Government of Western Australia
Department of Health

WA HEALTH RESEARCH PROTOCOL

The effect of oral insulin on subcutaneous insulin requirements and glycaemia in T1DM

Version 4

Dated: 06th December 2021

Table of Contents

1 Trial Details			
Protocol/Clinical Trial Title:	The effect of oral insulin on subcutaneous insulin requirements and glycaemia in T1DM		
Protocol Number (Version and Date):	V4 (06.12.2021)		
Amendment (Number and Date):			
Trial Start Date:	01/01/2022	**Trial Finish Date:**	31/12/2022
Coordinating Principal Investigator Name:	Prof T W Jones		
Coordinating Principal Investigator Contact Details:	Dept of Endocrinology & Diabetes L2E, Perth Children's Hospital Email: Tim.jones@health.wa.gov.au		

1.1 Trial Summary

Subcutaneous insulin therapy in the form of insulin injections or insulin pump therapy has been the cornerstone of insulin delivery for people with Type 1 diabetes (T1D). Despite advancements in monitoring and improved delivery systems, most people with T1D are not able to achieve optimal glucose levels. This raises the need to look for alternative modes of insulin delivery which are non-invasive, likely to be less challenging and more acceptable in long-term. Apart from the mode of administration, oral insulin has the added advantage of replicating a near-physiological state with reduced levels of insulin in blood and thereby confers a 'lower risk of hypoglycaemia'.. Many oral insulin preparations have been trialled, especially in the last two decades, although with limited success, especially due to the challenges in absorption of the oral medications. Improved oral drug delivery systems designed to address these barriers have provided a new horizon to explore this avenue further.

A multicentre 12-week clinical trial using oral insulin has recently demonstrated efficacy in adults with early-stage of Type 2 diabetes. Oral insulin caused a clinically meaningful reduction in glucose levels without hypoglycaemia. Hence, there is promise in exploring its potential in T1D. This proposed study is designed as the first step to explore the possibility of using oral insulin in T1D as an adjunct to current management.

The proposed pilot study is a 12-week single-arm observational study in 10 adolescents/adults with T1D in Western Australia. Oral insulin will be administered to participants on closed loop therapy and a range of clinical, metabolic and safety outcomes will be collected. The proposed study aims to provide preliminary data of whether oral insulin is acceptable and can be used as an adjunct therapeutic intervention in individuals with T1D, and to use the information obtained to inform a future randomised controlled trial specifically designed to assess the efficacy of oral insulin as an adjunct to current insulin therapy. The 12-week study will provide sufficient duration to review glycaemic outcomes that can be measured by HbA1c and metrics from continuous glucose monitoring (CGM).

There are no potential ethical issues in the proposed study.

2 Rationale / Background

2.1 Background summary

Replacement of exogenous insulin is critical in the management of T1D. However, this replacement requires subcutaneous insulin delivery, either as multiple daily insulin injections or by continuous insulin infusion through an insulin pump. Despite advancements in monitoring and improved delivery systems, more than three quarters of people with T1D are not able to achieve optimal glycaemic control (1). Administration of insulin remains a relatively invasive process and is not the most convenient form of

delivery; hence, engagement with insulin administration may be sub-optimal. Oral insulin, however, may be perceived as a more attractive form of insulin delivery, although this has remained an elusive goal. In addition to the ease of administration with an oral preparation, the more significant advantage lies in the different pharmacokinetics having an ability to replicate a near-physiological state, closely mimicking the portal delivery of endogenous insulin. Oral insulin is absorbed by the gastrointestinal tract with its action at the liver, the primary organ of glycaemic control (high portal insulin and low peripheral insulin levels), whereas subcutaneous injections induce high systemic insulin levels, with greater risk of hypoglycaemia and weight gain. Oral insulin, by reducing systemic insulin levels, has the potential to minimise hypoglycaemia, weight gain and may also restore β cell function by reducing the immune response in tissues (2). The multiple perceived benefits of oral insulin delivery have led to various formulations of oral insulin, currently limited to small clinical studies (3).

