Clinical Study Protocol

Title: The effect of low-dose empagliflozin on glucose control in adult patients with type 1 diabetes on a closed-loop insulin system: a randomized cross-over controlled trial.

Protocol #: 2021 – 6542

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Table of Contents

Version Tracker/Revision History

#	Date	Author	Description	REB Submission date **Response date**	ITA Submission date **Response date**	NOL Submission date **Response date**
7	2020-04-28	Melissa-Rosina Pasqua	Initial submission draft (different versions = internal edits).	N/A	2020-05-01 **2020-06-11** **(Response)**	N/A
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15	2021-05-10	Melissa-Rosina Pasqua	1) Direct entry pathway for those already on closed-loop therapy 2) Ongoing recruitment in between DSMB assessment	To be submitted	To be submitted	To be submitted

NB: versions 1 - 6 were edited internally
Versions 7 and 8 were originally intended for the RI MUHC's REB.

1 Background and Rationale

Type 1 diabetes is a chronic medical condition that is caused by autoimmune destruction of the insulin-producing beta cells; though it only accounts for 10% of all cases of diabetes mellitus, it is marked by the need for lifetime insulin therapy as well as risk of ketoacidosis and micro- and macrovascular complications.(1) Though many advances have allowed for new methods of glycemic monitoring, novel insulin formulations, and different methods of insulin administration, the gold standard for treatment remains intensive insulin therapy,(2) which has been linked to improved long-term outcomes in reduction of micro- and macrovascular complications.(3,4) Limitations include risk of hypoglycemia and increased disease burden to mimic the many variables in glycemic control.(2,4) Because of this, many patients with type 1 diabetes do not meet glycemic levels reflecting a target HbA1c of $\leq$ 7% recommended by Canadian diabetes guidelines.(2,5)

The rise of diabetes technology has greatly mitigated the treatment of glycemic variability. Continuous subcutaneous insulin pump therapy (CSII) is now, like basal-bolus insulin therapy, considered standard of care for type 1 diabetes management,(2) though has been shown to improve both HbA1c and quality of life in comparison to multi-daily injections (MDI).(6) This, combined with continuous glucose monitoring (CGM), allows patients with type 1 diabetes to finetune their insulin therapy to daily life.

A step further is the combination of both technologies, i.e. closed-loop insulin system, also referred to as the "artificial pancreas" (AP). A closed-loop insulin system refers to an insulin delivery system utilizing both CGM and CSII, where insulin delivery is modified based on glucose readings from CGM. Multiple studies have shown the benefit of closed-loop insulin systems on glycemic control,(7–13) with thus far one system commercially available in Canada, i.e. the Medtronic 670G.(12) The strength of closed-loop insulin delivery (as seen in the aforementioned studies) is nocturnal euglycemia, while post-prandial hyperglycemia remains a challenge given the need for accurate carbohydrate counting as well as decreased insulin absorption.

Though optimization of diabetes technology is one way to mind this gap, novel medication therapies previously used for type 2 diabetes are also under investigation. Sodium glucose-linked cotransporter inhibitors (SGLT2i's) are a relatively new medication which allows for increased urinary glucose excretion and, in doing so, euglycemia. Their use is predominantly in type 2 diabetes, both for improved glucose control as well as concomitant renal and cardiovascular protection.(14–16) Empagliflozin specifically was shown to reduce admission rates for heart failure, cardiovascular mortality, and all-cause mortality.(16)

However, various studies have demonstrated improved glycemic control with SGLT2i use as adjunct to insulin therapy in the treatment of type 1 diabetes, though this is not yet standard of care.(17–19) The use of both closed-loop insulin therapy in conjunction with SGLT2i therapy is thus a novel treatment for optimizing glycemic control in type 1 diabetes, in particular those who do not yet reach target time in range despite being on a closed-loop system.

1.1 Summary of our team's prior closed-loop system studies in adults with type 1 diabetes

Our research group focusses on innovative methods for closed-loop insulin therapy, including the impact of closed-loop insulin pump therapy itself (the algorithm created by our research group) as well as the use of dual hormone pump systems, such as the use of insulin in conjunction with pramlintide or glucagon.

More than 12 studies with more than 200 participants have been performed by our research group thus far.(7–10,20,21) These studies use the McGill Artificial Pancreas (MAP) system (see Section 4.3 for more details). Our studies have demonstrated decreased hypoglycemia (particularly nocturnal) as well as increased time in range in single-hormone closed-loop insulin delivery compared to conventional insulin pump therapy, with further improvements with the use of dual-hormone artificial pancreas with pramlintide or glucagon (see Figure 1).(9,11)

