Remission Evaluation of a Metabolic Intervention in Type 2 Diabetes (REMIT) with Forxiga

Protocol

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ALT	alanine transferase
BhCG	beta human chorionic gonadotrophin
bid	twice daily
BMI	body mass index
CDA	Canadian Diabetes Association
Cr	creatinine
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
MDRD	The Modification of Diet in Renal Disease equation to estimate GFR
OD	once daily
pc	postcibum (postprandial)
PHRI	Population Health Research Institute
po	taken orally
RCT	randomized controlled trial
SAE	serious adverse event
sc	taken subcutaneously
SGLT2	sodium glucose co-transporter 2
SMBG	self-monitoring of capillary blood glucose
T2DM	type 2 diabetes mellitus

1. INTRODUCTION

1.1 Background and rationale

The current approach to treating type 2 diabetes mellitus (T2DM) is to add progressively higher doses and numbers of glucose-lowering drugs to lifestyle approaches. People with type 2 diabetes are therefore taking such drugs from shortly after diagnosis until the end of their lives. A different, novel approach that intensively treats patients with several agents and lifestyle approaches for up to 2-4 months, followed by cessation of all drugs, may achieve a drug-free metabolic remission that could last for months to years. Such an approach has not been formally tested. However, a) evidence from small studies suggesting that approximately 40% of newly diagnosed patients can achieve a remission with short-term intensive treatment with insulin; b) a growing list of glucose-lowering drugs with novel mechanisms of action; and c) the appeal of remission-induction versus lifelong chronic therapy highlights the need to characterize strategies for metabolic remission of diabetes and to identify the optimal therapies and regimens for achieving remission.

We have just completed a peer-reviewed pilot trial of this approach at our centre. Eighty three people with T2DM diagnosed within the prior 3 years were randomized to 3 treatment groups: a) an 8-week intensive metabolic intervention; b) a 16-week intensive metabolic intervention; and c) standard diabetes therapy. The intensive metabolic intervention combined lifestyle therapy and basal insulin glargine, metformin and acarbose and aimed at achieving normoglycemia on therapy. We found that an 8-16-week course of therapy was safe and feasible and induced remission in up to 40% of people with early T2DM. These data illustrate that metabolic interventions such as the one proposed herein can be successfully implemented and have the potential to induce diabetes remission not requiring glucose-lowering therapies. The proposed multicentre randomized controlled trial will assess the remission-related efficacy of a sodium glucose co-transporter 2 (SGLT2) inhibitor-based regimen in a broader set of patients.

1.2 Hypothesis and research questions

Hypothesis:
In patients with early type 2 diabetes, a short-term intensive metabolic intervention comprising dapagliflozin (Forxiga), metformin, basal insulin glargine and lifestyle approaches will be superior to standard diabetes therapy in achieving sustained diabetes remission.

Primary research question:
In patients with recently-diagnosed T2DM, does a 12-week course of Forxiga, metformin, basal insulin glargine and lifestyle approaches achieve drug-free diabetes remission in a higher proportion of patients than standard diabetes therapy at 24 weeks after randomization? Diabetes remission is defined as a HbA1C<6.5% off glucose-lowering agents for at least 12 weeks.

Secondary research questions:

1) Compared to the control group, does this therapeutic approach achieve drug-free diabetes remission in a higher proportion of patients than standard diabetes therapy at 36, 48 and 64 weeks after randomization?
2) Compared to the control group, does this therapeutic approach achieve drug-free HbA1C <6.0% in a higher proportion of patients than standard diabetes therapy at 24, 36, 48 and 64 weeks after randomization?
3) Compared to the control group, does this therapeutic approach achieve drug-free diabetes regression in a higher proportion of patients than standard diabetes therapy at 24, 36, 48 and 64 weeks after randomization? Diabetes regression is defined as HbA1C 6.5-6.9% off glucose-lowering agents for at least 12 weeks.
4) What HbA1C levels are achieved in the intervention group and the control group at 12, 24, 36, 48 and 64 weeks after randomization?
5) What rates of hypoglycemia are observed in the intervention group and the control group during 64 weeks of follow-up?
6) What is the change in weight, body mass index (BMI), waist circumference and waist/hip ratio from baseline to 12, 24, 36, 48 and 64 weeks in the intervention group and the control group?
7) Are age, gender, ethnicity, diabetes duration, smoking, family history of diabetes, baseline BMI, waist circumference, HbA1C or fasting plasma glucose (FPG) determinants of diabetes remission at 24 weeks after randomization?