There are multiple barriers in the oral delivery of unmodified insulin. Degradation of the insulin peptides by the acidic environment of the gut, and poor permeability of the relatively large insulin molecule across the intestinal mucosa are two of the recognised barriers that limit the bioavailability of oral insulin to <1% (4). Developments were therefore aimed at protecting the insulin molecule and facilitating its absorption into the blood stream. An oral insulin preparation (Capsulin) developed by Diabetology Ltd is based on their patented Axcess delivery system (5). It is enteric-coated and has components of well-characterised and "generally regarded as safe" (GRAS) substances. The design of this capsule protects insulin from degradation by proteases in the gut and also enables effective intestinal absorption. The capsule is stable at room temperature for 18 months.

Preliminary data: Whitelaw et al first demonstrated reduction in glucose levels with oral insulin in eight adults with T1D in a cross-over study which evaluated the plasma insulin and glucose response with a single dose of 150 IU and 300 IU Capsulin (6). Thereafter, a proof of concept study by *Luzio et al* demonstrated a glucose-lowering effect, with only a minimal increase in plasma insulin concentrations with use of Capsulin in 16 individuals with type 2 diabetes (*Figures 1a and 1b*) (7). They also reported a small but significant decrease in HbA1c, weight and triglycerides during the 10-day study period during which participants received 150 IU twice a day of Capsulin.

Figure 1a

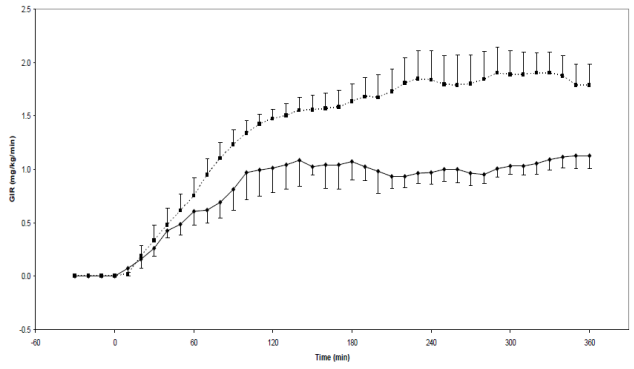
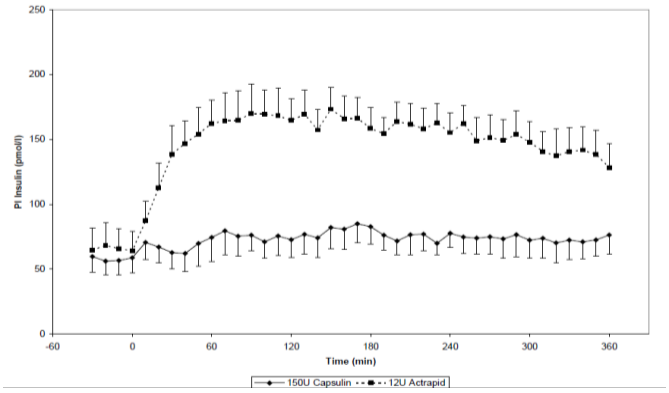
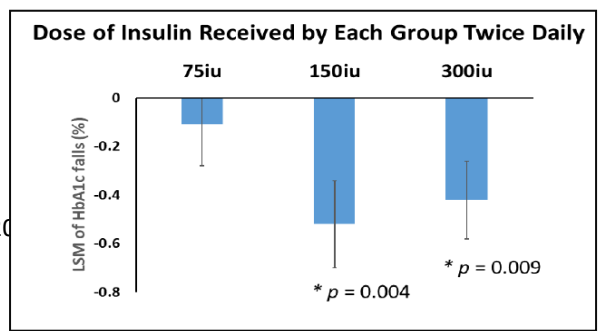


Figure 1b



Likewise, a phase 2B trial for type 2 diabetes has just recently been completed (8). This study was a multicentre 12-week trial in 137 participants with a mean HbA1c of 8.1%, randomised to one of the three groups: Group A 75 IU BD, Group B 150IU BD, Group C 300IU BD. *Figure 2* shows HbA1c reduction in the three groups. A reduction in HbA1c >0.5% was met in Group B, while participants with a higher baseline HbA1c (>9%) demonstrated the greatest benefit with a reduction of 1.5%. Furthermore, there were no episodes of hypoglycaemia during the 25,000 dosing events over the 12-week study period. There was also a significant

Figure 2



improvement in the lipid profile with 10% improvement in LDL and total cholesterol and 20% for triglycerides. These promising findings open up avenues to explore the potential of oral insulin in people with T1D.

