar to dosages used in patients in standard clinical practice.

1.2.3 Rationale for Study Population

DN the most common cause of end-stage renal disease (ESRD) in the US and also accounts for nearly half of all new patients starting dialysis in Singapore, the highest in the Asia-Pacific region. ESRD is also a major cause of death, accounting for over 65% of deaths in T1DM patients with nephropathy and the 5-year survival rate being typically less than 10% in elderly patients with T2DM. Despite these sobering statistics, little progress has been made in early diagnostic markers or the availability of increased treatment options for the clinical management of DN. Current mainstay of therapy relies on control of hyperglycemia and blood pressure and pharmacologic blockade of the renin-angiotensin system (RAS) with ACE inhibitors or
angiotensin receptor blockers (ARBs). Despite these treatments, DN typically progresses over time. Finally, no new therapies for DN have been offered the past few years and to our knowledge, there are only a couple of ongoing clinical trials in the US for potential new treatments for DN (clinicaltrials.gov).

1.2.4 Rationale for Study Design

We will conduct a single arm intervention study to examine the effects of a standard dose of fenofibrate (taking into account the subject’s estimated CrCl for dose variation) on fuel oxidation patterns in patients with type 2 diabetes and DN. No randomization or blinding will be performed as the response to fenofibrate is stereotypical and the measured parameters are objective and thus not subject to observer bias.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

Our study hypothesis is that dysregulated mitochondrial fuel oxidation, as measured by changes in the circulating metabolomics pattern of DN patients, is a major driver of diabetic nephropathy. Furthermore, treatment with fenofibrate over a period of 30 days will reverse the metabolomics changes seen in patients with DN.

2.2 Primary Objectives

The primary objective is to study the effects of fenofibrate on fuel metabolism patterns in patients with DN. We will conduct a single arm intervention study to examine the effects of a standard dose of fenofibrate on fuel oxidation patterns in patients with type 2 diabetes and DN. Since we are interested in understanding the metabolic effects of the drug, we propose to administer the drug for a period of 30 days. We will perform a comprehensive analysis of the state of fuel metabolism in these patients before and after the administration of fenofibrate using targeted metabolomics and other approaches. Our goal is to discover key changes in fuel metabolism in DN patients receiving fenofibrate.

2.3 Secondary Objectives

Fenofibrate has been demonstrated to improve clinical outcomes of diabetic retinopathy. We will further evaluate changes in the retinal vasculatures of DN patients using ocular computer tomography after short-term treatment with fenofibrate.

2.4 Potential Risks and Benefits:

2.4.1 Potential Risks

Venepuncture

This study requires blood to be drawn from a vein in the arm. For most people, blood draws using needle punctures do not cause any serious problems. However, drawing blood may result in pain at the point of puncture, a feeling of faintness, irritation of the vein and bruising or bleeding at the site of needle puncture. There is also a very slight possibility of an infection at needle puncture site. An experienced staff will perform these procedures and every precaution will be taken to prevent infection.
Indirect calorimetry
Indirect calorimetry involves the placement of a transparent plastic hood with ventilation over the head for 30 minutes intervals during the 1st and 3rd study visit. It is well tolerated but some people may feel claustrophobic. To avoid this, a brief trial run will be performed for subjects to familiarize with the equipment and measurement.

Adverse Effects Related to Fenofibrate
A) Allergic Reactions
All drugs have a potential risk of an allergic reaction. Allergic reactions ranges from mild reactions such as skin itchiness, rash, eye swelling to more severe allergic reactions that affects the blood pressure (allergic anaphylaxis). Severe allergic reactions could become life threatening if not treated quickly.

B) Elevated Liver Function Test and Pancreatitis
Fenofibrate can cause abdominal pain, stones in the gall bladder, jaundice (yellowing of the skin and/or whites of the eyes, indicating possible liver problems), and elevated liver tests (elevation in transaminases). In the majority of cases, elevations in transaminases are transient, minor and asymptomatic. Pancreatitis has been reported in patients taking fenofibrates but it is unclear whether this is due to a drug effect. Subjects with a history of chronic liver disease, known gladder disease, previous pancreatitis will not be eligible to join the study. In addition, liver function will be monitored closely during the study.