1.3 Benefit/risk and ethical assessment

Participants with type 2 diabetes will be randomly allocated to continue with standard care or to receive a 12-week course of intensive lifestyle and glucose-lowering drug therapy which includes Forxiga. All participants will be informed that: a) the trial is testing a new short-term therapeutic approach to treating type 2 diabetes which could eliminate the need for glucose-lowering drugs and possibly promote remission; and b) all therapies will be used for their approved indications. All participants will also provide written informed consent.

2. STUDY OBJECTIVES

2.1 Primary objective

To determine whether the 12-week metabolic intervention that includes Forxiga is more effective in achieving drug-free remission of type 2 diabetes than standard diabetes therapy when evaluated at 24 weeks after randomization.

2.2 Secondary objectives

To determine whether the 12-week metabolic intervention that includes Forxiga is more effective than standard diabetes therapy in achieving diabetes remission and regression when evaluated at 36, 48 and 64 weeks after randomization.

2.3 Safety objective

To determine rates of severe and non-severe hypoglycemic episodes in the treatment groups during 64 weeks of follow-up.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a randomized, open-label, 2-arm pilot trial in 152 patients with early T2DM. Participants will be randomly assigned to (i) an intensive metabolic intervention of 12 weeks in duration, or (ii) standard diabetes therapy, and followed for 64 weeks. In the intervention group, the intensive metabolic intervention will combine lifestyle therapy and intensive treatment with Forxiga, metformin and insulin glargine. Glucose-lowering medications will then be discontinued in all participants with a HbA1C<7.3% on therapy, and participants will be encouraged to continue with lifestyle modification and regular home glucose monitoring. Participants with HbA1C ≥ 7.3% on therapy during week 12 of the trial or those with HbA1C ≥ 7.0% at or after the 24-week visit will receive standard glycemic management as informed by the 2013 Canadian Diabetes Association clinical practice guidelines. The visit schedule for study participants is shown in Table 1 in Appendix A.

4. SUBJECT SELECTION CRITERIA

The Remission Evaluation of a Metabolic Intervention in Type 2 Diabetes with Forxiga trial will be conducted in participants with the following inclusion and exclusion criteria:

4.1 Inclusion criteria

1) men and women 30-80 years of age inclusive;
2) type 2 diabetes mellitus diagnosed by a physician within 8 years prior to patient enrollment;
3) anti-diabetic drug regimen (either drug or dose of drug) unchanged during 8 weeks prior to screening and randomization;
4) HbA1C 6.5-9.5% inclusive on no hypoglycemic agents or HbA1C ≤ 8.0% on up to 2 glucose-lowering agents;
5) body mass index ≥ 23 kg/m^2;
6) ability and willingness to perform self-monitoring of capillary blood glucose (SMBG);
7) ability and willingness to self-inject insulin;
8) provision of informed consent.

4.2 Exclusion criteria

1) current use of insulin therapy;
2) history of hypoglycemia unawareness, or severe hypoglycemia requiring assistance;
3) history of end-stage renal disease or renal dysfunction as evidenced by eGFR<60 mL/min/1.73 m^2 by MDRD formula;
4) history of lactic acidosis or diabetic ketoacidosis;
5) active liver disease or elevated alanine transferase (ALT) levels ≥ 2.5 times upper limit of normal at the time of enrollment;
6) history of bladder cancer or undiagnosed hematuria;
7) history of breast cancer;
8) history of polycythemia;
9) evidence of volume depletion or hypotension (systolic blood pressure < 90 mmHg);
10) systolic blood pressure > 180 mmHg or diastolic blood pressure > 105 mmHg;
11) diagnosed cardiovascular disease (unless cleared for a moderate intensity exercise program by a specialist) including:
    a. any history of acute coronary syndrome, hospitalization for unstable angina, myocardial infarction, or revascularization with coronary artery bypass grafting or percutaneous coronary intervention;
    b. other evidence of coronary artery disease;
    c. peripheral vascular disease, valvular heart disease, cardiomyopathy, aortic dissection, tachyarrhythmias, bradyarrhythmias, prior stroke or TIA;
    d. prior hospitalization for heart failure; or
    e. ECG findings concerning for ischemic heart disease (i.e. pathological Q-waves, ST-segment-T-wave abnormalities in contiguous leads, left anterior hemiblock, left bundle branch block, second or third degree atrioventricular block).
12) dependence on oxygen;
13) history of any disease requiring frequent intermittent or continuous systemic glucocorticoid treatment;
14) history of bariatric surgery, or planned bariatric surgery in the next 1.5 years;
15) history of any major illness with a life expectancy of < 3 years;
16) history of injury or any other condition that significantly limits participant's ability to achieve moderate levels of physical activity;
17) any history of excessive alcohol intake, acute or chronic;
18) currently pregnant, or breastfeeding, or not using a reliable method of birth control for the duration of the trial in all females with childbearing potential; reliable methods of birth control include oral contraceptive (birth control pill), hormonal injection, implant, patch, or vaginal ring, intrauterine device, barrier method (condom and spermicide), tubal ligation, partner vasectomy or abstinence;
19) known hypersensitivity to Forxiga, metformin, or insulin glargine.

