WA HEALTH RESEARCH PROTOCOL

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

Version No: 3.0

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1 Trial Details

Protocol/Clinical Trial Title:	Evaluating the biological activity of a single dose of encapsulated oral semaglutide in healthy adults over a period of one week.		
Protocol Number (Version and Date):	V3.0 (26 Jun 2024)		
Amendment (Number and Date):	..		
Trial Start Date:	08 Jul 2024	**Trial Finish Date:**	31 Jul 2025
Coordinating Principal Investigator Name:	Prof TW Jones		
Coordinating Principal Investigator Contact Details:	Tim.jones@health.wa.gov.au		
Sponsor Name (if applicable):	N/A		
Laboratory Name (if applicable):	N/A		

Trial Summary

Semaglutide is a long-acting GLP-1 analogue used in the treatment of patients with type 2 diabetes (T2D) has shown to improve glycaemic control and result in meaningful weight loss. The drug has a well described safety profile including a low risk of hypoglycaemia.

This short duration pilot study will evaluate the biological activity of a single dose of 4mg of oral Semaglutide in Diabetology's Axcess formulation. Eight healthy volunteers will receive 4mg of the encapsulated semaglutide on an empty stomach with a glass of 100ml of water, on Day 0. They would also have received a placebo 2 days prior to this. Both the placebo and the semaglutide will be administered on the same day, in a fasting state. An intravenous glucose tolerance test (IVGTT) will be conducted two hours after placebo and treatment, before any food is consumed. The IVGTT will also be performed at approximately the same time on days 1, 4 and 6 post-treatment.

The primary aim of the study is to determine whether, compared to a placebo, orally delivered encapsulated semaglutide is associated with a difference in plasma blood glucose levels during an intravenous glucose tolerance test (IVGTT). The secondary aims are to 1) explore changes in plasma insulin during an IVGTT, and 2) to explore the duration of action over a span of 7 days.

2 Rationale / Background

Background summary

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown themselves to be effective agents for the treatment of Type 2 diabetes mellitus, leading to the reduction of blood glucose levels and a reduction in body weight[1-4]. GLP-1 itself can stimulate insulin release from the pancreas, and can synergise with insulin, upregulating insulin receptors in various tissues in the body. It can influence satiety, reducing appetite and food intake. GLP-1 is secreted by L cells in the intestine in response to ingestion of food and interacts with receptors in the gut and portal vein (vagal afferents) which send messages to the CNS. GLP-1 can also activate hepatocytes, and can bring about changes in the liver, although the receptor involved in this activity has not been identified. There are also receptors for GLP-1 in the pancreas and the brain, although it is not clear, in the healthy individual, whether or not the GLP-1 required by these receptors is satisfied by local production, rather than systemic supply from the intestine. GLP-1 secreted by the intestine is broken down very rapidly by the enzyme DPP-4 in the bloodstream, resulting in a very short half-life for GLP-1 of less than 5 minutes in humans. Consequently, elevated levels of GLP-1 tend to be transient in the systemic circulation.

In contrast to insulin, it is not clear whether Type 2 diabetes is associated with deficiency of GLP-1, but it is certain that supplementation with additional GLP-1 has a strong impact in patients with Type 2 diabetes. Unfortunately, the modes of administration of GLP-1 RAs for therapeutic purposes introduce the peptide into the body in a very non-physiological fashion. Treatment with GLP-1 RAs such as liraglutide or semaglutide, with half-lives of hours or days when administered by injection, results in high prolonged levels in the bloodstream, and little or no peptide interaction with the intestinal

receptors. Probably related to this is the fact that significant side effects are seen with the current treatments, which are not associated with endogenous GLP-1 secreted by the gut. In particular, GLP-1 RA treatment is accompanied by nausea in up to 30% of patients, sometimes for long periods of time, resulting in significant numbers of patients withdrawing from the treatment. In addition, a serious side-effect of semaglutide (whose half-life is extended as a result of linkage to a long lipid chain) is initiation or exacerbation of diabetic retinopathy in approximately 10% of patients, and which is classified as a severe adverse effect. Those side effects are seen even with Rybelsus (oral semaglutide) where the peptide is transported into the body across the stomach wall, thus missing out on interaction with the receptors in the intestine.

