MONASH University

EXPLANATORY STATEMENT

(Relevant Participant Group)

Project: The Effects Tocotrienol-rich Vitamin E from Palm Oil (Tocovid) on Diabetes and Diabetes-Related Complications in the Kidneys (Nephropathy), Eyes (Retinopathy) and Nerves (Neuropathy).

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You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate in this research. If you would like further information regarding any aspect of this project, you are encouraged to contact the researchers via the phone numbers or email addresses listed above.

Why were you chosen for this research?

You are invited to participate in this research study because you have *type 2 diabetes mellitus with early nephropathy,* diabetes retinopathy (type of eye disease) and peripheral neuropathy (type of nerve disease) and we postulate that *supplementary tocotrienol*-rich vitamin E from palm oil (Tocovid) will be able to help prevent the progression of these diabetes microvascular complications such diabetic nephropathy, diabetic retinopathy and peripheral neuropathy.

Your contact details have been obtained from your existing records at the research centre.

What does the research involve?

The purpose of this study is to determine the benefits of tocotrienol (a form of Vitamin E) from palm oil in patients with Type 2 Diabetes Mellitus with early Diabetic Nephropathy (type of kidney disease caused by diabetes), diabetes retinopathy (type of eye disease caused by diabetes) and peripheral neuropathy (type of nerve disease caused by diabetes).

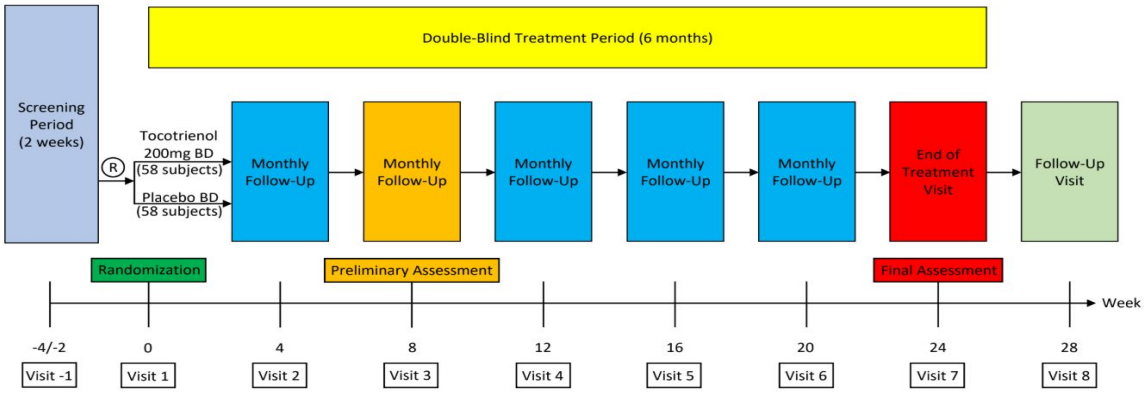
This research is necessary because diabetic nephropathy, retinopathy and neuropathy are common but essentially preventable complications of diabetes. If left untreated, diabetic nephropathy, retinopathy and neuropathy can lead to kidney failure, blindness and amputation, respectively which will greatly affect your health and quality of life. Tocotrienol-rich vitamin E has shown a great promise in our previous studies as an antioxidant capable of preventing the development and progression of diabetic-related complications. Hence, this study is important as it is the pioneer in identifying the benefits of tocotrienol-rich vitamin E in patients with early diabetic nephropathy retinopathy and neuropathy.

Currently, diabetic nephropathy are conventionally treated by encouraging a healthy lifestyle, optimizing blood pressure control if you have high blood pressure and reducing blood sugar to near-normal levels with oral anti-diabetic tablets and insulin. In addition, diabetic retinopathy is monitored annually using retinal camera and may require treatment such as photocoagulation (laser treatment) to stop retinal bleeds. Peripheral neuropathy is assessed by the presence or absence of sensation in your lower limbs (i.e. numbness, pain, ulcers etc) and is also treated by improving blood glucose and supplements (i.e. Vitamin B12). However, all these treatments may not be enough to prevent the progression of diabetic nephropathy, retinopathy and neuropathy. Therefore, addition of Tocotrienol-rich Vitamin E acts as a potent antioxidant to reduce certain harmful compounds which we believe are important causes of diabetic nephropathy, retinopathy and neuropathy. This will not affect or change your current treatment.

Timeline of Study

- Your participation will be a total of approximately 8 months.
- There will be 8 visits in total
- The Screening Visit, Visit 1, 3, 5 and 7 will take approximately 3.5 hours each.
- Visit 2, 4, 6 will take approximately 2 hours .
- Refer to the Diagram below to see an overview of the timeline of the study.