5. STUDY CONDUCT

5.1 Screening and baseline evaluation

At the screening assessment, informed consent will be obtained, and eligibility criteria will be assessed by performing an interview and physical examination. Blood will be drawn for creatinine, ALT, fasting plasma glucose (FPG), and HbA1C. Fasting serum samples will also be taken for storage at the screening visit in participants who agree to it. A urine pregnancy test (urine BhCG) will be performed in women with childbearing potential. A baseline electrocardiogram (ECG) will also be performed to assess for any evidence of ischemic heart disease or arrhythmia. Baseline weight, height, body mass index, waist circumference and hip circumference will be obtained in all study participants. Physical activity and food frequency questionnaires will also be administered at baseline.

5.2 Randomization and blinding

5.2.1 Procedures for randomization

Eligible participants will be randomized 1:1 to (i) an intensive metabolic intervention of 12 weeks in duration, or (ii) standard diabetes therapy. An independent statistician will prepare a randomization schedule for each site using a computer-generated random number sequence. Concealment of allocation will be ensured by carrying out study group allocation through a central online system. In view of the differences in the treatment regimens, duration, and glycemic goals in the treatment groups, it will not be possible to blind participants or research staff to the intervention. However, the primary and key secondary outcomes of the study are based on objective measurements of blood glucose and HbA1C level, and lab personnel will be blinded to the treatment group assignment.

5.2.2 Procedures for handling subjects incorrectly enrolled or randomized

Participants incorrectly enrolled in the study will be followed till the study end. They will remain in the group they were randomized to. Participants with contraindications to a specific study medication will have that drug discontinued. Participants incorrectly started in the wrong group (i.e. to which they were not allocated) will be switched to the correct treatment group.

5.3 Interventions and monitoring

5.3.1 Intensive metabolic intervention (induction phase of the trial)

An intensive metabolic intervention will be used in intervention group participants for induction of a normoglycemic state. It will be 12 weeks in duration and will include intensive lifestyle therapy and intensive treatment with Forxiga, metformin and insulin glargine. Participants will be asked to discontinue all other glucose-lowering medications.

5.3.1.1 Treatment with and handling of Forxiga

Participants randomized to the intervention group will be started on Forxiga 5 mg po daily for 4 days and then the dose will be increased to 10 mg po daily. Participants will be continued on this dose for 12 weeks. Forxiga will be manufactured and shipped by AstraZeneca. Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines for labeling. The drug will be stored at room temperature (15-30°C) in accordance with the storage conditions specified on the package label. Creatinine will be checked 2 weeks after drug initiation, and then monthly during the intensive metabolic intervention. Forxiga will be permanently discontinued if eGFR falls to <60 mL/min/1.73m^2. Forxiga contains lactose and may cause abdominal discomfort in lactose-intolerant individuals. Forxiga will be temporarily stopped or permanently discontinued if a participant develops side effects.

5.3.1.2 Titration of other glucose-lowering medications

In drug-naive patients, metformin 500 mg po (orally) once daily (OD) will be administered for 4 days, then increased to 500 mg po twice daily (bid) for 4 days, then 1,000 mg po bid. Patients already on metformin will be continued on it with further titration to maximal tolerated doses.