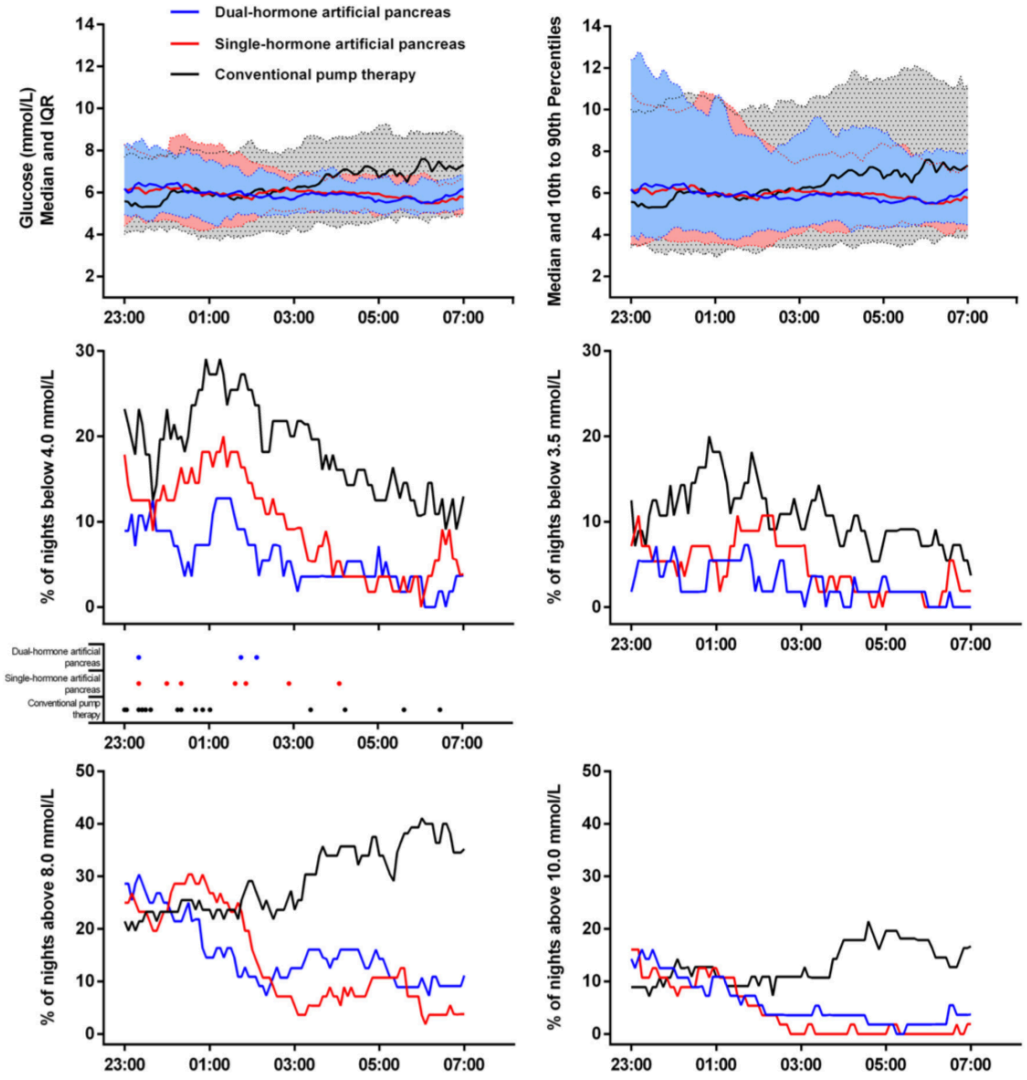


Figure 1. Taken from Haidar *et al.,* 2016 in JCEM. Glucose levels, percentage of nights in hypoglycemia (need for treatment indicated below) and percentage of nights in hyperglycemia in 28 participants with type 1 diabetes, using one of the three interventions: dual-hormone artificial pancreas (insulin and glucagon), single-hormone artificial pancreas (insulin), and conventional insulin pump therapy. See the original article for further details.(9)

1.2 Summary of prior studies using SGLT2i in adults with type 1 diabetes

Various SGLT2i agents have been used to improve glycemic control in type 1 diabetes as adjunctive therapy with intensive insulin therapy.

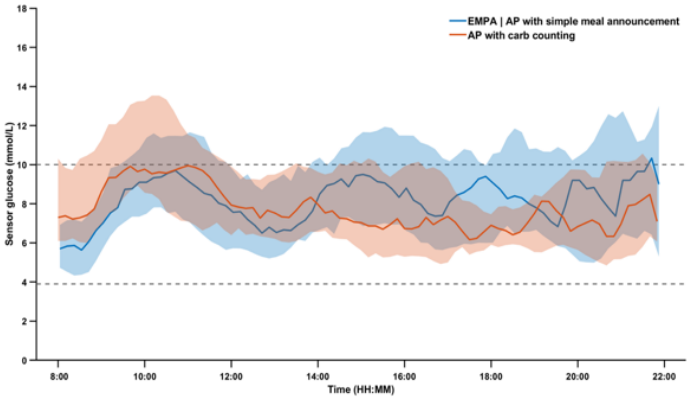
Dapagliflozin was one of the first SGLT2i's to be studied in type 1 diabetes patients.(22) More recently, in the DEPICT-2 trial, dapagliflozin 5 mg vs 10 mg vs placebo were tested in adults with type 1 diabetes in conjunction with either MDI or CSII; overall those on dapagliflozin had significantly reduced HbA1c, body weight, and total daily dose, with a 2 – 3% risk of DKA compared to 0% in placebo group.(18) It is with this data that the National Institute for Care and Health Excellence accepted approval of dapagliflozin as adjunctive therapy in type 1 diabetes patients with a BMI > 27 kg/m^2 not achieving glycemic target.(23)

Sotagliflozin and empagliflozin have also been studied in type 1 diabetes with reduction in HbA1c and total daily dose of insulin without increased hypoglycemia.(24,25) The EASE trials demonstrated that empagliflozin as low as 2.5 mg oral daily, a quarter of the starting dose for type 2 diabetes, was able to improve HbA1c, reduce body weight, improve blood pressure, and lower total daily dose; unique among the studies was that the 2.5 mg dose was equivalent in risk of DKA compared to placebo, while the higher doses at 10 and 25 mg had approximately triple the risk.(19,25) This dose produces an optimal balance in glycemic improvement without the increased risk of diabetic ketoacidosis. It is with this basis that our study desires to further the knowledge concerning the benefit of SGLT2i's in reducing glycemic variability in type 1 diabetes patients.