Proposed Study: This pilot study will expand on the findings from these previous studies by exploring the utility of oral insulin in individuals with T1D over a 12-week period.

The proposed study aims to provide preliminary data of whether oral insulin is acceptable and can be used as an adjunct therapeutic intervention in individuals with T1D, and to use the information obtained to inform a future randomised controlled trial specifically designed to assess the efficacy of oral insulin as an adjunct to current insulin therapy. The 12-week study will provide sufficient duration to review glycaemic outcomes that can be measured by HbA1c and metrics from continuous glucose monitoring (CGM) which include time in hypoglycaemia, time in target glucose range and time in hyperglycaemia. We predict a reduction in total subcutaneous insulin dose with supplemental oral insulin will lead to a reduction of systemic hyperinsulinemia. This in turn, has the potential to further reduce hypoglycaemia, which still remains a concern in individuals with T1D (9, 10). This study will also enable us to explore trends of glycaemic variability with daily oral insulin therapy. Improvement in these glycaemic measures are known to reduce the long-term risk of diabetes macro and microvascular complications (11, 12). Liver is the primary site of insulin delivery with oral insulin, unlike subcutaneous insulin, where systemic insulin levels are high in target organs which include liver, muscle and adipose tissue. Hence, the study will also review metabolic parameters with the potential role of oral insulin being cardio-protective.

Our ultimate aim is to improve our understanding of oral insulin and make recommendations for future research to enhance improvements in clinical care to better support people with T1D.

2.2 Intervention

Name and description of the intervention or product(s) used in this trial, including investigational product(s) and comparator product/s (if applicable). Include status of product registration (i.e. registration on Australian Therapeutic Goods Registry, or equivalent).

1. Oral insulin: Capsulin (Diabetology Ltd) 150 IU once a day, increased to twice a day after a week; to be administered half an hour before food for study duration. This investigational product has been trialled in type 2 diabetes, but not in type 1 diabetes.
2. Hybrid closed loop (HCL) insulin delivery system – Medtronic 670G or Medtronic 770G. This will be the participant's own insulin delivery system
3. Dexcom G6 for participants on Medtronic 670G, as the Medtronic 670G does not have the follow-function to enable monitoring of these participants whilst on the investigational oral insulin.
4. Track caps (Aardex) – The oral insulin capsules will be provided to the participants in bottles fitted with caps which will track how many times the bottles are opened and at what time of day they will be opened. We have used this system effectively in a previous clinical trial (AdDIT-RGS0000002353)

3 Trial Aims / Objectives / Hypotheses

The hypothesis of this study is that oral insulin will reduce the patient's dose of subcutaneous insulin. The research question is "Is oral insulin an effective and safe adjunct to conventional therapy in adolescents/adults with T1D?"

The *aims* of this study are to:

1. To perform a pilot study to gather preliminary data required for a randomised controlled trial to assess the effectiveness and safety of oral insulin therapy as an adjunct to standard treatment in individuals with T1D.
2. Determine participant acceptability of adjunct oral insulin therapy and the study procedures.