C) Muscle Toxicity
All lipid-lowering medications including fenofibrate have the potential of causing muscle toxicity such as muscle aches (myalgia), elevated the muscle enzyme creatinine phosphokinase (myositis) and, in very rare cases, rhabdomyolysis (severe elevation of muscle enzyme). The risk of muscle toxicity increases if fenofibrate is used together with other lipid-lowering medications such as HMG Co-A inhibitors (statins). The incidence of muscle toxicity is also greater in elderly individuals (above 70 years old), and in those with kidney disease, hypothyroidism, muscle disorders, and high alcohol intake. Subjects with significant kidney impairment, untreated hypothyroidism, and muscle disorders will be excluded from the study. All subjects will be educated on signs of muscle toxicity.

D) Elevated Creatinine Levels
Fenofibrate can lead to an elevated kidney function test (elevated creatinine levels). The clinical importance of this increase is unknown and these elevations tend to return to baseline following the discontinuation of fenofibrate. Subjects with more severe kidney impairment will be excluded from this study and the dosage of fenofibrate will be reduced in subjects with mildly impaired kidney function. All subjects will have their kidney function tested to ensure they are suitable to participate in this study.

E) Drug interactions
Fenofibrate can cause significant drug interaction with medications such as: amodiaquine, ciprofibrate, cyclosporine and Vitamin K antagonist (e.g. warfarin), factor Xa inhibitors (e.g. rivaroxaban, apixaban, dabigatran), colchicine and tacrolimus. Subjects taking these medications would not be eligible for the study.

F) Other adverse effects reported with fenofibrate use are: headaches, change in taste, and certain abnormalities in blood cells (low white cell count, decrease in haemoglobin).
Adverse Effects Related to Fundus Photography, Optical Coherence Tomography (OCT and Optical Coherence Tomography Angiography (OCTA))

The fundus photography, OCT and OCTA examinations are non-invasive and considered standard examinations in the clinic. They will be done after dilation for your clinical examination at the diabetic retinopathy clinic, so you will not be inconvenienced by then to be dilated a second time. The eye drops may cause some blurring of vision and will make your eyes more sensitive to light for a few hours. As a consequence of this blurred vision, you may be more prone to slipping, falling down or possible clumsiness. As such, we will require that you remain on the hospital premises until your vision has normalized. The eye drop effect will usually last up to 4 hours.

Issues Related to Pregnancy and Breast-Feeding

There are no adequate data from the use of fenofibrate in pregnant woman. Therefore, pregnant or breast-feeding women cannot participate in this study. Sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are considered to be abstinence (not having sex), oral contraceptives (the pill), intrauterine device (IUD), DepoProvera, Norplant, tubal ligation (tubes tied) or vasectomy of the partner. An acceptable although less reliable method, involved the careful use of condoms and/or a spermicidal foam or gel along with a diaphragm, cervical cap, or sponge. Study subjects would be encouraged to discuss this issue further with their doctor if they any questions.

2.4.2 Potential Benefits

There is unlikely any direct benefit from participating in this study as treatment with fenofibrate for one month is unlikely to provide any long-term benefit. However, completion of the study will provide us with a better understanding of the relationship between mitochondrial fuel oxidation, fenofibrate and the biochemical changes surrounding the development of DN. The study may also point the way to more targeted therapies with fewer potential deleterious side effects.

3 STUDY POPULATION

3.1 List The Number and Nature of Subjects to be Enrolled.

A total of 300 subjects with DN will be enrolled. We have determined that this would provide adequate power to detect differences in metabolic parameters in study patients.

3.2 Criteria for Recruitment and Recruitment Process

This will be a single-centre study conducted in SGH. Subjects from this trial will be patients attending the Diabetes and Metabolism Centre (DMC) clinics. Physician at the DMC can refer any interested and suitable patients to the study.

We will also invite subjects from our previous diabetic nephropathy study (CIRB Ref: 2015/2004) through phone calls to participate in this trial. Re-contacting will only be done for subjects who had provided written informed consent to be re-contacted for participation in clinical studies.