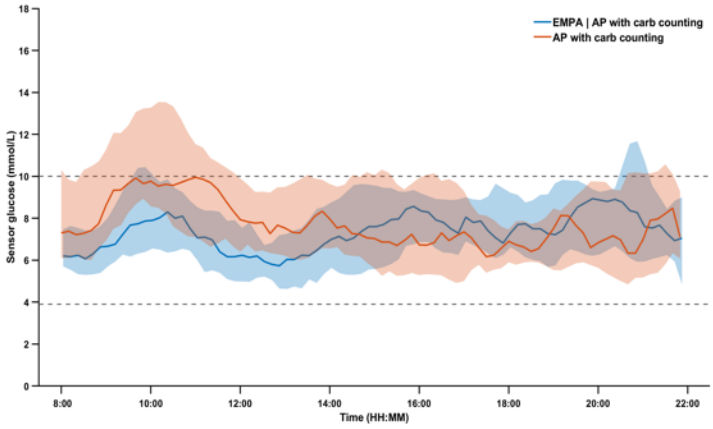
1.3 Summary of our prior studies using both closed-loop system and SGLT2i in adults with type 1 diabetes

Our research group has previously studied SGLT2i use in conjunction with a single-hormone artificial pancreas.(26) The objectives of the prior study (with manuscript in process) aimed to assess alleviation from carbohydrate counting with the use of empagliflozin and single-hormone closed loop insulin system. The treatment arms included (all with the closed-loop system but with or without empagliflozin 25 mg once daily): no carbohydrate counting, simple carbohydrate counting (i.e. meal announcement input into the pump), or full carbohydrate counting. The study was not only safe but that the use of empagliflozin with meal announcement demonstrated meal glucose and time in range (TIR) of glucose readings between 3.9 and 10.0 mmol/L [i.e. mean glucose 8.5 mM $\pm$ 1.4 mM, TIR 68% $\pm$ 16%] that were non-inferior to the closed-loop system with full carbohydrate counting [i.e. mean glucose 8.5 mM $\pm$ 1.5 mM, TIR 70% $\pm$ 23%] (Figure 2A). Of all the arms, carbohydrate counting with empagliflozin had the lowest mean glucose and TIR [mean glucose 7.4 mM $\pm$ 1.3 mM, TIR 84% $\pm$ 11%] (Figure 2B).

Though this project's aim was to assess alleviation of carbohydrate counting, it managed to demonstrate an increase of time in range between 3.9 and 10 mmol/L with the use of empagliflozin and the artificial pancreas. This was with the use of a large dose of empagliflozin, lower doses have been shown to benefit patients with type 1 diabetes without risk of DKA.(19,25) Our study aims to not only focus on time in range, but whether the lowest doses of empagliflozin can result in glycemic improvements while on the artificial pancreas to achieve therapeutic effect without increased adverse effects.



A)



B)

Figure 2. Average serum glucose as measured by CGM over 24 hours in participants with type 1 diabetes using various arms with or without empagliflozin (25 mg) and carbohydrate counting. A) CGM data for artificial pancreas with carbohydrate counting (red) or with simple meal announcement and empagliflozin (blue); empagliflozin with simple meal announcement was shown to be non-inferior to AP with carbohydrate counting ($p < 0.05$). B) CGM data for empagliflozin (blue) on AP and carbohydrate counting results in more time in range than AP alone ($p < 0.002$). All data to be included in the manuscript in process.(26)

2 Objective, Design, and Hypotheses

2.1 Objective

The objective of our study is to assess the effectiveness of low-dose empagliflozin (2.5 mg and 5 mg) on glucose control in adult patients with type 1 diabetes on a closed-loop insulin pump system, who would not otherwise be within a time in range (TIR) of $\geq$ 70% on the system.

2.2 Study Design

This is a three-way, randomized, cross-over double-blinded trial to compare the baseline closed-loop insulin pump system with placebo, empagliflozin 2.5 mg daily, and empagliflozin 5 mg daily (with a wash-out period of 7 – 21 days between each). A run-in period of 14 days will be done to identify participants who have TIR < 70% despite being on the MAP closed-loop system who do not otherwise use closed-loop therapy for routine diabetes care (alternative inclusion includes those who obtain TIR < 70% on at-home closed-loop therapy in the last 14 days).

2.3 Hypotheses

The primary hypotheses of the study are the following:

1) The use of empagliflozin 2.5 mg daily will increase time in range of 3.9 to 10.0 mmol/L compared to placebo for those on the closed-loop system.
2) The use of empagliflozin 5 mg daily will increase time in range 3.9 to 10.0 mmol/L compared to placebo for those on the closed-loop system.