In contrast, the formulation pioneered by Diabetology is one which transports the peptide across the intestinal cell wall, mimicking natural physiology. In preclinical studies, presence of semaglutide in the portal vein has been demonstrated, indicating that it crosses the gut, and can interact with portal vein receptors. At the same time, evidence was gathered of a pharmacodynamic effects (change in glucose and insulin levels).

It is believed that the lipid chain associated with semaglutide helps the molecule to remain in the intestinal tissue, prolonging time of contact between the peptide and GLP-1 receptors in the vagal afferents. In addition, only low levels of semaglutide will appear in the bloodstream, reducing the possibility of occurrence of side-effects such as nausea and diarrhoea commonly observed with semaglutide administered by other approaches.

Animal studies have shown that encapsulated Semaglutide can exert a significant change in markers of efficacy, namely change in blood glucose levels, and stimulation of insulin secretion (see Figs 1-2). The primary aim of the study is to determine whether, compared to a placebo, orally delivered encapsulated semaglutide is associated with a difference in plasma blood glucose levels during an intravenous glucose tolerance test (IVGTT)[5]. The secondary aims are to 1) explore changes in plasma insulin during an IVGTT, and 2) to explore the duration of action over a span of 7 days.

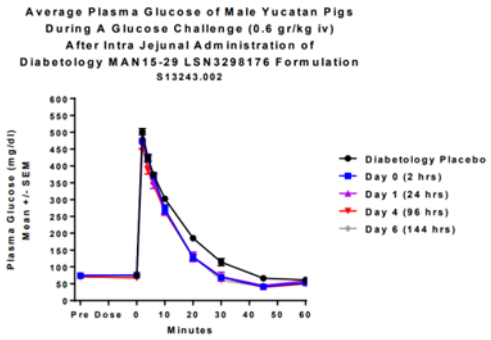

Figure 1: Plasma Glucose Response during IVGTT

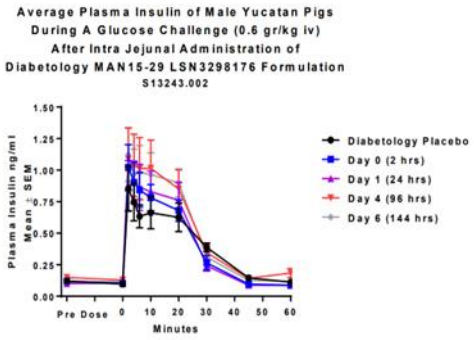

Figure 1: Plasma Insulin Response during IVGTT

Intervention

- Encapsulated Oral Semaglutide (Oral Semaglutide in Diabetology's Axcess formulation)

3 Trial Aims / Objectives / Hypotheses

Aim

The primary aim of the study is to determine whether, compared to a placebo, orally delivered encapsulated semaglutide is associated with a difference in plasma blood glucose levels during an intravenous glucose tolerance test (IVGTT). The secondary aims are to 1) explore changes in plasma insulin during an IVGTT, and 2) to explore the duration of action over a span of 7 days (Day 0 – Day 6).

Primary objective

The primary objective is to determine whether, compared to a placebo, a single dose of orally delivered encapsulated semaglutide (4mg) is associated with a difference in glucose area under the

curve (BGL-AUC0-60) during an intravenous glucose tolerance test conducted two hours after drug delivery.

Secondary objectives

1. To explore whether, compared to a placebo, a single dose of orally delivered encapsulated semaglutide (4mg) is associated with a difference in insulin area under the curve during an intravenous glucose tolerance test conducted one hour after drug delivery.
2. To examine the same markers on the third and sixth day after drug delivery to explore the pattern in duration of action.