4 Trial Design

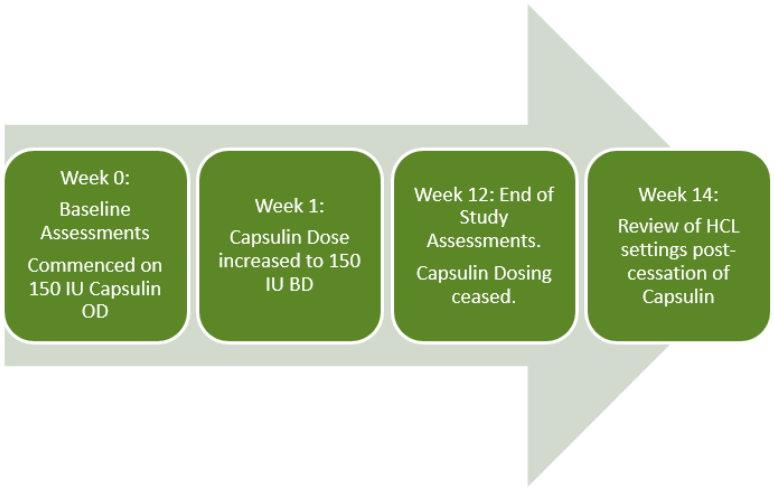
The scientific integrity of the trial and the credibility of the trial data depend substantially on the trial design and methodology.

4.1 Study Endpoints

Not applicable to this pilot, single-arm observational study.

4.2 Study Design

The proposed pilot study is a prospective, 12-week single-arm observational study in 10 adolescents/adults with T1D in Western Australia. The study design is shown in Figure 2, below:



4.3 Bias

All participants will receive the same treatment, in this pilot study.

4.4 Blinding and Randomisation

All participants will receive the same treatment, in this pilot study.

4.5 Device Tracking

Not applicable

4.6 Intervention/Product Description

Capsulin™ is, an oral insulin developed by Diabetology Ltd and is based on their patented Axcess delivery system (5). Capsulin is an enteric-coated capsule which contains unmodified human recombinant insulin with a mixture of well-characterized and "generally regarded as safe" (GRAS) substances which facilitate the transport of insulin through the intestinal wall and into the portal circulation. The capsule is stable at room temperature for 18 months.

Capsulin comes in 150 IU dose capsules, and will be provided to the participants in bottles fitted with a tracking cap (Aardex), which have been effectively used in a previous clinical trial – AdDIT (RGS0000002353), to monitor adherence to prescribed dose and time of dosing.

Dose: Capsulin 150 IU BD

This dose is chosen as higher dose (300 IU BD) has no added benefit in a Phase 2A study (8). Oral insulin is absorbed over a period of 1-2 hours and slowly increases to a peak at about 4-5 hours post ingestion. Data suggest that 150 IU dose leads to a reduction of 2 mmol/mol in blood glucose. Capsulin delivers insulin to the liver, where it suppresses hepatic glucose production. As the production of glucose within the liver is related to the concentration of the glucose in the bloodstream, increasing the dose of Capsulin between 150 IU and 300 IU does not lead to a greater fall in glucose. Dose of 150 IU BD resulted in reduction in HbA1c and improvement in metabolic profile with no side-effects.

4.7 Product Accountability Procedures

The study investigators will be responsible for patient safety during the study. Capsulin use will be monitored using the cap tracker count (Aardex history), the study logbook, the patient's pump data, and a manual count of the remaining capsules.

4.8 Trial Duration/Schedule

Expected duration of the study is 12 months. Each participant's time in the study is 12 weeks. The visits, assessments and visit duration for every participant is listed in the table below.

Visit Sequence	Visit Duration	Assessments	Comment
VISIT 1 (Week0) **STUDY START**	8.5h	Informed Consent confirmed.	
		Height, weight, BP, Date of Birth, Date of Diagnosis, Date of pump start, Date of start of closed loop Pump download for pump settings and CGM data	Ensure participants are well and that the prior two weeks representative of routine diabetes management
		Glycaemic measures: HbA1c, total insulin dose, insulin sensitivity factors, insulin-carbohydrate ratios and CGM metrics	
		Metabolic measures (2mls blood): lipid profile, liver function tests	Fasting bloods
		Meal Challenge (following an overnight fast) with standard SC pre-meal bolus via pump. Measure gut hormone responses over 5h - plasma GLP-1 (glucagon like peptide), GIP (glucose dependent insulinotropic polypeptide), plasma glucagon and free insulin. A total of 106 mls will be drawn for 15minutely blood BGL testing and gut hormones during the meal challenge.	SC bolus to be administered for standard meal. Meal is to be eaten within 20 minutes under supervision. No other oral intake (excluding water) for the next five hours.
		Dexcom G6 set-up and training for those on 670G. Provided with sufficient sensors for 2 weeks .	As Medtronic 670G users do not have the follow-function (available with 770G), participants using 670G will be offered an additional continuous glucose monitor (Dexcom G6) to obtain glucose data during the first three weeks of the study period. The device has a share function which will permit the research staff to review the glucose levels in real-time.
		Participants are commenced on once daily dose of 150 IU	Participants will be commenced on oral