The secondary hypotheses of the study are the following:

1) The use of empagliflozin 2.5 mg daily will do the following (compared to placebo):
   - Increase the percentage of time spent:
     - Between 3.9 and 7.8 mmol/L
   - Decrease the time spent:
     - Below 3.9, 3.3 and 2.8 mmol/L
     - Above 7.8, 10, 13.9, and 16.7 mmol/L
   - Proportion of participants having a TIR of 3.9 - 10.0 mmol/L of $\geq$ 70%
   - Result in improved quality of life
   - Decrease average total daily dose
   - Result in no change in ketone level compared to placebo
2) The use of empagliflozin 5 mg daily will do the following (compared to placebo):
   - Increase the percentage of time spent:
     - Between 3.9 and 7.8 mmol/L
     - Between 3.9 and 10 mmol/L
   - Decrease the time spent:
     - Below 3.9, 3.3 and 2.8 mmol/L
     - Above 7.8, 10, 13.9, and 16.7 mmol/L
   - Proportion of participants having a TIR of 3.9 - 10.0 mmol/L of $\geq$ 70%
   - Result in improved quality of life
   - Decreased average total daily dose of insulin
   - Result in no change in ketone level compared to placebo

3 Study Population

3.1 Criteria

The trial will enroll 25 participants above 18 years old with type 1 diabetes who meet the below criteria (after the run-in period).

3.1.1 Inclusion Criteria

1) $\geq$ 18 years of age
2) A clinical diagnosis of type 1 diabetes for at least one year, as per their treating diabetes physician in agreement with the primary investigator's clinical judgment (confirmatory C-peptide and antibodies will not be required)
3) HbA1c between 7 and 10.5% (both extremes inclusive), performed within the last 6 months prior to study inclusion
4) Insulin pump use (of any modality) for minimum 3 months
5) Agreement to the use of highly effective method of birth control in women of child-bearing age and active avoidance of pregnancy during the trial. *Child-bearing potential*

refers to participants of the female sex post-menarche and have not reached menopause or have a disclosed medical condition causing sterility (e.g. hysterectomy). *Post-menopausal state* refers to the absence of menses for 12 months without any alternative cause.

6) Time in range (3.9 – 10.0 mmol/L) < 70% as per CGM readings of the last 10 days during a 2-week run-in period on the closed-loop insulin delivery system.

Alternative inclusion: Time in range (3.9 to 10.0 mmol/L) < 70% as per CGM readings of the last 14 days from the participant's at-home closed-loop system (if time spent in closed loop is minimum 50%), downloaded within 7 days of the admission visit.

3.1.2 Exclusion Criteria

1) Current or < 2 week use of any anti-hyperglycemic agent other than insulin
2) Current or ≤ 1 month use of supraphysiological doses of oral glucocorticoids.
3) Requirement for regular use of acetaminophen (which may decrease CGM fidelity)
4) Planned or ongoing pregnancy
5) Breastfeeding individuals
6) Severe hypoglycemic episode within the last 3 months, defined as an event where glucose was < 4 mmol/L resulting in seizure, loss of consciousness, or need to present to the emergency department
7) Severe diabetic ketoacidosis within the last 3 years ("severe" referring to need to present to medical attention and requirement of intravenous insulin)
8) Active infection of any kind at the time of study enrollment, or any active foot ulcer
9) Recurrent infections (i.e. more than 2 in 1 year) of the following: genital, urinary tract infections, soft tissue, joint, or bone
10) Known severe peripheral vascular disease including the following: symptomatic claudication, loss of peripheral pulses, signs of peripheral arterial insufficiency as per initial clinical exam, previously documented insufficiency as per ankle or toe brachial index, prior amputations due to peripheral vascular disease
11) Osteoporosis defined as prior fragility fracture, previously measured bone mineral density with T or Z score < -2.5, or need for anti-osteoporotic medications
12) Glomerular filtration rate less than 30 mL/minutes/1.73 m^2 as per CKD-EPI formula as measured by creatinine level taken within the last 12 months.
13) Any serious medical or psychiatric illness likely to interfere with study participation as per the judgment of the investigator (e.g. cirrhosis, active cancer, decompensated schizophrenia)
14) Prior adverse reaction to SGLT2i
15) Inability to travel to the research center within 3 hours if needed during the study interventions
16) Failure to comply to the study protocol and/or research group's recommendations (e.g. change in pump parameters, ketone measurement)
17) Inability or unwillingness to comply to safe diabetes management in the view of the study group (e.g. inappropriate treatment of hypoglycemia or lack thereof)
18) Anticipation of a significant change in exercise regimen between initiation of the intervention blocks (i.e. starting or stopping an organized sport)
19) Any demonstrate of difficulty in using the iMAP System following training, as per investigator's judgment

20) Concern for safety of the participant, as per the clinical judgment of the primary investigator

3.1.3 Discontinuation Criteria

Participation in the study can be withdrawn prior to completion for the following reasons:

1) Failure to comply with the study's protocol and/or instructions given from the study team
2) Pregnancy
3) Withdrawal of consent to participate or desire to no longer take part in the study
4) The required use of medications listed in the exclusion criteria
5) Severe hypoglycemia
6) Diabetic ketoacidosis
7) Hospitalization or acute illness for any reason
8) Decision by the study group to prematurely terminate the clinical trial

3.2 Study Withdrawal

The participant of the clinical trial may cease participation at any time. Their clinical data from the study prior to cessation will be collected nonetheless; decision to use the data will depend on its completeness and the opinion of the investigators. It will be advisable that the participant complete the "End of Study" visit prior to exit, to ensure the participant's safety, to screen for any problems within the study and its materials, and to assess for reason for discontinuation that may affect the study. The study team will continue to follow the participant for an additional week to aid in transition from the closed loop system and off the medication (placebo vs empagliflozin) back to the participant's usual regimen.