Hypothesis

Encapsulated oral semaglutide will cause a reduction in blood glucose levels and stimulate insulin secretion.

4 Trial Design

The scientific integrity of the trial and the credibility of the trial data depend substantially on the trial design and methodology.

Study Endpoints

Primary Endpoint:

The primary endpoint of the study will be glucose area under the curve as assessed over a one-hour intravenous glucose tolerance test (BGL-AUC0-60). BGL-AUC0-60 will be calculated using plasma blood glucose levels collected at the following time points (0, 5, 15, 25, 35, 45, 60 min) using the trapezoidal method. BGL-AUC0-60 will be measured in the placebo condition (Day -2), on the day of ingesting encapsulated semaglutide (Day 0), and on the first, fourth and sixth-day following ingestion (Day 1, Day 4, and Day 6).

The primary comparison of interest will be between Day 0 (encapsulated semaglutide) and Day -2 (Placebo). Secondary exploratory analysis comparing Day -2 to Day 1, Day 4 and Day 6 will be conducted.

Secondary Endpoint:

The secondary endpoint of the study will be insulin area under the curve as assessed over a one-hour intravenous glucose tolerance test (Ins-AUC0-60). This will be calculated using the trapezoidal method based on plasma insulin measured at the same time points listed above for the primary outcome. Baseline (Day -2) will be compared to Day 0, Day 1, Day 4 and Day 6.

Study Design

This will be a single-arm, open label, pharmacodynamic study conducted under controlled conditions in a clinical research setting. All participants will receive the placebo on Day -2, and a once-off treatment on Day 0.

Eligible participants will be consented to the study and screened within 2 weeks prior to receiving the placebo. The treatment with 4mg encapsulated oral semaglutide will be conducted on Day 0. All participants will attend an intravenous glucose tolerance test (IVGTT), conducted by an experienced clinical research nurse, on Day -2, Day 0, and Days 1, 4 & 6. A history of treatment emergent and other adverse events, and concomitant medicines will also be ascertained at each visit.

Description of Treatment:

All eight healthy volunteers receive a placebo only (excipients i.e. formulation ingredients only, but no semaglutide) and single dose of 4mg of Semaglutide in Diabetology's Axcess formulation; administered by mouth on an empty stomach with a glass of 100ml of water. The placebo will be administered on Day -2 and the treatment will be administered at the same time on day 0; by mouth with 100ml water. An intravenous glucose tolerance test (IVGTT) will be conducted two hours after placebo and treatment, before any food is consumed. The IVGTT will also be performed at approximately the same time on days 1, 4 and 6 post-treatment.

Study Procedures:

- Screening Visit: within 2 weeks of placebo
    - 8mls bloods to confirm exclusion criteria are not met
    - Medical History Assessment (Screening Visit to confirm eligibility)
    - Eligible participants will be informed that their General Practitioner's will be notified of their enrollment in the study
- IVGTT: An intravenous glucose tolerance test is performed in the morning of Days -2, 0,1, 4 and 6, with the participant having fasted for 10h, except for water. During this time, they are also to abstain from cigarettes, alcohol, caffeine, and vigorous exercise.

  The IVGTT testing[5] involves an intravenous administration of 0.5g/kg of intravenous glucose (50% sterile solution); to a maximum dose of 35g. Blood samples (32mls of blood) for serum total insulin and plasma glucose levels are collected at 5min and 0min pre-glucose IV administration, and 5, 15, 25, 35, 45, and 60 min post-glucose IV administration. The IV glucose is administered over 3mins.

- Questionnaire: Subjects will be provided with a questionnaire on Day-2 to be used for recording any potential study-related effects (eg: nausea, vomiting, diarrhoea, headache, vision irregularities, hunger, loss of appetite). The clinician will review this record at each subsequent visit to determine whether any of these signs are treatment related or not.

Bias

N/A. All eight participants in this pilot study will receive the same treatment in this pilot study.

Blinding and Randomisation

N/A.