Diagram showing Timeline and Overview of Study



A total of 25ml of blood will be taken in the following visits: Screening visit, Visits 3, 5 and 7.

A total of 20ml of urine will be taken in all the visits (Screening Visit, visits 1 to 7).

An electrocardiogram (ECG) is a test which measures the electrical activity of your heart to show whether or not it is working normally. You will be asked to lie down and small electrode patches will be put on the skin of your chest, arms and legs. It is a non-invasive and painless procedure. This test will be done at Screening, Visits 3, 5, 7, and 8.

A nerve conduction study is a test which measures how fast or slow the nerve activity travels down your nerves. You will be asked to lie down on a bed and small electrode patches will be put on the skin of your leg. A small current will be conducted on the nerves in your leg to measure the electrical impulse travelling in the nerves of your leg. You might feel a small amount of discomfort (i.e. a small tingling sensation) when the current is being conducted in your nerves. The test will take approximately 15 to 20 minutes. This test will be done at Screening, Visits 3, and 7.

A fundal camera test is a test which views the back of your eye (retina) and allows the researcher to see if there are any bleeding in the retina. The pupils of your eyes will be dilated using an eyedrop. It might take 15-20 minutes for your pupils to be fully dilated. Once you are ready, you will be called to sit in a darkened room by the researcher. The researcher will take several views in order to get the best view of the retina. The test will take approximately 15-20 minutes. This test will be done at Screening, Visits 3, and 7.

During the randomisation, we will divide you 1:1 into either the active group (tocotrienol-rich Vitamin E from palm oil) or the control group (inactive drug or placebo containing cooking palm oil). The randomisation is done manually according to your age, gender and duration of diabetes. The drugs will be labelled as “study drug A” or “study drug B”. Both drugs will look similar and the identity will not be known by the investigator or the patient until the end of the study.

What You Should Do Before Coming for Each Visit

Before coming all the visits, you are required to:

✓ Fast for at least 8 hours (only plain water allowed)

✓ Medication

- DO NOT take morning dose of anti-diabetic medication (as you will be fasting)
- Take usual dose antihypertensive and other medications
- Bring study drug
- Bring all new medications and supplements

✓ Laboratory/Diagnostic Test Results

- Bring all investigative test results for review

✓ Inform us if you are having your period so that we can arrange for another suitable appointment [females only]

✓ Inform us if you are unable to come for the appointment date so that we can arrange for another suitable appointment

Additionally, before coming for the Screening Visit, Visit 1, Visit 3, Visit 5, Visit 7, you are required to:

✓ Avoid strenuous activity the night before

Risks of withholding Morning Dose of Anti-Diabetic Medication

You may experience signs and symptoms of low blood sugar such as fatigue, shakiness, sweating and dizziness if you withhold your morning dose of anti-diabetic medication. In order to address this, once your blood samples are taken, including fasting blood sugar, you will be given a complimentary Hot Beverage (hot chocolate, tea or coffee) and some biscuits. Then, you will be allowed to take the morning dose of your anti-diabetic medication.

Depending on the severity of your symptoms, you may have to consume a sugary drink or snack immediately. Subsequently, your blood glucose levels will be monitored until it is optimised. If you cannot tolerate orally, we will administer a medication through your veins. If your condition deteriorates, you will be referred to the nearest hospital for additional treatment.

Source of funding

This study is sponsored by Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia *and Fundamental Research Grant Scheme (FRGS) from the Ministry of Higher Education (MOHE), Malaysia.* The study drugs are donated by *Hovid-Integrated Global Pharmaceutical Partner Berhad*.

There is no conflict(s) of interest or any competing interest(s) with the sponsor or among the study team members.

Consenting to participate in the project and withdrawing from the research

The details of the research trial are described in this document. It is important that you understand why the research is being done and what it will involve. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign two informed consent forms; one is for you to keep and the other must be returned to the investigator.

Your participation in this study is voluntary. You do not have to be in this study if you do not want to. You may withdraw from it at any time. You may also refuse to answer any questions that you do not wish to answer. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

If you withdraw from the study, any data collected from you up to your withdrawal will still be used for the study and you will be asked to attend one last follow-up visit (discontinuation visit) to ensure that you are healthy. During this visit, the investigating team will take your history, perform a physical examination and conduct several safety tests.

Participants who require counselling services will be referred directly for consultation to the chief investigator, Professor Khalid Abdul Kadir. If necessary, he will arrange for referral to counsellors or psychologists at the appropriate facilities.