3.3 Recruitment and Study Centres

The study will be conducted in Montreal, Quebec at the Clinique Médicale Hygea, affiliated with McGill University. Enrolment will consist of 25 adult participants after the run-in period (therefore more may be required to attain this number). Recruitment will predominantly take place among the clinic for adult type 1 diabetes care seen by specialists in Endocrinology & Metabolism at the Clinique Médicale Hygea, where patients will be approached by the study team and/or their endocrinologist. However, affiliate members of the division of Endocrinology & Metabolism at McGill University may also invite patients to the study, after which they will be approached by the study team. Prior participants of previous closed-loop studies performed by the research group will also be invited if they have previously written consent to be contacted for future studies.

Of those participants interested in the study, the study team will describe in detail what the study entails, answer any questions the participants have, and record clinical details pertaining to inclusion and exclusion criteria, and obtain consent (via an official consent form) from the participants.

4 Study Drugs and Materials

4.1 Study Drugs

Empagliflozin	Empagliflozin is an SGLT2 inhibitor that aids in glucose reduction through the urination of excess glucose in the context of hyperglycemia (see Section 1). The medication will be used once daily, at either 2.5 mg or 5 mg oral dose.
Placebo	A placebo pill (i.e. a pill that includes only buffer and no empagliflozin) that mimics the appearance of empagliflozin quarters to mitigate perceived changes due to "placebo effect". The placebo will also be used to conceal the dose of empagliflozin.

4.2 Study Devices and Materials

The following are the devices and materials that will be used by study participants:

t:slim Tandem Diabetes Care insulin pump, and associated materials	This is the choice of continuous subcutaneous insulin infusion (CSII) administering rapid-acting insulin, on which the closed-loop system administers insulin. The insulin pump is a small machine with a computer-driven piston administering insulin via a reservoir-tubing-catheter pathway, with which the catheter is inserted subcutaneously. Each study participant will receive one pump, with the infusion sets and reservoirs as needed.
Dexcom G5/G6 Continuous Glucose Monitor (CGM)	The device measures interstitial glucose continuously, on the basis of which the algorithm modifies insulin delivery. The device itself is inserted subcutaneously onto the patient and the data transmitted via Bluetooth technology.
FreeStyle Precision Neo meter with glucose and ketone test strips	This will be the meter of choice for the study to measure capillary blood glucose and ketones. This is required for Dexcom calibration, to detect measurement errors, and to measure ketones to assess for baseline ketone bodies while on SGLT2i and to rule out ketoacidosis in the event of illness and unexplained high glucose. Participants will be asked to check ketones daily. In the event of Precision Neo malfunction, participants will be requested to use other means of ketone measurement available at home until the meter may be repaired or replaced as soon as possible. Other options include other Abbott ketone meters (such as the Freestyle Libre reader) or urine ketone test strips. Blood samples will be highly recommended over urine.
Study Smartphone	The main algorithm for the closed-loop system is set on this device via the iMAP application (see section 4.3). The smartphone, pump, and sensor communicate via Bluetooth. Each study participant is given one smartphone.
Empagliflozin	Empagliflozin 2.5 mg and 5 mg tablets will be used. To ensure dose is concealed, tablets will be encapsulated to ensure the tablets appear identical.
Placebo	Participants' encapsulated pills may placebo pills with identical appearance to the treatment medication.

Emergency kit	The kit includes fasting acting glucose tablets, insulin syringes, and intranasal glucagon. This will be given to all participants.

4.3 McGill Artificial Pancreas (MAP) System

The McGill Artificial Pancreas (MAP) is an insulin delivery closed-loop system that uses an algorithm to modify continuous subcutaneous insulin administration based on continuous glucose monitoring, with communication through Bluetooth technology. The system is comprised of the following:

1) Glucose sensor (via the Dexcom G5 or G6)
2) A mobile application, called iMAP, on a study smartphone
3) An insulin pump, via the t:slim Tandem pump

Figure 4. Depiction of the McGill Artificial Pancreas.

5 Trial Design

5.1 Phases of treatment therapy

This is an outpatient randomized cross-over trial to compare the following medications while on insulin closed-loop system (MAP):

1) Placebo
2) Empagliflozin 2.5 mg daily
3) Empagliflozin 5 mg daily

Treatment period: Each patient will use each of the pills for 2 weeks, with a washout period of 7 – 21 days between each intervention. The order of medication use will be randomized, though each participant will use each of the 3 interventions during the study.

5.2 Questionnaires

Participants' quality of life will be measured by the following questionnaires:

- Type 1 Diabetes Distress Scale

- Hypoglycemic Fear Survey – II
- INSPIRE questionnaire for adults
- Study drug symptom questionnaire (to rule out symptoms at baseline)

Participants will fill out the questionnaires at the admission visit, and after each intervention remotely (documents will be mailed to participant). All questionnaires will be collected at the End-of-Study Visit.

