

ADULT INFORMATION SHEET

Evaluating the biological activity of a single dose of encapsulated oral semaglutide or tirzepatide in healthy adults over a period of one week

Why are we doing the study?

Rybelsus and tirzepatide are medications used in Type 2 diabetes management and can also help with weight loss. We want to see how a single dose of Rybelsus (encapsulated oral semaglutide) or tirzepatide in a capsule/tablet form will affect blood glucose and insulin responses when a person who is healthy is subjected to an intravenous glucose tolerance test (IVGTT). This is an investigator-led study and sponsored by The Kids Research Institute Australia (The Kids). It will be conducted at the Nedlands Clinical Trial Centre (Linear B Block facility) with the study medication being provided by Diabetology Limited. This study is a novel trial investigating encapsulated oral semaglutide, as Rybelsus, and oral tirzepatide. In a previous study, encapsulated oral encapsulated semaglutide was tolerated without adverse effects.

Why are we asking you?

We are asking you to take part in this study because we need to test it in people without diabetes first, and you are a healthy adult aged between 18-60 years old.

You can participate in this study if you:

- Are healthy with no medical conditions.
- Are a female and have a negative serum pregnancy test (blood test) at screening and will practice effective birth control during the study period.
- Are male and agree to practice effective contraceptive methods during the course of the study.
- Are willing to comply with all study investigations.

However, you cannot participate in this study if at the screening visit, we find out that you:

- Are a female who is pregnant or breastfeeding or plan to breastfeed during the course of the study.
- Are involved in a weight loss program and are not in the maintenance phase
- Have started on weight loss medication within 3 months prior to screening.
- Have had or plan to have bariatric surgery during the course of the study.
- Have a history of gastrointestinal disorders or delayed gastric emptying
- Have a history of pancreatitis.
- Have a history of cardiac disease.
- Have abnormal liver function, thyroid function and lipid profile.
- Evidence of infectious diseases.
- Have a history of a tumor or cancer within the past 5 years.
- Are using recreational or illicit drugs or have had a recent history (within 1 year of screening)
- Have a drug or alcohol abuse or dependence. (Alcohol abuse includes heavy alcohol intake >3 drinks per day or >14 drinks per week or binge drinking).
- Are using cannabinoid products during the 1 week prior to each visit.

- Are enrolled in another clinical trial involving an investigational product within 30 days of the screening visit.
- Have any condition or other factor (at the Investigator's discretion) that makes you unsuitable for enrolment into the study.

Who is carrying out the study?

The study is being carried out by **Professor Timothy Jones** and the research team of the Children's Diabetes Centre, The Kids.

What will the study tell us?

This study will tell us how one dose of encapsulated oral semaglutide or tirzepatide will affect blood glucose response and insulin response, during an intravenous glucose tolerance test (IVGTT), over 7 days, as compared to before taking the study medication.

Do you have to take part?

No, you do not have to take part in this study. Participation in this study is entirely voluntary. You may withdraw from the study at any time by contacting any member of the research team and signing the withdrawal of consent form at the end of this document.

What will you be asked to do if you decide to take part in this study?

If you take part in this study, you will need to attend **Nedlands Clinical Trial Centre (Linear B Block Facility)** on six separate occasions. You will be paid for your time, travel, parking and meal with \$170 (\$150 reimbursement and \$20 for meal) for the screening visit and for each of the 5 IVGTT sessions.

What happens at each study visit and how long each visit takes is outlined in the study schedule below:

Visit Sequence	Visit Duration	Visit assessments/investigations
VISIT 1 (within 14 days before Visit 2) SCREENING	Approx 2h	THIS IS A FASTING VISIT. Please fast for 8h for this screening visit, but you can have water to drink. At this visit: • We will confirm that you understand what the study involves. • We will take your medical history to ensure that you meet the inclusion criteria and do not meet the exclusion criteria. • We will then have you sign the Informed Consent. • We will measure your height, weight, and vital signs. • If you are a female, we will ask you when your last menstrual period was. We will also do a serum pregnancy test as a study requirement. • We will take 8mL of blood for investigating your lipid profile, liver function, thyroid function, HbA1c and c-peptide. • We will provide you with two data logs to collect information about any adverse events/illnesses you may have until the next visit, and any medication that you might take. • We will provide you with EMLA (numbing cream) for use before each of the following visits, if you require it. • We will also advise all females to practice effective contraception from this visit to the last visit