The study team will provide additional details regarding this study to all interested patients and they will be scheduled for consent taking and screening visit at the SGH Clinical Trials Research Centre (CTRC).
3.3 Inclusion Criteria

Subject must meet all of the inclusion criteria listed below to participate in this study:

1. Man or woman between 21 to 100 years of age

2. Type 2 diabetes mellitus as defined by:
   - Fasting plasma glucose >7.0 mmol/l, or
   - Symptoms of hyperglycemia with casual plasma glucose >11.1 mmol/L, or
   - 2 hour plasma glucose >11.1 mmol/l after a 75 gram oral glucose load, or
   - Known type 2 diabetes mellitus diagnosed by a medical practitioner

3. Increased urine protein excretion as defined as:
   More than one measurement in the past 1-year with:
   - Urine microalbumin/creatinine ratio (ACR) > 3.3 mg/mmol creatinine or
   - Urine total protein/creatinine ratio (PCR) > 0.2 g/urine creatinine

4. Known diabetes duration > 3 months

5. HbA1c < 9% (within 3 months prior to enrolment)

6. Stable diabetes therapy for > 3 months as defined as:
   - No change in dose of diabetes medications by more than two-fold or new agents added within the previous 3 months

7. Stable lipid therapy for > 3 months
   - No change in dose of lipid-lowering medications by more than two-fold or new agents added within the previous 3 months

8. Capable of providing informed consent

We will not be studying children or adults above the age of 100. All methods of contraception allowed.

3.4 Exclusion Criteria

Exclusion criteria were selected to enhance safety and adherence. All subjects meeting any of the exclusion criteria at baseline will be excluded from participation.

1. Type 1 diabetes mellitus
2. Known intolerance or allergic to statins
3. Known intolerance or allergic to fenofibrate
4. Known intolerance or allergic to peanut or arachis oil or soybean lecithin or related products
5. Concurrent use of:
   - Fibrates
   - Colchicine
   - Nicotinic Acid
   - Cyclosporine
   - Tacrolimus
   - Amodiaquine
   - Bile acid sequestrants
   - Chenodiol
- Ciprofibrate
- Oral anticoagulants: vitamin K antagonist (e.g. warfarin), factor Xa inhibitors (e.g. rivaroxaban, apixaban and dabigatran)
- Anti-obesity medications (e.g. phentermine, orlistat)
- Systemic steroids (e.g. prednisolone, hydrocortisone, dexamethasone)

6. Chronic liver disease:
   - Hepatitis B
   - Hepatitis C
   - Autoimmune hepatitis
   - Hemochromatosis

7. Previous pancreatitis

8. Serum alanine aminotransferase or aspartate aminotransferase above 2x upper limit of normal

9. Serum creatinine kinase (CK) above upper limit of normal

10. Significant renal impairment:
    - CrCl < 30 ml/min**
    - Renal replacement therapy

11. Presence of any non-DN renal glomerular disease
    (e.g. IgA nephropathy, lupus nephritis, membranous glomerulonephritis, focal segmental glomerular sclerosis)

12. Any previous organ transplantation

13. Previous bariatric surgery

14. Gallbladder disease

15. Untreated hypothyroidism

16. Untreated thyrotoxicosis

17. Hemoglobin < 10 g/L

18. Any clinically significant blood dyscrasias (e.g. leukopenia, thrombocytopenia)

19. Cancer within the last 5 years (except basal cell carcinoma)

20. Medical condition likely to limit survival to less than 3 years

21. Currently participating in another clinical trial

22. Pregnancy, or currently trying to become pregnant

23. Nursing mothers

24. Hospitalization within 1 month prior to enrolment

25. Significant alcohol intake (> 1 unit per day for women and > 2 units per day for men)

26. Any factors likely to limit adherence to interventions (e.g. dementia; alcohol or substance abuse; history of unreliability in medication taking or appointment keeping; significant concerns about participation in the study from spouse, significant other or family members)

27. Any ongoing acute medical illness

28. Failure to obtain informed consent from participant

** CrCl [mL/min] = 1.23 * Sex * (140 - Age[yr]) * Weight[kg] / SerumCreat[mcmol/LCr] (Men = 1; Female = 0.85). Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41. [PubMed 1244564]

3.5 Subject Replacement

There will be no replacement of subjects who drop out of the study.

4 STUDY DESIGN

In this single-centre, open label study, 300 adults with DN will be recruited over 3 years. Following screening and baseline metabolic evaluations, eligible subjects will be treated with fenofibrate for 30-days
and re-assessed.