		Capsulin, at the end of the meal challenge. They are provided with lunch half an hour after the oral insulin dosing, and observed for a further 2h prior to discharge. Participants are educated on the appropriate timing of the oral insulin dosing: Capsulin is to be taken half an hour before a main meal. Review home hypoglycaemia management with participant &/or parent.Provide oral insulin for a week	insulin 150 IU OD, to ensure stability of the closed loop algorithm. Dose increased to 150 IU BD after one week As per ISPAD & Diabetes Australia guidelines.
VISIT 2 (Week 1)	1.5h	Clinical review of total insulin dose, insulin sensitivity factors, insulin-carbohydrate ratios and CGM metrics.	
		Assessment of Capsulin use, and adverse events	Review of logbook and Aardex history
		Commenced on twice daily 150 IU Capsulin– with appropriate education of use. Provide oral insulin for 5 weeks	
VISIT 3 (Week 6)	45 min	Pump download for pump settings and CGM data. Clinical review of total insulin dose, insulin sensitivity factors, insulin-carbohydrate ratios and CGM metrics.	
		Assessment of Capsulin use, and adverse events	Review of logbook and Aardex history
		Provided with further Capsulin for remaining 6w; twice daily 150 IU dose. Participants are educated on the appropriate timing of the oral insulin dosing: Capsulin is to be taken half an hour before two main meals.	
		Participant to return Dexcom G6 transmitter to researcher	
VISIT 4 (week 12) **(STUDY END)**	6.5h	Height, weight, BP,	
		Pump download for pump settings and CGM data Glycaemic measures: HbA1c, total insulin dose, insulin sensitivity factors,	

		insulin-carbohydrate ratios and CGM metrics	
		Metabolic measures (2mls blood): lipid profile, liver function tests	Fasting bloods
		Meal Challenge (following an overnight fast) with an oral insulin pre-meal bolus. Measure gut hormone responses over 5h - plasma GLP-1 (glucagon like peptide), GIP (glucose dependent insulinotropic polypeptide), plasma glucagon and free insulin. A total of 106 mls will be drawn for 15minutely blood BGL testing and gut hormones during the meal challenge.	
		Participant report of outcomes determined – Appetite and impact on dietary intake, perceived weight loss and well-being.	
VISIT 5 (14w)	30 min	Pump download for pump settings and CGM data	This visit is to ensure that participants are back on baseline therapy.

NOTE:

Visits 1 and 4 are face-to-face; however other visits can be done via telehealth if required.

*In the 1st three weeks from commencement of the oral insulin, participants will be followed in real-time using the follow-function of the closed loop system or Dexcom G6. Low alerts will be enabled on the phone which will permit immediate correction of hypoglycaemia. Adjustments will be made to the pump settings if required.

*Subsequently, there will be weekly contact with the participants by research staff to monitor and review CGM and pump data to make adjustments to pump settings (if required) and to monitor safety.

4.9 Trial Termination

Study participation is voluntary, and participants may withdraw at any time.

In general, once a participant is in the study, he/she will remain in the study unless the investigator believes it is not safe for the participant to continue. The criteria below will be used to determine safety:

1. Severe hypoglycaemia (seizure or coma or any episodes requiring glucagon).
2. Severe diabetic ketoacidosis (venous ph <7.2)

3. Non-compliance with the medication which in the judgment of the investigator increases risk for the participant

Criteria for Suspending/Stopping Overall Study

The DSMB will provide guidance to the Lead Investigator as to whether the overall study should be stopped. This will be conveyed to the ethics committee within 72h of the DSMB notification.