Device Tracking

N/A

Intervention/Product Description

- Encapsulated Oral Semaglutide (a glucagon-like peptide-1 receptor agonist) - 4mg of Semaglutide in Diabetology's Axcess formulation.

Product Accountability Procedures

N/A. All participants will receive the placebo and treatment on site. These will be dispensed by the clinical trial pharmacy.

Trial Duration/Schedule

The study will be run over nine days, excluding the screening visit which will be done within 2 weeks prior to the 1st IVGTT testing**.** The schedule of testing is tabled as follows:.

SCHEMATIC OF STUDY PROCESSES:

Day	Screening (≤14 days from Day-1)	Day -2	Day 0	Day 1	Day 4	Day 6
Blood Tests	✓					
Medical History	✓					✓
Urine Pregnancy Test (females)			✓			
Serum pregnancy Test (females)	✓					
Informed Consent	✓					
Placebo Administered		✓				
Study Medication Administered			✓			
Adverse Events	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓	✓	✓		✓	✓
IVGTT		✓	✓	✓	✓	✓

Trial Termination

Criteria for the termination of the trial. Description of the discontinuation criteria for individual participants, parts of the trial and entire trial.

Data identification

Every participant will be given a unique study number. This unique identifier will be used to identify both the participant's data (CRFs – case report forms) and their blood samples. A separate password-protected excel log will link the participant to their unique identifier, in the event that we need to contact them and/or their physician regarding abnormal results.

5 Source and Selection of Participants

Source of Participants

Healthy adults, both male and female, aged 18-60y old will be recruited from the general population using social media.

Participant inclusion criteria.

- Adequate renal function defined as a GFR ≥ 30 mL/min/1.73m^2.
- Female patients of childbearing potential must have a negative serum pregnancy test at screening and practice effective birth control for the duration of the trial.
- Male patients must agree to practice effective contraceptive methods during the course of the study.
- Are able and willing to sign an informed consent to participate in the study.
- Able and willing to adhere to the study requirements, specifically: follow the study visit and assessment schedules, take the study medications as indicated.

Participant exclusion criteria.

- Type 1 diabetes
- Type 2 diabetes
- Diabetes attributable to other secondary causes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).
- Treatment involving GLP-1 receptor agonists within 3 months prior to Visit 1.
- Have a history of acute or chronic pancreatitis.
- Have a known clinically significant gastric emptying abnormality (*e.g.*, severe diabetic gastroparesis or gastric outlet obstruction).
- Have undergone or plan to have bariatric surgery during the course of the study.
- Have uncontrolled hypertension defined as SBP/DBP ≥ 160/100 mmHg.
- Have a history of cardiac disease.
- Have an estimated GFR < 30 mL/min/1.73m^2
- Any condition that is currently being treated or may be treated with systemic corticosteroids or biologics during the course of the study; topical, intra-nasal and inhaled corticosteroids are allowed.
- Any current or history of any condition that may affect the patient's participation in the study.
- Any current or history of any condition that in the opinion of the investigator participation in the study may increase the risk to the patient.
- Female patients that are pregnant or are breastfeeding or plan to breastfeed during the course of the study.
- Laboratory abnormalities at screening including:
    - C-peptide < 0.4 ng/mL
    - Abnormal serum thyrotropin (TSH) levels below the lower limit of normal or >1.5X the upper limit of normal; a single repeat test is allowable.
    - Elevated liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) >3X the upper limit of normal; a single repeat test is allowable.
    - Very high fasting triglyceride levels (>600 mg/dL); a single repeat test is allowable.
- Any relevant abnormality that would interfere with the study assessments.
- History of or current active liver disease (other than non-alcoholic hepatic steatosis), primary biliary cirrhosis, or active symptomatic gallbladder disease.
- Positive results for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus ribonucleic acid (RNA).
- Active or history of neoplastic disease (except for adequately treated non-invasive basal cell and/or squamous cell carcinoma or carcinoma in situ of the cervix) within the past 5 years prior to Baseline.
- Use of the following medications:
    - Thyroid preparations or thyroxine (except in subjects on stable replacement therapy) within 6 weeks prior to screening.
    - systemic (oral, intravenous, intramuscular) glucocorticoid therapy (in the last 12 months) or may require them for more than 2 weeks during the study period. Intra-articular and/or topical corticosteroids are not considered systemic.
    - Any medications known to modify glucose metabolism or to decrease the ability to recover from hypoglycemia such as oral, parenteral, and immunosuppressive or immunomodulating agents. Inhaled nasal steroids are permissible.
- Involvement in a weight loss program and is not in the maintenance phase, or subject has started weight loss medication (e.g., orlistat or liraglutide) within 3 months prior to screening.