### 4.1 Randomisation and Blinding

No randomization or blinding will be performed as the response to fenofibrate is stereotypical and the measured parameters are objective and thus not subject to observer bias.

### 4.2 Contraception and Pregnancy Testing

There are no adequate data from the use of fenofibrate in pregnant woman. Therefore, pregnant women cannot participate in this study. Female subjects of childbearing potential will be tested for pregnancy using urine pregnancy test kits during their screening (Visit 1) and (Dosing Visit). Sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are considered to be abstinence (not having sex), oral contraceptives (the pill), intrauterine device (IUD), DepoProvera, Norplant, tubal ligation (tubes tied) or vasectomy of the partner. An acceptable although less reliable method, involved the careful use of condoms and/or a spermicidal foam or gel along with a diaphragm, cervical cap, or sponge. Study subjects would be encouraged to discuss this issue further with their doctor if they any questions.

### 4.3 Study Visits and Procedures

Subjects will have their written informed consent taken during Visit 1 at the SGH CTRC and undergo screening and baseline assessments. Eligible subjects will return within the next 14 days for the initiation of study drug (Visit 2). The post-treatment and final visit (Visit 3) will take place 30 ± 7 days after Visit 2. Details of study visits are described in Table 1.

Table 1. Study Procedures

<table>
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<th>Visit 3b</th>
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<td>Day -14 to -1</td>
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<td><strong>Laboratory Procedures</strong></td>
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</table>

a. Visit 2 will take place within 14 days from Visit 1
b. Visit 3 will take place 30 ± 7 days from Visit 2
c. Weight will be measured to the nearest 0.1 kg on a balance scale and height with a stadiometer three times and then averaged
d. Waist circumference will be measured from the inferior margin of the last rib and hip circumference measured at the crest of the ileum to the nearest 0.1 cm three times and averaged
e. Indirect calorimetry using a canopy hood will be performed for 30 minutes for measurement of basal energy

DYANMO Study Protocol V2.0 Dated 6 May 2019
expenditure, CO₂ production and O₂ consumption
f. Analysis at clinical laboratory
g. Performed using bedside urine pregnancy test kit
h. Blood and urine will be collected and stored for metabolomic profiling
ALT = Alanine Transaminase, AST = Aspartate Transaminase, CK = creatinine kinase, A; CrCl = creatinine clearance calculated based on Cockcroft-Gault equation
i. Eye tests that will be performed at either Singapore Eye Research Institute (SERI) or Singapore National Eye Centre (SNEC). Eyes tests that will be done are fundus photography, Optical Coherence Tomography (OCT) and Optical Coherence Tomographic Angiography (OCTA).

4.3.1 VISIT 1: Informed Consent and Screening

Interested patients will be scheduled for their first study visit (Visit 1) at SGH CTRC. Written informed consent will be taken by the principal or co-investigators assigned by the PI. After consent has been taken, study procedures in Table 1 will be performed. The PI or Co-Is assigned by the PI, will review screening results to determine whether subjects are eligible to continue with the study.

4.3.2 VISIT 2: Initiation of Study Drug

Subjects who satisfy the inclusion and exclusion criteria will return to the CTRC within the next 14 days to receive the study drug, fenofibrate (Trolip®). Fenofibrate is to be taken orally for 30 days. The dose of fenofibrate will be adjusted based on the estimated CrCl during Visit 1 as below.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Fenofibrate Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>300mg/day</td>
</tr>
<tr>
<td>30-59</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Subjects will take the first dose of fenofibrate under supervision of the clinical research coordinator at SGH CTRC. They will be given a drug diary to record their intake.

Before the initiation of the study drug, subjects will first head over to Singapore Eye Research Institution (SERI) or Singapore National Eye Centre (SNEC)) for eye tests as mentioned in the following paragraphs.

