**Protocol for Clinical Study**

1. **Title:**

A 4-week, placebo-controlled, dose-ramping study to investigate the safety and optimal dose of Dahlia Extract in people with either pre-diabetes or type 2 diabetes.

***Short Title:***

A study to investigate safety and optimal dose of Dahlia Extract in people with pre-diabetes or type 2 diabetes.

1. **Objective:**

* To establish optimal dose, frequency and time of administration of Dahlia extract in people with pre-diabetes and type 2 diabetes.
* To document any side effects when extract is taken daily for a period of 4 weeks.

1. **Research Design and Methods:**

A placebo controlled dose-ramping study randomised for dose frequency and time of administration.

* 1. **Participants**:

We will recruit 40 people aged 18 years and over with pre-diabetes and an HbA1c ≥45mmol/mol and those with already confirmed Type 2 diabetes with an HbA1c 50-60 mmol/mol. Participants may be using Metformin but no other glucose lowering drug. The dose of Metformin will remain unchanged for the duration of the study.

* 1. Inclusion:
* Males and females ≥ 18 years
* Pre-diabetes or type 2 diabetes with HbA1c ≥ 45 mmol/mol and ≤ 60 mmol/mol
* Willing to maintain a stable lifestyle throughout the study
  1. **Exclusion:**
* Using any diabetes drug other than Metformin
* Previous bariatric surgery
* Pregnancy or breast feeding
* Liver disease or AST/ ALT >3x ULN
* Diabetic nephropathy with an eGFR <60.
* Stage 3 or 4 NYHF heart failure
* Proliferative retinopathy
* Allergy to sports tape
* Any other long-term condition considered inappropriate by principal investigator.

1. **Protocol**

Participants will be randomised into four equal groups stratified by metformin use and by HbA1c.

* 1. **Enrollment**

The study will be conducted by the Centre for Endocrine, Diabetes and Obesity Research (CEDOR), at Capital and Coast health, Wellington. Participants will be recruited from an existing database of people with pre-diabetes who have recently taken part in other research, including those who participated in the first-in-man study of this extract. Participants will also be recruited through advertising.

Potential participants who have expressed interest in taking part will be contacted via letter, e-mail or telephone and provided information about the study, given an opportunity to ask questions about the study and go through a screening questionnaire. Informed consent will be obtained in a 2-step process. Participants will be asked to complete the first section of the consent form at home and return via email prior to having screening blood tests, if these are not available from existing tests within one month. If they meet the inclusion criteria, they will be asked to attend CEDOR to complete enrollment and sign a consent form to continue in the study. Participants will be required to agree to use adequate contraception for the duration of the study.

* 1. **Treatment schedule**

Participants will attend CEDOR for baseline measurements.

* Height
* Weight
* Blood pressure
* Screening physical examination
* ECG

They will then be randomized into one of four treatment arms. Each group will then complete a dose-ramping protocol over four weeks as outlined in Figure 1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Dose | Placebo | 30mg | 60mg | 120mg |

1

1-hour before meal

N=40

Randomised 1:1:1:1

2

3

Immediately before meal

4

Week 2

Week 3

Week 4

Week 1

Week 0

Group 1 and 3 will receive the extract twice daily and groups 2 and 4 three times daily.

**Figure 1.** Schedule of Treatments in Part 1.

*Dosage:* Based on previous study, we will use dosages 15, 30 and 60mg/m2. From a mean body surface area of 2m2 the following doses will be used.

* Small – 30mg
* Medium – 60mg
* Large – 120mg

Capsules will be dispensed in daily blister packs to assist participants with adhering with dosing protocol.

After the first 10 participants have been completed, an interim analysis will determine whether the upper dose should be increased to 150mg for the remaining participants.

All participants will have a Freestyle Libre continuous glucose monitor inserted on the arm and educated how to use it. This is a standard piece of glucose monitoring equipment used in clinical practice and usually inserted by the patient themselves. Participants will be asked to scan the device at least three times per day, at least 8-hourly to ensure collection of a full 24 hours of glucose data.

Participants will be asked to return after two weeks to have the libre removed and download the first two weeks data. A blood test and urine sample will be taken for safety bloods. A second libre will be inserted. Participants will follow the same instructions for a further two weeks and return to have the device removed and second two weeks data downloaded. Another blood test and urine sample will be taken at this final visit for safety tests. Participants will be questioned at this final visit on their experience with taking the extract, timing relative to meals and frequency per day, as well as any potential side effects.

Participants will be instructed to continue to follow their usual diet and activity patterns during the study. Participants will be asked to return any unused capsules. These will be counted as a measure of adherence.

***Outcomes:***

Glucose data from the Libre will be analysed to determine area under the curve for glucose over 24 hours, and divided into 3-5 hour postprandial periods for each meal. Data will be extracted and averaged for days 4-7 of each treatment dose to allow for steady state to be reached.

***Statistics:***

Data will be analysed by treatment group.

A secondary analysis will also be conducted by aggregating data and comparing BD vs TDS dosing for AUC over 24 hours. An analysis will also be conducted by aggregating data based on timing of doses before meals, for AUC over the 5-hour post prandial period following meals where a dose has been given.

* 1. **Safety:**

Participants will be asked to provide a venous blood sample at each study visit for safety tests. These will include

* Full Blood Count
* Renal Function
* Liver Function

**Study Flow Chart**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Part 1 | | | |
|  | Screening | | Treatment Period | |
| Visit | Pre Clinic | 1 | 2 | 3 |
| Week | -4 - -1 | 0 | 2 | 4 |
| Online Informed Consent | X |  |  |  |
| Informed Consent |  | X |  |  |
| Inclusion / Exclusion | X | X |  |  |
| Demographics |  | X |  |  |
| Pt contact Info Collected / Updated | X | X | X | X |
| Medical / Surgical History | X | X |  |  |
| Medication History | X | X |  |  |
| Vital Signsa / Weight |  | X | X | X |
| Height |  | X |  |  |
| Physical Examination | X |  |  |  |
| ECG | X |  |  |  |
| Dispense IMP and Educate on Dose Timing |  | X | X |  |
| IMP accountability & Compliance |  |  | X | X |
| Libre Education |  | X |  |  |
| Insert Libre |  | X | X |  |
| Remove and Download Libre |  |  | X | X |
| AE’s / SAE’s / Hypo Data |  |  | X | X |
| Concomitant Medications |  |  | X | X |
| HbA1c | Xb |  |  |  |
| Renal Bloods | Xb |  | X | X |
| LFTs | Xb |  | X | X |
| FBC | Xb |  | X | X |
| Pregnancy Test | X |  |  |  |

a Weight, B/P

b If there are results from within 1 month of screening these do not need doing.