- Subject is a user of recreational or illicit drugs or has had a recent history (within 1 year of screening) of drug or alcohol abuse or dependence. (Note: Alcohol abuse includes heavy alcohol intake as defined by >3 drinks per day or >14 drinks per week or binge drinking) at screening. Occasional intermittent use of cannabinoid products will be allowed provided that no cannabinoid products have been used during the 1 week prior to each visit.
- A history of gastrointestinal disorders (e.g., hypochlorhydria) or gastroparesis with the potential to interfere with drug absorption.
- Any condition or other factor (at the Investigator's discretion) that is deemed unsuitable for subject enrolment into the study.
- Enrolled in another clinical trial involving an investigational product within 30 days of the screening visit.
- Is not able to understand and sign the informed consent of the study.

Participant withdrawal criteria

Participants can withdraw at any time from the study, without having to provide a reason for doing so. Those who withdraw from the study after commencing on oral semaglutide, will be followed-up for adverse events and concomitant medications for the full week after taking the semaglutide. Should any treatment-emergent adverse events be reported, this will also be included in the DSMB report. Participants who withdraw from the study will need to be replaced, as the study is powered for a sample size of 8 with completed data.
All data and biological samples belonging to the participant will be destroyed as per PCH data management policies.

6 Treatment of Participants

Description and justification for treatments, interventions or methods to be utilised

- Product: Encapsulated Oral Semaglutide (a glucagon-like peptide-1 receptor agonist) - 4mg of Semaglutide in Diabetology's Axcess formulation.
- Dosing Schedule and Route:
  - The placebo is administered orally two days before the IP on Day minus 2
  - The IP is administered orally on Day 0 only.
- Participants will be followed up for one week following treatment administration

This pilot study will test the efficacy of encapsulated oral semaglutide. This will then determine if there is basis for testing the superiority of this formulation against current formulations, with regards to both glucose modulation and weight loss in participants with Type 2 Diabetes.

Permitted medications/treatments

Oral hypoglycaemics, steroids and weight loss medication are not permitted.

Monitoring of participant compliance

N/A as both placebo and semaglutide will be administered on-site.

7 Assessment of Efficacy

Outcomes

The primary objective is to determine whether, compared to a placebo, a single dose of orally delivered encapsulated semaglutide (4mg) is associated with a difference in glucose area under the curve during an intravenous glucose tolerance test conducted one hour after drug delivery.

The outcome measures are:

1. Plasma Blood Glucose Levels will be measured at the following time-points of the IVGTT: -5, 0, 5, 15, 25, 35, 45, 60
2. Plasma total insulin will be measured at the following time-points of the IVGTT: -5, 0, 5, 15, 25, 35, 45, 60
3. History of treatment emergent and other adverse events, and concomitant medicines will be ascertained at each visit

Efficacy assessment

The paired t-test indicates that BGL-$AUC_{0\text{-}60}$ on Day 0 (semaglutide) is lower than Day -1 (placebo) with a p value of < 0.05

8 Assessment of Safety

Risks and benefits

Benefits: There are no immediate benefits to the participant in this short-duration pilot. However, should any of the investigations reveal abnormalities in the participant's screening profile or their IVGTT sessions, the investigator will discuss the results with the participants, and email a discharge summary to their general practitioner.