**Fundus Photography, conventional OCT and Assessment and grading of DR**

The presence and severity of DR or DME will be assessed from digital fundus photographs and OCT. Following pupillary dilation, 7-field ETDRS photography using a non-mydriatic 45º fundus cameras will be obtained for each eye. The modified Wisconsin protocol will be used for DR grading. DR will be considered present if any characteristic lesion as defined by the ETDRS severity scale is present: microaneurysms (MA), hemorrhages, cotton wool spots, intraretinal microvascular abnormalities (IRMA), hard exudates (HE), venous beading, and new vessels. For each eye, a retinopathy severity score will be assigned according to a scale modified from the Airlie House classification system. Macular edema is defined by hard exudates in the presence of MA and blot hemorrhage within 1 disc diameter from the foveal center or presence of focal photocoagulation scars in the macular area. Clinically significant macular edema (CSME) is considered present when the macular edema involved is within 500 mm of the foveal center or if focal photocoagulation scars are present in the macular area. DR is categorized as minimal non-proliferative DR (level 20), mild non-proliferative DR (level 35), moderate non-proliferative DR (level 43 through 47), severe NPDR (level 53), and proliferative retinopathy (>60). Vision-threatening retinopathy is defined as the presence of severe NPDR, PDR, or CSME. Presence of DME (centre involving and non centre involving) and central retinal thickness will also be assessed on OCT.

**Ultrawide field imaging**

Stereoscopic 200-degree-field ultrawide field images of each subject will be obtained using the Optos
P200MA instrument. Unlike traditional fundus cameras, Optos imaging relies on proper eye positioning by the imager and correct patient fixation on a target, rather than the imager viewing the retinal structures for focus. The UWF200 images are centered on the fovea, covering approximately 25% and 82%, respectively, of the retinal area, including the optic disc, macula, and major vascular arcades. Grading of UWF imaging will be performed using the ETDRS protocol to determine the presence and severity of the following lesions: hemorrhages, microaneurysms, or both (H/Ma); intraretinal microvascular abnormalities (IRMA); venous beading (VB); cotton wool spots; hard exudates; retinal thickening; new vessels on the disc; new vessels elsewhere (NVE) on the retina; preretinal hemorrhage; vitreous hemorrhage; and traction retinal detachment. This test will be optional.

**Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA)**

Spectral Domain Optical Coherence Tomography and optical coherence tomographic angiography will be performed in both eyes to obtain scans of the macular, macular thickness, retinal nerve fiber thickness optic disc, and optic nerve head.
4.3.3 VISIT 3: 4-Week Post-Treatment Visit

Visit 3 will take place 30 ± 7 days from Visit 2. Subjects who are still on the study drug should continue to take the study drug on the morning of Visit 3 with plain water. Subjects will be assessed to quantify changes in metabolic fuel utilization after treatment with fenofibrate. These changes are determined based on metabolomic profiling of acyl-carnitines, organic acids and amino acids, indirect calorimetry measurements and the eye tests. The list of procedures performed is listed in Table 1.

SAMPLE COLLECTION

Up to a total of 47 ml (~3.2 tablespoons) of blood and 90 ml (~6.0 tablespoons) of urine will be collected for the entire study. During Visit 1 (Screening), approximately 25 ml (~1.7 tablespoons) of blood and 30 ml (~2.0 tablespoon) of urine will be collected. During Visit 2 (Dosing visit), 30 ml of urine will be collected and during Visit 3 (post-treatment & final visit), approximately 22ml (~1.5 tablespoon) of blood and 30 ml (~2.0 tablespoon) of urine will be collected.

Subjects who developed drug-related adverse reactions may require additional blood and urine taken for clinical assessment.

LABORATORY MEASUREMENTS

A) Blood Chemistry
Screening and standard laboratory tests including full blood count, Potassium, Creatinine, ALT, AST, β-HCG, CK, lipid panel, glucose and HbA1c will be measured in the clinical laboratory using standard methods.

B) Metabolomic Profiling
Metabolomic profiling of lipids, acylcarnitines (ACs), organic acids and ketones will be measured using liquid and gas chromatography and tandem mass spectrometry (LC-MS/MS and GC-MS/MS) at the Duke-NUS metabolomics laboratory.

ACs represent intermediaries of metabolic fuel oxidation and provides a “snap-shot” of in vivo metabolism at the cellular level. The measurement of the various long-, intermediate-chain ACs provide an indicator of fatty acid oxidation efficiency. Ceramides are toxic lipid intermediaries that are implicated in the pathogenesis of insulin resistance. Lactate, pyruvate, succinate, fumarate, malate, alpha-ketoglutarate and citrate are organic acids involved in TCA cycle activity. Beta hydroxybutyrate is a ketone which will also be measured with the organic acids.