5.3 Randomization

Randomization will be done by block-balanced randomization (block size 6) to randomize to whichever sequence of interventions. This will be performed by a study member after inclusion into the study (i.e. after the run-in period).

5.4 Blinding

This study will be double-blinded, so that both participants and investigators will not know the sequence of interventions for each participant. The participants will be given encapsulated identical tablets of either placebo, empagliflozin 2.5 mg, or empagliflozin 5 mg.

5.5 Visit Schedule

The overall time within the study for each participant upon inclusion will be 9 – 15 weeks. For any visit (i.e. initial visit, training visit, or end-of-study visit), if there are any concerns or issues preventing the patient from physically coming in to the hospital or clinic setting, the meeting can be done by teleconference. If research material will be required during the teleconference, this will be securely mailed to the participant to be used during the visit, and then securely mailed back to the research group. If laboratory investigations are required in this remote setting, they can be done using a bloodwork requisition at the closest laboratory centre to the patient.

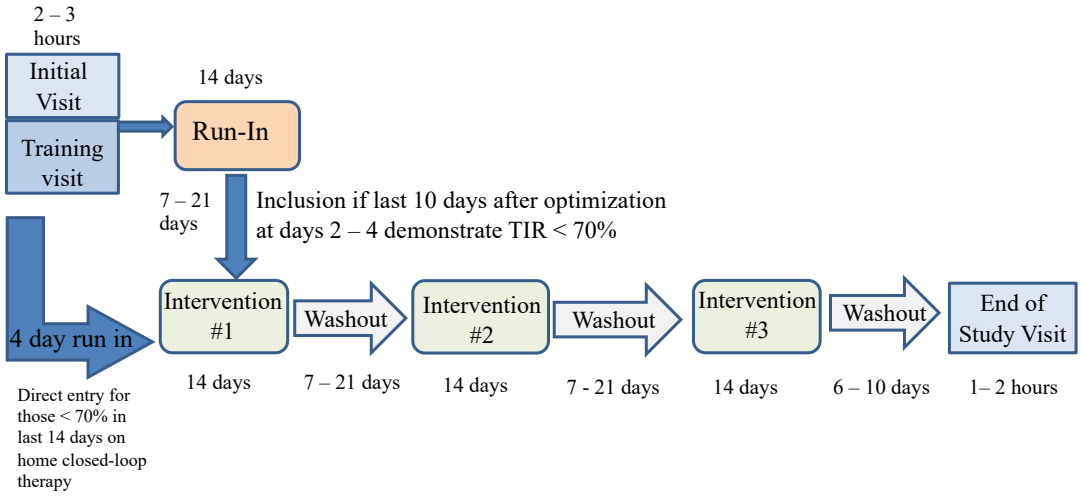


Figure 5. Timeline of study interventions for each participant. Each intervention will consist of either placebo, empagliflozin 2.5 mg daily, or empagliflozin 5 mg daily, depending on the patient's randomized sequence of treatment. This results in 6 different sequences (see Section 6.4.1).

6 Study Procedures

6.1 Initial study visit

The initial study visit with the participant will be conducted by one of the members of the study group, and will entail the following.

General procedures	- Explanation of the study and answering of questions - Assessment of inclusion and exclusion criteria - Signing of consent form
Medical history	- Complete past medical history, both of their type 1 diabetes and other medical conditions - Current diabetes care (frequency of glucose checks, recent difficulties in glycemic control, history of DKA, etc.) - Current diabetes regimen and doses, in particular the last 7 days of insulin therapy - Social history and habits (work, education, exercise, smoking, etc.) - Other medications, over-the-counter medications, and supplements
Physical examination	- Blood pressure - Height and weight - Foot and peripheral vascular exam - Signs of lipo-hypertrophy in areas of insulin catheter sites
Blood laboratory investigations	5 mL of serum via intravenous catheter will be taken to assess HbA1c for glycemic control, creatinine to ensure appropriate renal function, and (if woman of child-bearing age) beta-HCG to rule out pregnancy. Beta-hydroxybutyrate, bicarbonate, and basic electrolytes (sodium, potassium, and chloride) will be used as a baseline for level of ketosis and for possible risk of ketoacidosis during the study. At the visit, finger-prick testing on the patient's study meter will be done for glucose and ketone level (as measured on the meter) for a baseline.
Questionnaires	Participants will be given time to fill out quality of life questionnaires (see section 5.2).
Discussion of risks of empagliflozin	Along with the discussion of risks and benefits of empagliflozin in the consent form, participants will be taught to identify the symptoms of urinary tract infections, fungal infections, dehydration, or any other acute illness or infection, and what to do in each scenario. A prescription for clotrimazole 1% cream will be given to treat any topical fungal infection on an as-needed basis (this will be given if participant is accepted after the run-in study). The patient will be asked to seek medical attention for any other concerns of infection.
Emergency kit	An emergency kit (see Section 4.2) will be given if its contents are not already possessed by the participant. The participant will be instructed to carry these items at all time. A study wallet card

	must be carried by the participant at all times, which will include the following: - Study title - Protocol number - Devices - Medication names - Physician contact information in the case of emergency

Given the current pandemic and the delays in seeking laboratory investigations, there will be an option to use the laboratory investigations from the initial visit to be used as inclusion criteria if there have not been recent tests within the last 6 months. If this is done, the MAP will not be started until results are back.