Risks:

- The common side-effects of semaglutide are nausea and diarrhoea. Participants will be assessed for gastrointestinal disturbances and other side effects and treated as indicated.
- There is small risk of bruising, bleed or skin reaction at the insertion of the cannula for the intravenous glucose testing and the phlebotomy at the screening visit. This risk is reduced by appropriate site location, and adherence to CAHS policies related to hand hygiene, sterile/aseptic technique, cannula care, and blood sampling by adequately trained research staff.
- Another possible low risk is syncope-like event or syncope from sensor insertion or cannulation. To minimise this risk – all procedures will be conducted while participant is on the bed. And if such events were to occur, participant's vital signs will be monitored and if participant recovers spontaneously, fluids and/or food will be provided as necessary. Oxygen will be administered if indicated.
- In the event that the participant is unable to tolerate frequent sampling during the intravenous glucose testing, the session will be stopped and not repeated on the day.
- Female participants must have a negative serum pregnancy test at the screening visit, a urine pregnancy test on Day 0, prior to dosing. They will also need to practice effective contraception from time of screening, to end of the study. However, in the unlikely event that they do become pregnant, we will monitor the outcomes of the pregnancy in conjunction with their GP.
    - No specific monitoring of the baby is required. However, we will monitor the outcomes of the health checks performed at birth, and the 6week check-up, to confirm that the baby is healthy and that there aren't any problems. If there are problems, steps will be taken to ascertain if there is any likely relationship to the drug, and these outcomes will be reported to the DSMB and the ethics committee..

All staff involved with participant care in-clinic will be trained in GCP and basic life support. They will also be clinically trained to conduct the intravenous glucose testing. A resuscitation trolley will be always available during these studies.

Safety

The safety population will consist of all study participants. Incidence of AEs and targeted adverse events of interest will be reported descriptively. All AEs will be coded according to the MedDRA dictionary of terms.

The occurrence of the following events will be ascertained and adjudicated by a Data Monitoring and Safety Committee:

- Major adverse cardiovascular events (MACE):
  - myocardial infarction
  - hospitalisation for unstable angina
  - hospitalisation for heart failure
  - coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention)
  - cerebrovascular events, including cerebrovascular accident (stroke) and transient ischaemic attack
- Pancreatic adverse events.

Individual stopping rules:

a) Participant choice where they could choose to stop at any anytime

b) Participant is unable to tolerate the IVGTT sessions.

Overall study stopping rules:

On advice of the DSMB.

Data and Safety Monitoring Board

A Data and Safety Monitoring Board, will be set up prior to study commencement. This will include an adult endocrinologist, a clinical trials pharmacist and a biostatistician.

Adverse event reporting

All adverse events will be captured on an Adverse Event log. Adverse events will be reported, as they occur, descriptively to the DSMB as they occur. Similarly all concomitant drug use during the study period will also be captured.

Follow-up of Adverse Events

As clinically indicated.

9 Data Management, Statistical Analysis and Record Keeping

Statistics and Interim Analysis

No interim analysis will be performed.

General Considerations:

Descriptive statistics will be produced for relevant demographic and clinical characteristics of the study sample; means (with standard deviations), medians (with interquartile ranges), or count/percentages will be presented as appropriate.

Means (with standard deviations) and medians (with interquartile ranges) will be presented BGL-AUC_{0-60} and Ins-AUC_{0-60} at each study day (-1,0,3,6).

To meet the primary aim of the study, a paired t-test comparing placebo (-1) and drug delivery day (day 0) will be conducted for BGL-AUC_{0-60}; the mean difference and 95% confidence intervals will be presented.

To explore the duration of action of BGL-AUC_{0-60} and Ins-AUC_{0-60}, one-way repeated measures ANOVA will be conducted. Planned pairwise comparisons between baseline (-1) and later study days (0, 3, and 6) will be conducted using Dunnet's method to control for multiple comparisons.