C) Urine Protein Excretion
Urine ACR and PCR will be performed to quantify urine protein excretion.

4.3.4 Post Study Follow up and Procedures

Subjects will continue their routine follow-up with their regular physicians upon completion of the final study visit. There will be no post study follow-up procedures.
4.4 Discontinuation/Withdrawal

4.4.1 Discontinuation Criteria

Study drug will be discontinued upon meeting any of the criteria listed below:

1. Any allergic reaction to study drug
2. Hepatic Toxicity as defined as:
   - An increase in serum ALT or AST above 3-fold upper limit of normal (ULN)
3. Muscle Toxicity as defined as:
   - Diffuse myalgia, muscle cramps, and weakness and/or
   - An increase in serum CK above 5-fold ULN
4. An increase in creatinine by > 50% compared to baseline

4.4.2 Discontinuation Visit and Procedures

Should any suspected study drug-related adverse reactions occur, study subjects can contact the study coordinator and they will be scheduled for a visit at SGH CTRC within the next 72-hours. A member of the study team, who is also registered medical practitioner, will assess the subjects for adverse drug reactions and determine their suitability to continue with the study drug. Subjects may be referred back to their primary physician or other physicians as necessary upon the discovery of any drug-related adverse reaction. In the event of any medical emergency or urgency, subject will be referred to the Emergency Department.

Subjects who withdrew from this study (voluntary withdrawal or discontinuation due to adverse reaction) after Visit 2, are encouraged to return for Visit 3 to complete the planned study procedures as listed in Table 1. Subjects who withdrew before Visit 2 (i.e. subjects who had not taken any study drug) will not be asked to return for any subsequent study visits.

5 TRIAL MATERIALS

5.1 Trial Product (s)

Information on trial product is detailed in the package insert as attached in Appendix.

5.2 Storage and Drug Accountability

Fenofibrate (TROLIP®) will be stored in the original package in order to protect from light and moisture, at a room temperature not exceeding 30 °C. It will be stored securely in the investigator product cabinet at the SGH CTRC IP Room with restricted access. Study drug will be stored securely and the study coordinator will maintain a dispensing log. Investigational products (IP) will be monitored by a 24-hour Temperature Monitoring System (TMS) and reports will be generated on a fortnightly basis. Alarms to any excursion will be triggered and the CTRC staff and FRS will be informed.
6  TREATMENT

6.1  Rationale for Selection of Dose

Dosage of fenofibrate used in study is similar to dose used for the treatment of dyslipidemia in clinical practice. Eligible subjects will be given fenofibrate to be taken orally for 30 days according to their CrCl calculated during Visit 1 as described in section 4.3.2

6.2  Study Drug Formulations

Study drug will be dispense as fenofibrate (TROLIP®) 300mg or 100mg capsules.

6.3  Study Drug Administration

Study drug is to be taken orally. The first dose of the study drug will be taken under the supervision of the study coordinator at Visit 2. Subjects will be warned to look out for the development of allergic reactions such as new rash, muscle aches that may indicated muscle toxicity, and jaundice that may indicate muscle toxicity. A dosing diary will also be provided.

6.4  Specific Restrictions / Requirements

Individuals should not take the following medications while taking fenofibrate:
- Fibrates not prescribed by this study (stocks outside of study)
- Nicotinic acid
- Amodiaquine
- Bile acid sequestrants
- Chenodiol
- Cyclosporin
- Warfarin
- Anti-obesity medications (e.g. phentermine, orlistat)
- Systemic steroids (e.g. prednisolone, hydrocortisone, dexamethasone)
- Colchicine
- Cyclosporine
- Tacrolimus
- Oral anticoagulants: vitamin K antagonist (e.g. warfarin), factor Xa inhibitors (eg. rivaroxaban, apixaban and dabigatran)
- Systemic steroids (e.g. prednisolone, hydrocortisone, dexamethasone)
6.5 Blinding

This is an open-labelled study

6.6 Concomitant therapy

All medications (prescription and over the counter), vitamin and mineral supplements, and / or herbs taken by the participant will be documented.