6.2 Training of study materials

Another meeting on a separate day will potentially be held for the training of study materials. If a participant lives far away enough that having both the initial clinic visit and the training visit be the same day, this will be offered.

During the training visit, participants will receive the following devices:
- T:slim Tandem insulin pump and required materials
- Dexcom G5 or G6 sensors and transmitter
- Study smartphone with pre-installed iMAP application
- Freestyle Precision Neo meter with glucose and ketone strips

Training on the use of t:slim Tandem insulin pump will be provided (if not already in use by the participant), as well as for the installation and use of Dexcom G5 or G6 transmitter and sensors and the iMAP system (all with accompanying user guides).
- The member of the study group will insert patient's current pump parameters into the new device and assist with the physical transition from usual to study pump.
- Participants will be reminded to calibrate their Dexcom G5/G6 with the Freestyle Precision Neo meter and instructed when to check for ketones. Additional training will be performed to ensure safe diabetes and glucose management.
- Discussion on how to titrate insulin-to-carbohydrate ratios due to reduced insulin requirements on the pill will be provided.
- Participants will be instructed that insulin-to-carbohydrate ratios should be reduced by 10% at the beginning of each intervention (unless told so as per clinician judgment due to hyperglycemia); the effect of this will be reassessed remotely with the research team.
- The risks and possible side effects of empagliflozin will be discussed with the patient. Instructions on how to proceed in the case of nausea, illness, high levels of ketones, or any concern for DKA will be given.
- Participants will be instructed to measure point-of-care ketones daily. If ketone bodies rise above 0.6 mmol/L or symptoms of impending ketoacidosis are present, participants must follow study instructions for DKA.
- If there are any concerns from the study team that the patient is not capable of following these instructions, the patient will not be included in the study.

6.3 Closed-loop run-in period

After the initial study visit and completion of training with transition to the MAP in the office, a run-in period of 14 days will take place. On the first day of this run-in period, participants will be asked to activate "exercise mode" of the closed-loop system before driving any vehicle for more than 10 minutes to prevent hypoglycemia while driving.

Participants are encouraged to contact the on-call staff (available 24/7 throughout the study) if technical issues or questions arise. There is a remote follow-up with the study team 2 – 4 days after initiation of the run-in period, which is done via email, phone call or text message, or other communication. This is to ensure the participant's safety and comfort on the system.

After the run-in period, CGM data will be analyzed for time in range. If the time in range is less than 70% during the last 10 days, the participant will be included in the study. Data will also be reviewed to optimize any insulin to carb ratios or parameters that need adjustments. If the participant is not to be included in the study, the participant must return the study devices back to the research group.

6.3.1 Alternative Path: For Patients Already on Closed-Loop Therapy

The use of commercial forms of closed-loop therapy in routine diabetes care has become more prominent since the development of the original protocol. The participant's experience with their own system may be more reflective of deficits in optimized control with closed-loop therapy, and still reflects the objective of the study. Therefore, participants are able to bypass the full run-in assessment if they use a closed-loop insulin system (with use of closed-loop minimum 50% of the time) and their time in target range (3.9 to 10 mmol/L) is less than 70% within the last 14 days, from data downloaded within 7 days of the admission visit. This direct entry will only apply to participants after protocol approval.

Note that there may be circumstances where an eligible participant owns a pump with capacity for closed-loop insulin delivery but does not use this function or does not have the information available; this may be due to lack of sensor use, personal choice, or failure to download data. In this situation, the participant will undergo the 14-day run-in on the McGill Artificial Pancreas.

For participants entering the study directly, there will be 4 days of a small run-in to familiarize the participant to the system and optimize settings via 1 remote visit on a day between Days 2 to 4. After this optimization, the participant will be able to start Intervention 1 directly.

6.4 Interventions

After inclusion (whether after run-in or at the admission visit via direct entry), the participant will undergo randomization. The study drugs will be sent to the individual before each intervention in the order of the sequence chosen by randomization. For those undergoing direct entry, this will be given at the initial visit.

6.4.1 General Procedures for All Interventions (14 days)

For each intervention, the participant will switch from their usual diabetes regimen to the study insulin pump (MAP), which will require installation of the Dexcom G5/G6 sensor one day prior for calibration. The closed-loop algorithm will be initiated in the morning of Day 1. The

participant will be recommended to reduce mealtime boluses by 10% (i.e. carbohydrate ratios will be increased by 10%) prophylactically at the beginning of each intervention (unless told not to do so as per clinical judgment due to ongoing hyperglycemia) to avoid hypoglycemia from the study drug. The participant will take the study drugs each morning from Days 1 to 14 of each intervention.

A remote follow-up will be provided 2 – 4 days into each intervention (by similar means to the run-in period) to reassess safety, comfort, and to optimize insulin settings. Remote follow-up can also be performed as needed throughout the rest of the intervention. Because of the optimization the first 4 days, the last 10 days of CGM data will be used for analysis.

After each intervention, participants will fill out the questionnaires (Section 5.2); these however may be completed during the following wash-out period.