At randomization, participants will be concurrently started on insulin glargine 2-6 units sc (subcutaneously) at bedtime, and the dose will be titrated by the participant with guidance from the research team aiming to achieve a fasting glucose of 4.0-5.3 mmol/L on self-monitoring of capillary blood glucose (SMBG). Insulin glargine is chosen in view of the previous experience of our center in using this insulin analogue to achieve similar glycemic targets in patients with early type 2 diabetes and prediabetes in the ORIGIN trial, a multicenter randomized controlled trial with more than 12,500 participants. The overall goal will be to finish medication titration by the end of week 2, and to maintain the fasting glycemic target of 4.0-5.3 mmol/L for the remaining duration of the intensive metabolic intervention. No other glucose-lowering medications apart from insulin glargine, metformin and Forxiga will be used in intervention group participants during the intensive metabolic intervention. All study drugs will be kept in a secure place under appropriate storage conditions.

5.3.1.3 Intensive lifestyle intervention

The overall goals of the intensive lifestyle intervention are to achieve and maintain ≥ 150 min of moderate physical activity per week by week 12 and ≥ 5% reduction in baseline weight by week 24 of the trial. These goals might be modified depending on participant's baseline weight and physical ability. At baseline, participants randomized to the intervention group will meet with research staff who will prescribe a personalized low-calorie diet and a moderate-intensity exercise program based on participant's current physical activity patterns and cardiovascular history. Participants will be provided with a pedometer as an incentive to engage in physical activity. Participants in the intervention group will meet with research personnel every 1-2 weeks during the intensive metabolic intervention period for goal reinforcement, behaviour modification and problem-solving.

5.3.1.4 Monitoring during the induction phase of the trial

At the first study visit, intervention group participants will be taught how to self-monitor capillary blood glucose and how to inject insulin. Participants and their families will also be taught how to recognize and treat hypoglycemia. During the intensive metabolic intervention, participants will be asked to monitor glucose at least twice daily at varying times, including before and 2 hours after meals, and during exercise. Research staff will meet with intervention group participants once a week during the first 6 weeks of the trial and will contact them by telephone at least once a week between visits to review glucose readings, medication titration, medication adherence and side effects (see schedule in Table 1 in Appendix A). Research staff will continue to meet with intervention group participants every 2 weeks and will contact them by telephone every other week during week 7-12 of the trial. All hypoglycemic episodes will be documented and reviewed with an investigator promptly. Glucose-lowering therapy will be adjusted accordingly.

5.3.2 Control group follow-up during the induction phase of the trial

Participants assigned to the standard diabetes therapy group will meet with research personnel at the beginning of the trial who will review self-monitoring of capillary blood glucose, management of hypoglycemia, and the importance of healthy diet and regular exercise in diabetes management. Control group participants will also be provided with a pedometer as an incentive to be active. Glucose levels in standard group participants will be managed by their regular diabetes care provider according to the current Canadian Diabetes Association (CDA) Clinical Practice guidelines. Any approved glucose-lowering medication will be allowed in the control group.

5.3.3 Monitoring for hyperglycemia relapse during the maintenance phase of the trial

In all participants, HbA1C will be drawn during week 12 of the trial. At the end of week 12, glucose-lowering medications will be discontinued in all participants with a HbA1C <7.3%, and insulin will be tapered over a 5-day period. Participants will be encouraged to continue with lifestyle modifications and regular home glucose monitoring (i.e. at least 5 fasting capillary measures per week). They will meet with research staff every 2-4 months during the maintenance phase of the trial to review any challenges in achieving and maintaining exercise and weight loss goals. Participants will be assessed by research staff every 1-2 months by telephone to review adherence to lifestyle therapy, SMBG readings and to screen for symptoms of hyperglycemia.

It is possible that glucose levels may quickly rise after glucose-lowering drugs are stopped in some of the participants whose HbA1C is <7.3% on these drugs. This rise may not be detected with HbA1C levels due to the well-known time-lag between rising glucose levels and rising HbA1C levels.

In light of the above, hyperglycemia relapse will be defined as follows:

a. a HbA1C ≥ 7.0% at 24, 36, 48 and 64 weeks; or
b. reinitiation of glucose-lowering drugs; or

c. capillary glucose values ≥ 10 mmol/L on ≥50% of SMBG readings over 1 week in the absence of an acute illness.