Visit Sequence	Visit Duration	Visit assessments/investigations
VISIT 2 (Day -2)	Approx 3.5h	THIS IS A FASTING VISIT. Please fast for 10h for this visit, but you can have water to drink during this time. During this time, you are to avoid cigarettes, alcohol, caffeine, and vigorous exercise. This visit will happen at approximately 8am. On arrival we will measure your vital signs, and ask you details of any adverse events (eg: headaches, nausea) and of any drugs you may have taken for these adverse events. And if it is OK to proceed with the study procedures, we will give you the placebo capsule with 100ml water (Time 0). After which we will insert an IV cannula in one of your arms for the IVGTT testing. This involves administering a set amount of intravenous glucose, through the drip in your arm, to see how your body responds to the glucose. <i>*You are having a placebo today, so that we can see how your body responds to the IVGTT, when you only swallow the capsule without the study drug.</i> <u>IVGTT:</u> - The IVGTT will be done 2h after having taken the placebo capsule. The IVGTT takes 1h and involves the collection of 2 mL of blood (each for BGL and Insulin testing) at the following time points: -5, 0, 5, 15, 25, 35, 45, and 60 min post-administration of the IV glucose via the cannula. The total blood volume collected during this meal challenge is 32mL. - Once the IVGTT is completed you will have a meal before you are discharged.
VISIT 3 (Day 0)	Approx 3.5h	THIS IS A FASTING VISIT. Please fast for 10h for this visit, but you can have water to drink during this time. During this time, you are to avoid cigarettes, alcohol, caffeine, and vigorous exercise. This visit will happen at approximately 8am. On arrival we will measure your vital signs, and ask you details of any adverse events (eg: headaches, nausea) and of any drugs you may have taken for these adverse events. If you are a female, we will do a urine pregnancy test, and we will proceed with the visit only if it is negative. And if it is OK to proceed with the visit procedures, we will give you the study medication with 100ml water (Time 0). We will then insert an IV cannula in one of your arms for the IVGTT testing. This involves administering a set amount of intravenous glucose, through the drip in your arm, to see how your body responds to the glucose. <u>IVGTT:</u> - The IVGTT will happen at the same time or approximately the same time each day. The IVGTT takes 1h and involves the collection of 2 mL of blood (each for BGL and Insulin testing) at the following time points: -5, 0, 5, 15, 25, 35, 45, and 60 min post-administration of the IV glucose via the cannula. The total blood volume collected during this meal challenge is 32mL. - Once the IVGTT is completed, you will have a meal before you are discharged.

Visit Sequence	Visit Duration	Visit assessments/investigations
VISIT 4 (Day 1) VISIT 5 (Day 4) Visit 6 (day 6)	Approx 3.5h	THESE ARE FASTING VISITS. Please fast for 10h for these visits, but you can have water to drink during this time. During this time, you are to avoid cigarettes, alcohol, caffeine, and vigorous exercise. These visits will happen at approximately 8am. On arrival we will measure your vital signs, and ask you details of any adverse events (eg: headaches, nausea) and of any drugs you may have taken for these adverse events. And if it is OK to proceed with the IVGTT, we will insert an IV cannula in one of your arms for the IVGTT testing. This involves administering a set amount of intravenous glucose, through the drip in your arm, to see how your body responds to the glucose. <u>IVGTT:</u> - The IVGTT will happen at the same time or approximately the same time each day. The IVGTT takes 1h and involves the collection of 2 mL of blood (each for BGL and Insulin testing) at the following time points: -5, 0, 5, 15, 25, 35, 45, and 60 min post-administration of the IV glucose via the cannula. The total blood volume collected during this meal challenge is 32mL. - Once the IVGTT is completed you will have a meal before you are discharged.