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:
- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

7.2 Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

Reporting of adverse events involves the Principal Investigator submitting the SAE Reporting Form to CIRB within the stipulated timeframe. The Principal Investigator is responsible for informing the institution representative, the chairman medical board (when required by the institution for local SAE resulting in death), sponsor or regulatory bodies as required and appropriate. Collection of AE and SAE will start from the point of enrolment until the completion of the final study visit.

Reporting timeline to CIRB:
- Local unexpected SAE resulting in death that are related events should be reported immediately - within 24 hours of the Principal Investigator becoming aware of the event. This should be followed by a full report within 7 calendar days.
- Local unexpected, life-threatening SAE that are related events should be reported as soon as possible but no later than 7 calendar days after the Principal Investigator is aware of the event. This should be followed by a full report within 8 additional calendar days.
- Local unexpected, not life-threatening SAE that are related events should be reported no later than 15 calendar days after the Principal Investigator is aware of the event.
- An increase in the rate of occurrence of Local expected SAE that are related events, which is judged to be clinically important, should be reported within 15 calendar days after the Principal Investigator is aware of the event.
- Local unexpected AE that are related events should be reported at least annually (together
with Study Status Report for annual review).

- Non-local unexpected SAE that are fatal or life threatening and related should be reported not later than 30 calendar days after the Principal Investigator is aware of the event.

7.3 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

All SAEs that are unexpected and related to the study drug will be reported to HSA. Please refer to the HSA website for more information on Safety Reporting Requirements for Clinical Trials.

The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-up information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

7.4 Safety Monitoring Plan

Any adverse effects will be reported. The PI and Co-investigators will monitor and report to the CIRB and HSA of any SAE. There will be no DSMB. Risks of study drug will be continually reassessed throughout the study period. Closed monitoring meetings with the research team will take place every 4 weeks to discuss the data collected from monitoring reports.

7.5 Complaint Handling

Contact information of the study team and SingHealth CIRB will be provided to all study participants and available in the participant informed consent sheet.

8 DATA ANALYSIS

8.1 Data Quality Assurance

Discrepancy and inconsistent data will be resolved by looking at the source document.
8.2 Data Entry and Storage

Data will be stored in paper form and electronically. Paper documents will be stored in under lock and key. All electronic data will be de-identified and password protected. Electronically entered data will be stored in the network drive of Singapore General Hospital. Source documents will be retained until at least 6-years after the end of the study.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

The effect of short-term treatment with fenofibrate to cause a shift in metabolic fuel oxidation in DN is unknown. Factoring a screen failure rate of 1 in 3, an enrolment target of 300 subjects will provide a statistical power of 80% and alpha of 0.05.

9.2 Statistical and Analytical Plans

For the primary outcome, baseline and post-treatment values will be compared using the paired Student’s t-test. If the data are not normally distributed, the appropriate transformation will be used or a non-parametric approach will be considered. Hypotheses testing will be non-directional (two sided), with values < 0.05 as significance. Software programs SPSS (version 21; SPSS, Chicago, IL) and GraphPad Prism (version 6, GraphPad Software) will be used for all statistical analysis. There will be no planned interim analyses.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

All study team member will undergo protocol training to ensure adherence with the protocol and for accuracy in relation to source documents.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, will be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents.
12.1 Informed Consent

Informed consent will be taken during Visit 1 at SGH CTRC. Consent will be taken by the investigators assigned by the PI. There will be a provision for a translator for non-English speaking subjects. Illiterate subjects have the option to have a family member/impartial witness present during the consent taking process. Vulnerable subjects will not be recruited for this study. In obtaining and documenting informed consent, the investigator will comply with the GCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

12.2 Confidentiality of Data and Patient Records

Confidentiality of study participants will be respected and all potential participants will be assigned a study ID. Data and samples collected from study participants will be de-identified.

13 PUBLICATIONS

Publication-related decisions will be in discussed among all investigators and collaborators but the final decision lies within the PI.

14 RETENTION OF TRIAL DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as CIRB records and other regulatory documentation will be retained by the P.I. in a secure storage facility. The storage will be in accordance with SingHealth CIRB guideline on Retention of Research Data and Records. The records will be accessible for inspection and copying by authorized authorities.