All participants identified to have hyperglycemia relapse will receive standard glycemic management according to the judgment of their physician or investigator. Participants found to have HbA1C ≥7.3% on therapy during week 12 of the trial will also receive standard glycemic management. These participants will continue to be contacted by telephone every 1-2 months to review SMBG readings, medication adherence and side effects.

5.4 Methodological considerations

5.4.1 Planned recruitment

A total of 152 participants will be enrolled in this trial. Participants will be recruited at approximately 7 Canadian sites. Based on our experience in the pilot trial, we anticipate an average recruitment rate of 2 participants per month at each site. Total trial duration is estimated to be 2.5 years based on a 3-month start-up period, 12-month recruitment period and 15-month follow-up period. If recruitment rates fall behind schedule, we will expand the trial to additional sites. The trial will be coordinated through the Population Health Research Institute which has an extensive experience in conducting multicentre randomized controlled trials (RCT) and offers a large pool of experienced research personnel.

5.4.2 Treatment adherence

Adherence to intensive lifestyle and glucose-lowering therapy for participants in the intervention group will be encouraged during frequent clinic visits and telephone follow-ups. It will also be promoted by prompt attention to any side effects of the medications and the short, 12-week duration of the intervention period.

Medication adherence will be measured by inspecting medications at each study visit. Additionally, two six-point glucose profiles will be collected during the 6^{th} and 12^{th} week after randomization. Each six-point glucose profile will include pre-meal and 2-hour post-meal SMBG measurements taken on the same day. Adherence to lifestyle advice in both treatment groups will be measured by a physical activity questionnaire and food frequency questionnaires administered at baseline, 12, 24, 36, 48 and 64 weeks after randomization. Anthropometric measurements at study visits will also reflect adherence to the lifestyle intervention.

5.4.3 Losses to follow-up

Losses to follow-up are expected to be minimal as the study duration is only 64 weeks. The investigators will make every effort to contact participants who are lost to follow-up. In order to minimize losses to follow-up, participants who do not adhere to the assigned treatment or visit schedule will be encouraged to do HbA1C measurements through their regular diabetes care provider and will be contacted by telephone to collect key data. Participants who withdraw consent will be asked to return any study drugs to the study centre and encouraged to return to their regular diabetes care provider for assessment and further care.

5.4.4 Confidentiality and record retention

Personal information of study participants will be kept in strict confidence. Participants' names will be removed from the data and replaced with identification numbers. The study investigator will keep a participant identification list (identification numbers with the corresponding participants names) in a secure location. Study data will be stored on a computer at the Population Health Research Institute in accordance with local data protection laws. The health records related to this study will be kept by each site for up to 25 years after the end of the trial.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Study variables will be collected at enrollment and during follow-up according to the visit schedule (See Table 1 in Appendix A). Study data will be recorded on data collection forms and transmitted to the Population Health Research Institute (PHRI).

6.2 Study outcomes

6.2.1 Primary and secondary outcomes

The primary outcome is drug-free diabetes remission, defined as a HbA1C<6.5% without use of glucose-lowering agents for at least 12 weeks. Related outcomes to be analyzed include complete diabetes remission, defined as a HbA1C<6.0% without use of glucose-lowering agents for at least 12 weeks, and diabetes regression, defined as a HbA1C of 6.5-6.9% without use of glucose-lowering agents for at least 12 weeks.

HbA1C will be measured in the local labs at 12, 24, 36, 48 and 64 weeks after randomization, during which use of glucose-lowering medications will also be ascertained. FPG will also be measured in the local lab at 16 weeks. All FPG levels will be measured approximately 48 hours after the last dose of any glucose-lowering medication unless fasting capillary glucose rises above 12 mmol/L.

6.2.2 Other outcomes

Symptomatic and severe hypoglycemic episodes will be measured in both treatment groups. Anthropometric measures including height (at the screening visit only), body weight, waist and hip circumference will be measured in all participants (see schedule in Appendix A Table 1). Body mass index will be reported in kg/m^2. Waist circumference will be measured around the exposed abdomen at the level of the top of the iliac crest at the end of a normal expiration. Hip circumference will be measured as the maximal circumference over the buttocks over light clothing.