4.10 Data identification

Every participant will be given a unique study number. All data on the CRFs will be de-identified

5 Source and Selection of Participants

5.1 Source of Participants

We will recruit 10 individuals with type 1 diabetes attending the diabetes service of Perth Children's Hospital, Fiona Stanley Hospital and Sir Charles Gardiner. We will also recruit using social media (Facebook, Twitter), DRWA and NDSS. Recruitment will be over 6 months.

5.2 Participant inclusion criteria.

1. T1D of at least 1 year duration,
2. C-peptide < 0.1nmol/l (in the absence of hypoglycaemia)
3. Age 16 - 25 years
4. On Medtronic 670G/770G (using closed loop system for ≥ 70% of the time in last 2 weeks)
- No plans to change the management during the study period.
5. HbA1c < 7.5%
6. Ready to meet the requirements of the protocol.
7. Has the ability to download the insulin pump if on Medtronic 670G (Medtronic 770G users have automatic download)
8. English speaking, living in an area with internet and cellular phone coverage

5.3 Participant exclusion criteria.

1. Recent significant change in HbA1c exceeding 1.5% over the past 3 to 4 months.
2. Use of any non-insulin glucose-lowering agent.
3. Pregnancy, comorbidities: Renal dialysis/transplant or glomerular filtration rate <60ml/min/m^2, malabsorption, coeliac disease, active liver disease, islet cell/pancreatic transplant

5.4 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 insulin, will be asked to return all unused capsules to the research unit. They will not require any follow-up as the insulin is a quick acting insulin, without any carry-over effects.
Participants who withdraw from the study will need to be replaced, as the study is powered for a sample size of 10 with completed data.

6 Treatment of Participants

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

All participants will receive the investigational oral insulin (Capsulin) for the duration of 12w. They will first be commenced on 150 IU Capsulin for one week. They will then have their dose increased to the therapeutic dose of 300 IU (150 IU twice daily) for the remaining study duration.

6.2 Permitted medications/treatments

All participants will be on either the 670G or 770G Hybrid Closed Loop insulin regimen. They will continue on this regimen throughout the study duration.

6.3 Monitoring of participant compliance

All participants will be provided the Capsulin in bottles fitted with Aardex track cap. Adherence with the dosing schedule will be determined from the Aardex history and from the number of capsules remaining in the bottles when participants attend their clinical reviews and the final visit. Participants self-reporting of adherence will also be recorded.

7 Assessment of Efficacy

7.1 Outcomes

1. Total insulin dose (units/kg/day) and the proportion of basal and bolus insulin
2. CGM metrics (13): 12-week CGM data will be collected for variables: Mean SG, % time in range 3.9 to 10 mmol/l, % time in hypoglycaemia (< 3 and < 3.9 mmol/l), % time in hyperglycaemia (>10 and >13.9 mmol/l), and glycaemic variability (coefficient of variation and standard deviation)
3. Auxology: Body mass index Z-scores
4. Metabolic bloods: Lipid profile (Triglycerides, cholesterol, LDL and HDL), Liver function test, HbA1c
5. Gut hormone (glucagon, glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) responses to a standard meal challenge
6. Safety (Adverse events, Severe adverse events: Severe hypoglycaemia, diabetes ketoacidosis)
7. Recruitment and retention rates
8. Adherence to medication (track caps)
9. Patient-reported outcomes: experiences with oral insulin on appetite, GI disturbances and glycaemic outcomes

7.2 Efficacy assessment

The methods and timing for assessing, recording, and analysing efficacy parameters:

- Insulin profiles and CGM metrics will be assessed at each clinical review – Visit 1,2,3,4. They will also be monitored weekly using the Medtronic and Dexcom databases.
- Other clinical & metabolic outcomes will be measured at study start and study end – Visit 1 & 4
- Adherence to medication and adverse events will be determined at each clinical review – Visit 1,2,3,4
- Patient self-reported outcomes will be determined at the end of the study duration by means of a questionnaire

8 Assessment of Safety

8.1 Risks and benefits

All participants are on hybrid-closed loop therapy, whereby the patient's basal insulin delivery is adjusted on a 24h basis,. Hence any changes in glycaemia as a result of oral insulin use, will be offset by a change in the basal insulin delivered by the Hybrid Closed Loop system. Furthermore, oral insulin has been used with no increase in hypoglycaemic events.