Possible benefits and risks to participants

Tocotrienol is postulated to prevent the development and/or progression of complications arising from diabetes, including nephropathy, retinopathy and neuropathy. There may or may not be any benefits to you. Nevertheless, the information obtained from this study will help to improve the treatment or management of other patients with the same disease or condition.

There are no known side effects of Tocovid (active drug) or inactive drug (placebo containing cooking palm oil). According to the Drug Control Authority of Malaysia, Tocovid is approved as a health supplement safe for consumption. Nevertheless, you will be monitored for any side effects during the monthly follow-ups. If you have any concerns, you can contact the investigators either personally, by phone call or e-mail. If a side effect occurs, the investigator may choose to withdraw you from the clinical trial based on his/her discretion. Participants who are withdrawn will be followed up with a discontinuation visit as mentioned previously. The duration of follow-up of adverse event will be based on the investigator and study team's discretion.

The effect of the study product on an unborn child is not known. Female participants should not breastfeed her baby while in the study as the study product may be present in the breast milk. You should also avoid becoming pregnant or fathering a child while in this study. Women of childbearing age will be given a pregnancy test to confirm they are not pregnant. It is important that you use highly effective birth control methods consistently and correctly; the study doctor will discuss these methods with you. Notify your study doctor immediately if you think that you or your partner has become pregnant during the study. If you or your partner is pregnant, the study

therapy will be discontinued immediately and you will be removed from the study. However, we would like to follow your pregnancy until term to ensure the health of you and your newborn baby.

During randomization, your study subject number will be used to identify you instead of your name, therefore there is very minimal risk of disclosure of your personal information to the public. We will also inform you in a timely manner about any new findings or changes about the study product which may affect your health or willingness to continue in this study. Where necessary, you may be asked to re-consent to participate.

Research involving diagnostic testing or possible incidental findings

We will usually ask our participants if they wished to be informed of (i) any diagnostic findings, (ii) incidental findings, and/or (iii) only those adverse findings that would usually lead directly to treatment. You will also be asked whether you would like any these findings to be discussed by your family doctor, another doctor of your choice, or by a member of the research team.

If you have consented to any of the above, the research team will inform you accordingly throughout the trial. You will however, not be informed if you are taking the active drug or inactive drug as it will affect the results of the study.

Payment

You will be reimbursed RM*30* per visit for your travel expenses to our Clinical Research Centre, even if you choose to undertake only part of the requirements or withdraw from the research early.

Confidentiality

The nature of this clinical trial requires personal information to be collected from you through history-taking, physical examination and tests. However, only information pertaining to your eligibility for recruitment will be obtained. Once recruited, you will only be identified by a study subject number that has no relation to your personal information or personal identifiers. Each subject number is unique and accessible only by investigators. The master list which contains your particulars will only be made accessible to the Chief Investigator. Data collection on data sheets and subsequent analysis will utilize only your subject number. The master list of study subjects will be destroyed once findings for this study are published.

All your information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, your identity will not be revealed without your expressed consent. Investigators of this study, qualified monitors or auditors, study sponsor or its affiliates and governmental or regulatory authorities may inspect and copy your medical records, where appropriate and necessary.

Data from the study will be archived and may be transmitted outside the country for the purpose of analysis, but your identity will not be revealed at any time.

Storage of data

Data gathered for this study will be stored in a file kept in a locked cabinet in a locked room. Upon completion of the study, all data will be stored and handled by Monash University Malaysia for a minimum of 15 years after the study has ended.

The blood serum taken from you will be used to identify biomarkers for diabetic nephropathy, retinopathy, and neuropathy. A few millilitres of your serum samples will be kept for 2 years for future testing of other biomarkers once funds are available. No genetic testing will be conducted on your biospecimen. Your biospecimen will be coded and any information that can identify you will be removed. Only your study doctor and study staff will be able to link the code with you. The sponsor may share your biospecimen with other researchers but your identity will remain confidential. You can withdraw your consent and your biospecimen will be destroyed but any information previously obtained from your biospecimen can be used for this research study.

Use of data for other purposes

Data gathered for this study will not be used for any future study without prior approval from relevant regulatory bodies and/or ethical committee(s). Please be assured that only aggregate de-identified data may be used for other projects where ethics approval has been granted.

Results

The results of the trial will be made available by the end of this year. If you wish to access your test results during the study, you may contact your study doctor or the investigating team by phone, email or at the Clinical Research Centre.

Complaints

Should you have any concerns or complaints about the conduct of the project, you are welcome to contact the Coordinator of Bachelor of Medical Science(Hons), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia.

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Thank you,

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