In addition, 2 six-point glucose profiles will be collected during the 6th and 12th week after randomization. Each six-point glucose profile will include pre-meal and 2-hour post-meal readings taken on the same day. To standardize this measure, all participants will be provided with identical glucometers which will be calibrated regularly. Mean fasting and post-meal glucose values will be calculated for each participant from the two glucose profiles.

6.2.3 Stored blood

In addition to obtaining fasting serum samples at baseline, fasting serum samples will also be taken for storage at 16 weeks in participants who agree to it. They will be shipped and stored centrally. Genetic markers and analytes related to diabetes remission may be measured after the trial has finished.

6.3 Safety

6.3.1 Safety variables

Information on the following prespecified safety outcomes will be prospectively collected in all study participants during the trial:

1) Death (and cause of death as determined by a physician);
2) Non-fatal myocardial infarction or angina resulting in hospitalization or emergency room admission;
3) Non-fatal stroke or transient ischemic attack diagnosed by a physician;
4) Heart failure resulting in hospitalization or emergency room admission;
5) Resuscitated cardiac arrest or life-threatening arrhythmia (including documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity);
6) Cardiogenic shock diagnosed by a physician;
7) Diabetic ketoacidosis or hyperglycemic hyperosmolar state diagnosed by a physician;
8) Documented new fractures;
9) Newly diagnosed cancers;
10) Genitourinary infections diagnosed by a physician;
11) Moderate (eGFR 30-60 mL/min/1.73 m^2 by MDRD formula) or severe (eGFR<30 mL/min/1.73 m^2) renal dysfunction;
12) Symptomatic and severe hypoglycemic events (see below for definitions);
13) Hospital or emergency room admissions (and reasons for admission).

Participants will be asked to record all hypoglycemic episodes and symptoms in a diary that will be provided to them. Moreover, they will be explicitly asked about any episodes of symptomatic or severe hypoglycemia during every visit and telephone follow-up. *Symptomatic hypoglycemia* is defined as an event with clinical symptoms consistent with hypoglycemia, based on data recorded in the participant's diary. These will be further categorized as confirmed (i.e. with a concomitant home glucose reading ≤ 3.0 mmol/L) or unconfirmed. Symptomatic hypoglycemic events and those that result in alteration of any of the study drugs will be recorded.

Severe hypoglycemia is defined as an event with clinical symptoms consistent with hypoglycemia in which the participant required the assistance of another person, and one of the following: (i) the event was associated with a documented self-measured or laboratory plasma glucose level ≤ 2.0 mmol/L; or (ii) the event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Any episode of severe hypoglycemia will be recorded and reviewed within one working day.

All safety variables will be recorded on case report forms and supporting documentation will be obtained. Information on adverse events and pregnancies will be collected as described in Sections 6.3.2-6.3.5. The investigators will review safety data for this open trial monthly and more formally after the first 50 patients have completed the trial to determine if any modifications to the protocol are indicated.

6.3.2 Definitions of adverse events

6.3.2.1 Adverse events

An adverse event is any untoward medical occurrence that occurs in a person during the period of observation in a clinical study. It does not necessarily have to have a causal relationship with any treatment administered as part of that study. An adverse event can therefore be any unfavorable and unintended sign, symptom or disease, whether or not it is considered related to any medicinal product being taken at the time the event occurs.

6.3.2.2 Serious adverse events (SAEs)

A *serious adverse event* is one that at any dose (including overdose):

1) results in death;
2) is life-threatening (i.e. participant was at immediate risk of death at the time of the serious adverse event; it does not refer to an adverse event that hypothetically might have caused death if it were more severe);
3) requires inpatient hospitalization or prolongation of existing hospitalization;
4) results in persistent or significant disability or incapacity (i.e. there is a substantial disruption of a person's ability to carry out normal life functions);
5) causes a congenital anomaly or birth defect;
6) is an important medical event (Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above will be also considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in participant hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment will also be considered as medically important.)

6.3.2.3 Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache). The event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is

based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

6.3.3 Documentation and reporting of adverse events, pregnancies and overdoses

6.3.3.1 Documentation and reporting of non-serious adverse events

Any adverse event resulting in a change in dose (including temporary withholding) of any of the study medications (insulin glargine, metformin and Forxiga) will be documented on case report forms. Examples of such events could include gastrointestinal complaints or genitourinary infections. All changes in the medication dose will be recorded.