The risk is attributed to glycaemic fluctuations, if any, as a result of combined closed loop and oral insulin therapy. This could include both hypoglycaemia and hyperglycaemia. Previous studies with oral insulin have not reported any serious adverse events (Product Investigation Brochure-Phase IIa DTY 0001 in T1DM); however two of the eight participants in the study reported headaches associated with oral insulin. Symptoms suggestive of a common cold were reported to a lesser degree. All participants will be monitored for side-effects like gastrointestinal intolerance, headaches and allergy, if any, during the study.

The benefits to the participants are that they may achieve better glycaemic control with a reduction in sub-cutaneous insulin requirements. They may also benefit from better metabolic outcomes in their lipid profile.

8.2 Safety

1. The safety parameters and the methods and timing for assessing, recording, and analysing safety parameters. Include a description of emergency procedures if applicable.Risk of hypoglycaemia/hyperglycaemia:

The risk of hypoglycaemia with oral insulin is negligible. However, any patient receiving insulin at any time has the potential to develop hyper or hypoglycaemia.

a. The sensor glucose levels of all study participants are available to participants in real-time which will enable them to take appropriate clinical action as required. Participants will also be followed in real-time by research staff in the first three weeks of the study with commencement of oral insulin.

b. Hybrid closed loop system is semi-automated and is dependent on the sensor glucose levels and basal insulin delivery will be adjusted based on sensor glucose readings. HCL is therefore expected to mitigate any risk of hypo/hyperglycaemia while on oral insulin

2. Risk of immediate allergic reactions with oral insulin

   All participants will be monitored after the first dose for at least 30 minutes.

Emergency procedures:

- For severe hypoglycaemia, intramuscular glucagon can be administered.
- For ketosis > 0.6mmol/l with glucose > 15mmol/l, insulin (rapid-acting) is administered with an insulin pen.

This is taught to every family at the time of diagnosis of T1D and review of their knowledge is established in subsequent clinic follow-ups.

8.3 Data and Safety Monitoring Board

A data safety monitoring board, consisting of an endocrinologist, a statistician and a pharmacist, will be established to safeguard the interests of the trial participants, monitor the safety outcome measures, and monitor the overall conduct of the study. The board will receive and review information on the progress and accruing data and provide advice on the conduct of the trial to the investigators.

8.4 Adverse event reporting

Capsulin has been used effectively in type 2 diabetes management with no adverse outcomes. Further, as all participants are on hybrid-closed loop therapy, whereby the patient's insulin settings are adjusted on a 24h basis, minimal risks are expected during this study. Similarly, the risk of a serious adverse event is low. Any serious adverse event will be reported to Child Adolescent Health Service Human Research Ethics Committee using the Initial Serious Adverse Event Report Form within 72 hours of the event occurring or 24 hours if there is a material impact on the ethical acceptability of the study as considered by the principal investigator.

Adverse events will be elicited at each clinical review by means of clinician assessment and reviewing of the participant Logbooks. Further participants CGM and pump uploads are reviewed on a weekly basis for early pick-up of adverse events.

Adverse events are defined as:

-Gastrointestinal disturbances

-Skin rashes following oral insulin therapy and not related to pump/sensor therapy

-More than 40% increase in hypoglycaemia from baseline

-Hyperglycaemia with ketosis

Severe adverse events are defined as:

1. Severe hypoglycaemia: coma/convulsion/any episode requiring third party assistance for hypo treatment
2. Severe diabetic ketoacidosis: (venous pH < 7.2)
3. Any in-patient hospitalisation

8.5 Follow-up of Adverse Events

The type of follow-up required after an adverse event will be determined by the doctor on the study team according to clinical need.