15 FUNDING and INSURANCE

NMRC Large Collaborative Grant (LCG16MAY001)

This study will be covered under the National Clinical Trial Insurance Policy
List of Attachments

Appendix 1  Blood Sampling Summary

<table>
<thead>
<tr>
<th></th>
<th>TOTAL VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ml)</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
</tr>
<tr>
<td>Visit 1</td>
<td>25</td>
</tr>
<tr>
<td>Visit 2</td>
<td>0</td>
</tr>
<tr>
<td>Visit 3</td>
<td>22</td>
</tr>
<tr>
<td>TOTAL</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urine</th>
<th>(ml)</th>
<th>(TBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Visit 2</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Visit 3</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>90</td>
<td>6.02</td>
</tr>
</tbody>
</table>

*Values are an approximate volume
TBS= tablespoon
Appendix 2  Investigational Product Information

Please refer to the document upload on iSHARE for more details on the IP.

TROLIP®
Capsule

Composition:
TROLIP® 100 mg
Each capsule contains:
Fenofibrate 100 mg

TROLIP® 300 mg
Each capsule contains:
Fenofibrate 300 mg

Pharmacology:
Fenofibrate is phenoxyisobutyric acid. With clofibrate and other fibrate acid derivatives is used as lipid regulator by reducing total plasma cholesterol and triglyceride in healthy subjects and patients with hyperlipoproteinemias. The main action of fenofibrate is to increase lipoprotein catabolism which is rich in triglyceride by increasing lipase lipoprotein activity.

Indications:
TROLIP® is indicated to treatment:
- Hypercholesterolemia (type IIa).
- Hypertriglyceridemia (type IV).
- Mixed hyperlipidemia (type III and IV).

Contraindications:
- Patients with severe liver and renal dysfunction.
- Pregnancy and lactation.
- Hypersensitivity to fenofibrate.
- Patients with gallbladder disease.

Dosage and administration:
Adults:
Initial dose: 100 mg 3 times a day or 300 mg/day as a single dose.
If after strict cholesterol diet the concentration of cholesterol stays at > 4 g/L, dose can be increased to 100 mg 4 times daily.
Initial dose should be maintained until cholesterol level gets back to normal. If cholesterol level is stabilized, dosage of 100 mg twice daily can be given provided that cholesterol level is checked every 3 months. If there is a new increase in the plasma cholesterol concentration, dose should go back to initial dose of 100 mg 3 times daily.

Children:
Over 10 years: maximum 5 mg/kg daily.

Side effects:
In general, side effects are mild and rarely reported. In prolonged therapy, the following side effects have been reported:
- Gastrointestinal disturbances about 5 %.
- Headache about 1 %.
- Muscular spasm about 1 %.
- Transient elevation of transaminases and creatin phosphokinase.
- Skin allergic reactions.
- Fatigue and vertigo.

Drug interactions:
The effect of oral anticoagulant is potentiated by fenofibrate. This increase the risk of hemorrhage through displacement of their binding with plasma protein. Therefore, initial dose therapy with fenofibrate should be reduced to 1/3 of the normal dose. Adjustment of oral anticoagulant dose according to prothrombin time during therapy by fenofibrate and 8 days after its interruption.

Warnings and precautions:
- For the first year of therapy, serum transaminase should be monitored periodically, every 3 months. Therapy should be discontinued if there is an increase in SGPT concentration > 100 unit/L.
- Combination therapy of hepatotoxic substances like pimecillin meleate or IMAO is not recommended.
- If 3 months after therapy, the reduction of serum concentration of lipid is not satisfactory, other therapeutic (complementary or different) should be considered.

Presentation:
TROLIP® 100 mg: Box 5 blisters @ 10 capsules.
TROLIP® 300 mg: Box 5 blisters @ 10 capsules.

Registration Number:
TROLIP® 100 mg: DKL9600018001B1; SIN10688P
TROLIP® 300 mg: DKL9600018001B1; SIN10688P

ON MEDICAL PRESCRIPTION ONLY
STORE IN A DRY PLACE, BELOW 30°C, PROTECT FROM LIGHT.

Manufactured by:
DexaPharma
JL. BAMBANG UTOYO 138
PALEMBANG – INDONESIA
67039-4