6.3.3.2 Documentation and reporting of serious adverse events (SAEs)

Whenever an investigator judges an event to be an SAE, he/she will complete an SAE case report form within one working day and will notify the PHRI Project Office as well as local REB as per REB requirements. All SAEs will be reported by the PHRI to AstraZeneca (± Health Canada). If the event meets criteria of (i) serious and (ii) related to insulin glargine, metformin or Forxiga and (iii) unexpected, it will be subject to expedited reporting to AstraZeneca (± Health Canada).

Every attempt will be made to describe an adverse event in terms of a single diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded. If a clear diagnosis cannot be established, each sign and symptom will be recorded individually. It should be noted that conditions necessitating surgical procedures may be considered adverse events if they satisfy the definitions above. The surgical procedure in question should be regarded as a therapeutic intervention rather than as an adverse event.

All participants who are deemed to have had a serious adverse event will be followed to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the study, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up.

6.3.4 Documentation and reporting of pregnancies and overdoses

6.3.4.1 Pregnancies

Information on any pregnancies occurring during the study will be collected on specific forms and pregnancies will be followed to term. Any confirmed pregnancy will be reported within 1 working day of knowledge of the event, and study drugs will be stopped in concurrence with provision of follow-up medical care. Follow-up forms documenting the pregnancy outcome will also be completed.

6.3.4.2 Overdoses

Cases in which a “significant overdose” in the judgment of the investigator (for example, an overdose leading to severe hypoglycemia) of the study drug (insulin glargine, metformin or

Forxiga) was taken (regardless of whether or not any serious adverse event occurred) will also be reported on specific case report forms within 1 working day of knowledge of the event.

6.3.5 Period of observation

For the purposes of this study, the period of observation for collection of adverse events, SAEs, overdoses and any pregnancies extends from the time the participant gives informed consent until the end of the study.

7. BIOLOGICAL SAMPLING PROCEDURES

All bloods done locally will be collected according to local sampling procedures. Procedures for collection, shipment and storage of blood samples for future biochemical and genetic analyses (collected at baseline and at 16 weeks after randomization) will be detailed in the study lab manual.

8. ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted according to Good Clinical Practice Guidelines. Health Canada will be approached for the need to get Health Canada approval for this study. Investigators at each site will obtain approval of the protocol, informed consent form, advertisement and patient materials from local Research Ethics Boards prior to participant recruitment. Any changes to the protocol and informed consent form will need to be approved by local Research Ethics Boards (± Health Canada).

9. STUDY MANAGEMENT

Dr. Natalia McInnes (née Yakubovich) and Dr. Hertzel Gerstein will oversee execution of this multicentre trial which will be coordinated through the Population Health Research Institute. Dr. McInnes is an endocrinologist and Assistant Professor at McMaster University with an MSc in Health Research Methodology. She oversaw implementation of the REMIT pilot trial with guidance from Dr. Gerstein. Dr. Gerstein is an endocrinologist, epidemiologist and clinical trialist who has led many international trials related to diabetes prevention and treatment including DREAM, HOPE, ACCORD and ORIGIN. Each participating site will be led by a site PI and coordinated by local research staff.

A central research coordinator, biometric programmer and a statistician will assist with study implementation. Recruitment, protocol implementation and data collection will be monitored centrally by reviewing collected data in a blind manner.

10. DATA MANAGEMENT

Data management procedures will be outlined in the data management plan.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Proposed sample size and justification

The sample size calculation is based on the estimated proportion of patients achieving diabetes remission of 10% in the control group. The control group estimate of 10% is based on the proportion of patients in the conventional diabetes treatment group of 13% who achieved FPG < 7.0 mmol/L and HbA1C < 6.2% off therapy after 2 years of follow-up observed in the Dixon *et al.* trial, after adjusting for the longer duration of diabetes since diagnosis in participants in our trial (≤ 8 years versus < 2 years). A total sample size of 152 participants (76 per treatment group) will provide 80% power to show a risk difference of ≥20% in the induction of diabetes remission between treatment groups and 90% power to show a risk difference of ≥23%.