9 Data Management, Statistical Analysis and Record Keeping

9.1 Statistics and Interim Analysis

This will be a pilot study with 10 participants. This sample size was chosen based on providing estimates of the mean and variance of outcome measures to within a degree of precision acceptable to inform the power calculation for a definitive trial. Appropriate descriptive statistics (frequencies (%), mean (SD), median (IQR)) will be presented for all sociodemographic and clinical characteristics of the sample. Mean and standard deviation, along with their 95% confidence interval, will be presented for continuous/interval outcome measures of interest in each phase and for the paired difference between baseline and end of study. The SD for the primary outcome (change in average total daily insulin delivered subcutaneously) will be presented along with the upper value of a one-sided 80% confidence interval.

9.2 Sample Size

10 participants with complete data for the 12 week study – including adherence to the study drug, insulin profiles, CGM metrics, clinical and metabolic outcome measures. All participants will be seen at PCH, as both FSH and SCGH are only used for recruitment,

9.3 Study Power and Significance

Alpha of 5%

9.4 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.

9.5 Selection of participants for analyses:

All participants who have complete data for the 12w study duration – including adherence to the study drug, insulin profiles, CGM metrics, clinical and metabolic outcome measures; will be included in the analyses.

9.6 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.
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.
On completion of the project, data analysis and publication of the project outcomes, the paper records will be archived as per PCH archiving policy.

9.7 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

10.1 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.

10.2 Procedures for monitoring and auditing

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

11 Quality Control and Quality Assurance

11.1 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

11.2 Quality control

All staff will be trained to ensure appropriate data collection in accordance with ICH-GCP guidelines. They will be trained on how to fill out the CRFs to ensure quality of data and how to use

the cap tracker to assess compliance to the study. Study staffs are experienced diabetes educators and have been involved with research. A staff of the Children's Diabetes Centre, who not directly involved in the research study, will audit the data on a 3-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 future clinical treatment if they choose to withdrawal at a later stage or not to participate.

13 Budget, Financing, Indemnity and Insurance

This is an investigator (Prof TW Jones) led project. Funding is in-part from the company providing the investigational drug (Capsulin), and part-funding is being sought by Dr MB Abraham from DARP. 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 patients and families through the bi-monthly newsletter and parent evenings, and to the clinicians at the departmental meeting.

15 References

1. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes technology & therapeutics. 2019;21(2):66-72.
2. Wong CY, Martinez J, Dass CR. Oral delivery of insulin for treatment of diabetes: status quo, challenges and opportunities. J Pharm Pharmacol. 2016;68(9):1093-108.
3. Zijlstra E, Heinemann L, Plum-Mörschel L. Oral insulin reloaded: a structured approach. Journal of diabetes science and technology. 2014;8(3):458-65.
4. Carino GP, Mathiowitz E. Oral insulin delivery. Adv Drug Deliv Rev. 1999;35(2-3):249-57.
5. https://www.diabetology.co.uk/projects/capsulin/.
6. Whitelaw DC, Kelly CA, Ironmonger W, Cunliffe C, New R, Phillips JN. Absorption of orally ingested insulin in human type 1 diabetic subjects: proof of concept study. Diabetes. 2005;54(Suppl. 1).
7. Luzio SD, Dunseath G, Lockett A, Broke-Smith TP, New RR, Owens DR. The glucose lowering effect of an oral insulin (Capsulin) during an isoglycaemic clamp study in persons with type 2 diabetes. Diabetes, obesity & metabolism. 2010;12(1):82-7.
8. New RRC BM, Travers GN & Namjoshi G A Phase 2b Study of Oral Insulin (Capsulin(TM)) Administered to Patients with Type 2 Diabetes. ADA. 2021.
9. Van Name MA, Hilliard ME, Boyle CT, Miller KM, DeSalvo DJ, Anderson BJ, et al. Nighttime is the worst time: Parental fear of hypoglycemia in young children with type 1 diabetes. Pediatric diabetes. 2017.
10. Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2008;14(6):750-6.

11. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. The New England journal of medicine. 1993;329(14):977-86.
12. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes care. 2019;42(3):400-5.
13. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes care. 2019;42(8):1593-603.

16 Appendices

16.1 Investigator's Brochure

16.2 Device Manual

Not applicable.

16.3 Other appendices.

Participant Self-Reported Outcomes

Logbook for adverse events and concomitant medications

Hypoglycaemia Management Plan

Oral Insulin on Glycaemia Alert Card