Is there likely to be a benefit to me?

There is likely no benefit to you. However, should we find any abnormal results from the blood tests the investigator will discuss these results with you, and email a discharge summary with your test results to your general practitioner. Your GP can then act on these results as needed.

Is there likely to be a benefit to other people in the future?

The findings of this pilot study may add to the research data regarding improved type 2 diabetes management, with regards to treatment mimicking natural physiology and with less side-effects.

What are the possible risks and/or side effects?

Encapsulation is commonly used to deliver drugs. Tirzepatide in injectable form is approved for type 2 diabetes management and obesity. Further, semaglutide in injectable and tablet form is approved and used for type 2 diabetes management. Therefore, the risks from taking these medications in their encapsulated form are not considered high.

You may feel nauseous or have diarrhoea with the study drug. Should this happen, we will prescribe you with appropriate medication to relieve the symptoms.

There is small risk of bruising, bleeding or skin reaction at the insertion of the cannula for the intravenous glucose testing and the blood test at the screening visit. We will reduce this risk by appropriate location of the cannula insertion site, and following hospital guidelines for insertion of the cannula.

Some people feel faint with cannulation, so we will do the cannulation while you are lying on a bed.

What are the possible discomforts and/or inconveniences?

Some people may find the phlebotomy and cannulation uncomfortable. To minimise the discomfort, we can provide you with a tube of numbing cream and show you how to use it, before coming in for the IVGTT visits.

Where is our information kept?

All paper records will be stored in locked cabinets in The Kids office space on Level 6W of Perth Children's Hospital. Electronic data will be stored on a password protected network drive at The Kids, and an electronic study folder in a limited-access secure WA Health server. Once tested, all biological samples will be destroyed, once the results have been checked and any verification required is performed. De-identified data, that is data without your name or any personal details attached, will be sent to Diabetology Limited for their internal analysis. This data may be used in future studies for analysis and comparisons.

If you do not wish for your de-identified data to be sent to Diabetology Limited, please let the study team know prior to your first IVGTT visit. This data will still be used by The Kids for data analysis but will not be shared with Diabetology Limited.

Your data will be stored for 15 years after the grouped results are published; after which it will be destroyed as per The Kids research data management policies.

What about your privacy?

Your personal data will only be identified by a unique code, and only the investigators and the research team specific to the study will be able to link your results to you. Publications and presentations about the results of this study will not identify anyone by name. We will inform you of the results and publication via email.

However, we will inform your general practitioner (GP) that you are participating in the study. We will also inform them of any abnormal results from the blood tests, so that they can provide you with the necessary management or care.

Who has approved the study?

The WA Health Central Human Research Ethics Committee have approved this study (Reference number (PRN): RGS00000008128). This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2023) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Reviewing HREC name:	WA Health Human Research Ethics Committee
HREC Executive Officer:	Central Office of Research Ethics (CORE) Ethics Officer
Telephone:	(08) 9222 4214
Email:	HREC@health.wa.gov.au

Who to contact for more information about this study:

If you would like any more information about this study, please contact:

Name:	Diabetes Research Team
Telephone:	(08) 6456 8976
Email:	Diabetes.Research@health.wa.gov.au

Who to contact if you have any concerns about the organisation or running of the study?

If you have any concerns or complaints regarding this study, you can contact the following:

Complaints contact name:	The Kids Research Institute Australia Governance Office - Manager Human Research and Integrity
Email:	ResearchGovernance@thekids.org.au

Your concerns will be drawn to the attention of the Ethics Committee who is monitoring the study.

What to do next if you would like to take part in this research:

If you satisfy the inclusion and exclusion criteria listed in this information sheet and you would like to take part in this study, please contact Peter on (08) 6456 8976, to make an appointment for the screening visit. You will sign the consent form for participation in this study when you attend this appointment.

THANK YOU FOR READING THIS INFORMATION SHEET