Sample Size

Based on the results collected in animal studies of encapsulated oral semaglutide and blood glucose, this study is being powered to detect an effect size of 1.2. With alpha set at 0.05, a total of 8 participants, who complete all study visits, will be required to provide at least 80% power to detect this effect.

Study Power and Significance

A p-value of <0.05 will be considered statistically significant.

Statistical plan deviations:

Any deviations to the original statistical plan will be reported to relevant ethics committees as an amendment to the scientific protocol and in the manuscript.

Selection of participants for analyses:

Data from all participants who have completed their 6-days post treatment IVGTTs will be included in the study.

Data management

Any information collected in connection with this project will remain confidential. Following consent, the participant will be provided with a unique study number which will be used on data collection instruments, in place of identifying information, to protect participant confidentiality. The log which will link the participant identifiers to the unique ID will be password protected; with the password only known to the Investigator, clinical coordinator and the study nurse.

All paper records will be stored in locked cabinets in the Endocrinology/diabetes office space on Level 2 at PCH. Electronic data will be stored on password protected CAHS REDCap database and the W:\Endocrinology\PMH\Endo Research\Departmental\study folder, which are accessible only by the study team.

All biological samples from the screening visits will be sent to PathWest immediately. All biological samples from the IVGTTs will be stored on-site in the -80°C of Level 6, until they are sent to PathWest for analysis. Once analysis is completed and verified, PathWest will destroy these samples. The study samples will be managed by the study research assistant, who will send these samples to the PathWest Clinical Trials Laboratory as required.

On completion of the project, data analysis and publication of the project outcomes, the paper records will be archived as per PCH archiving policy, using Iron Mountain off-site archiving. All records will be retained for 15y after publication of the study findings, after which they will be destroyed as per CAHS policies for research data management.

Procedures for missing, unused and spurious data:

No imputation will be made on missing, unused, and spurious data i.e. only valid data will be used as collected.

10 Monitoring / Audit

Monitoring, Audit and Regulatory Inspections Statement

The investigators will permit all study-related monitoring, audits, and regulatory inspections, and provide direct access to source data/documents.

Procedures for monitoring and auditing

The study will be monitored by the coordinating principal investigator weekly. The DSMB will have access to the data.

11 Quality Control and Quality Assurance

Compliance statement

The trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements. All staff involved in this study will have GCP certification and will be well-versed in the study protocol including the consent process, adverse event management, and data collection

Quality control

All staff are experienced in performing clinical research studies, and are ICH-GCP certified. They will be trained on data collection and how to fill out the CRFs to ensure quality of data. A staff of the Children's Diabetes Centre, who is not directly involved in the research study, will audit the data on a monthly basis

12 Ethics

Potential participants will be provided with information sheets, and time to consider the study and ask any questions of the study team before providing consent. Participants are informed that their participation is voluntary and will not affect their relationship with their health care provider if they choose to withdraw at a later stage, or not to participate.

13 Budget, Financing, Indemnity and Insurance

This is an investigator (Prof TW Jones) led project. Both the investigational drug (Encapsulated Oral Semaglutide) and the placebo will be supplied by Diabetology Ltd, but all other project costs are met by the departmental research funds. The project is indemnified by CAHS. All the investigators and study personnel are indemnified for negligent harm by the CAHS or TKI.

14 Publication

The outcomes of this research will be submitted for publication in peer reviewed journals and for presentation at scientific meetings. The project results will be disseminated to participants via email, and to the clinicians at the departmental meeting.

15 References

1. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010;375(9724):1447-56.
2. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013;381(9861):117-24.
3. Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384(9951):1349-57.
4. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes: A 26-Week Randomized Controlled Clinical Trial. Diabetes Care. 2016.
5. Kaneko, J. J., Harvey, J. W., & Bruss, M. L. (Eds.). (2008). Clinical biochemistry of domestic animals. pp67-68. Academic press.

16 Appendices

- Diabetology Oraglutide IB V4 - Final
- Diabetology Oraglutide IB V3-Appendix 1
- IVGTT Worksheet V1.0