11.2 Statistical analyses

All group comparisons will be conducted according to the intention-to-treat principle with inclusion of data from all participants according to their treatment group assignment, regardless of adherence to therapy. The primary outcome in this study is the proportion of patients in the intervention group who achieve drug-free diabetes remission 24 weeks after randomization compared to the control group. The treatment groups will be compared using a chi-squared test with $\alpha = 0.05$ level of significance. The outcome will be reported as a risk difference in the induction of remission between the intervention group and the control group with 95% confidence interval. Any individual who withdraws/drops out prior to the 24, 36, 48 and 64 week visit will be classified as not having achieved drug-free diabetes remission at that point in time. Participants who fail to achieve remission or have hyperglycemia relapse will be censored with respect to diabetes remission outcomes.

For secondary analyses, a chi-squared test will be used for dichotomous outcomes and a two-sample t-test (or a non-parametric equivalent) for continuous outcomes. Secondary outcomes will be used only for generation of new hypotheses. Clinical and metabolic predictors of the successful induction of diabetes remission will be evaluated using logistic regression modeling. We do not plan to perform any interim analyses in this trial.

12. SIGNIFICANCE

This trial builds on our ongoing pilot trial and other trials to identify a menu of metabolic remission strategies that can then be refined and tailored to individual needs based on future

research. Such an approach represents a fresh innovative approach that could turn the therapy of type 2 diabetes from a lifelong burden of drugs to either one-time or intermittent remission-induction courses that may translate into better overall quality of life and health-related outcomes.

13. APPENDIX A

Table 1. Schedule of visits and assessments in the intervention group (I), control group (C), and both groups (X).

	Weeks after randomization																			
	-1	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	7	8	9	10	11	12
Eligibility criteria	X																			
Informed consent	X																			
Randomization		X																		
Start study medications		I																		
Stop diabetes medications																				X
Clinic visit	X	X		I		I		I		I		I		X		I		I		X
Telephone follow-up			I		I		I		I		I		I		I		I		I	
Adherence to medications and side effects			I	I	I	I	I	I	I	I	I	I	I	X	I	I	I	I	I	X
Review SMBGs			I	I	I	I	I	I	I	I	I	I	I	X	I	I	I	I	I	X
Height	X																			
Weight	X	X						I						X		I		I		X
Waist and Hip Circumference		X												X						X
Blood pressure	X	X		I		I		I		I		I		X		I		I		X
Physical activity and food frequency questionnaires*	X																			X
ECG	X																			
Fasting serum for storage**	X																			
FPG	X																			
Serum ALT	X																			
Serum creatinine	X					I								I				I		
Urine BhCG***	X																			
HbA1C	X																			X
Two glucose profiles****														X						X
Return to standard glycemic care if hyperglycemia relapse identified																				
AE/SAE Review and Reporting			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*A quality of life questionnaire will also be administered at -1, 12 and 64 weeks.
**Fasting serum sample will be taken for storage during the screening visit and at 16 weeks.
***Urine BhCG will be measured in women with childbearing potential.
**** Two six-point glucose profiles will be collected on separate days. Each six-point glucose profile will include pre-meal and 2-hour post-meal SMBG readings taken on the same day.

	Weeks after randomization													
	12.5	16	20	24	28	32	36	40	44	48	52	56	60	64
Eligibility criteria														
Informed consent														
Randomization														
Start study medications														
Stop diabetes medications														
Clinic visit		X		X			X			X				X
Telephone follow-up	X		X		X	X		X	X		X	X	X	
Adherence to medications and side effects	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review SMBGs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height														
Weight		X		X			X			X				X
Waist and Hip Circumference		X		X			X			X				X
Blood pressure		X		X			X			X				X
Physical activity and food frequency questionnaires*				X			X			X				X
ECG														
Fasting serum for storage**		X												
FPG		X												
Serum ALT		X												X
Serum creatinine		X												X
Urine BhCG***														
HbA1C				X			X			X				X
Two glucose profiles****														
Return to standard glycemic care if hyperglycemia relapse identified	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review and Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*A quality of life questionnaire will also be administered at -1, 12 and 64 weeks.
**Fasting serum sample will be taken for storage during the screening visit and at 16 weeks.
***Urine BhCG will be measured in women with childbearing potential.
**** Two six-point glucose profiles will be collected on separate days. Each six-point glucose profile will include pre-meal and 2-hour post-meal SMBG readings taken on the same day.