Note the above sequences are 6 possibilities:

1) Placebo → Empagliflozin 2.5 mg → Empagliflozin 5 mg
2) Placebo → Empagliflozin 5 mg → Empagliflozin 2.5 mg
3) Empagliflozin 2.5 mg → Placebo → Empagliflozin 5 mg
4) Empagliflozin 2.5 mg → Empagliflozin 5 mg → Placebo
5) Empagliflozin 5 mg → Placebo → Empagliflozin 2.5 mg
6) Empagliflozin 5 mg → Empagliflozin 2.5 mg → Placebo

6.4.2 Point-of-care ketone measurement during interventions

As there is a known increased risk of ketoacidosis in type 1 diabetes patients on SGLT2i, point-of-care ketone testing will be performed at the clinic visit, and daily during each intervention. This is not only to document a baseline level of ketones (as empagliflozin may slightly elevate baseline ketones without acidosis, independent of sugar levels), but also to predict any development of early ketoacidosis. Due to this unique form of ketosis, patients will be instructed on treatment in this specific context (i.e. bolus with carbohydrates). Any concerns at any time may be answered remotely by a member of the study team.

6.5 Wash-out period

The wash-out period between each intervention is 7 – 21 days. This is to allow for excretion and metabolism of any study medication in each participant to ensure no following intervention is affected by the prior. The half-life of empagliflozin is estimated at 12.4 hours (27), therefore by 7 days, a sufficient amount of the drug will be cleared. During the wash-out period, each patient will be able to return to their usual method of diabetes treatment outside of the study. Remote contact by the study group will be performed at day 4 ($\pm$ 2 days) of the wash-out period to ensure safety with their diabetes care and other matters of health.

6.6 End of study visit

An end of study visit will be conducted 6 to 10 days following completion of the final washout period. This will take approximately 1 – 2 hours, and will entail a detailed interview (Section 6.6.1), the return of quality-of-life questionnaires (Section 5.2), and the return of all study devices.

6.6.1 Interview

Initial questions	- Can you describe your experience concerning your diabetes care during the study?
Questions concerning the closed-loop system	- Can I ask you about your experience and feelings concerning being on a closed-loop system? o What did you like about this pump system? o What did you not like about this pump system? o What were your experiences with food and boluses on this system? o What were your experiences overnight with this system? o Would you replace your current regimen with this system?
Questions concerning the use of empagliflozin	- Can I ask you about your experience and feelings concerning the study drug? o Did you notice a difference in your overall diabetes care while taking the pill? o Is there anything you liked about taking the pill? o Is there anything you did not like about taking the pill? o What were your experiences with food and boluses while using the pill? o What were your experiences overnight with this system? o Did you notice differences between interventions? o Would you want to continue taking the pill?
Final question	- Is there anything else that you would like to tell us about your experience of these glucose management systems?

7 Risk and Risk Mitigation

7.1 Empagliflozin dose rationale

The doses of empagliflozin used stem from the EASE trials previously performed in patients with type 1 diabetes.(19,25) Though 10 and 25 mg of empagliflozin are the commercial doses for glycemic control in type 2 diabetes, these doses have demonstrated increased risk of diabetic ketoacidosis in those with type 1 diabetes. Empagliflozin 2.5 mg once daily was used in the EASE-1 and EASE-3 trails with therapeutic benefit, with equivalent risk of DKA compared to placebo in EASE-3.(19,25)(19,25) A dose of 5 mg adds an additional "low-dose" option to optimize euglycemia with little to no risk of ketoacidosis, which makes it a novel dose not seen previously in the literature but one that is used off-label by some endocrinologists.

7.2 Medical and Safety Monitoring

During the study, an endocrinologist involved with the research study will be on call at all times in the need for immediate assistance for medical guidance in the case of acute illness. For technical support, a study team member will be able to answer questions by participants at all times.

7.2.1 Monitoring

As described previously, remote visits will be performed to screen for any difficulties by the participant. To ensure no adverse events go unnoticed by the research team, adverse events (both passive and active surveillance through the questionnaires) and glucose outcomes will be verified by the study team after every 5 participants. If a non-physician notices a pattern concerning adverse events, this will be brought up to one of the physicians in the study.

7.2.2 Concomitant and prohibited medications

7.2.2.1 Empagliflozin

There are various medications that are discouraged and contraindicated to reduce the risk of adverse events in the use of empagliflozin (see Section 7.3.1):

- Medications that increase risk of dehydration
    - Loop diuretics, thiazide diuretics, alpha-blockers (e.g. tamsulosin)
    - Interventions for above: continued hydration, possible need to assess renal or blood pressure measurements
- Medications that increase risk of low blood pressure
    - Calcium channel blockers, loop and thiazide diuretics, ACE inhibitor, Angiotensin-receptor blocker, Angiotensin-receptor neprilysin inhibitor (ARNI), Clonidine
    - Interventions for above: continued hydration, possible need to assess renal or blood pressure measurements
- Medications that increase risk of hypoglycemia
    - Salicylates, fluoroquinolones, oral hypoglycemic agents (e.g. metformin), somatostatin analogues (e.g. octreotide), sulfonamide antibiotics, pramlintide
    - Intervention for above: fast-acting dextrose in the acute setting, decreased insulin doses in the chronic setting

7.2.2.2 Continuous glucose monitoring

- Acetaminophen may reduce fidelity of glucose monitoring. Therefore, avoidance of regular acetaminophen is highly recommended and the need for regular use of the medication is an exclusion criteria.

7.3 Risks Associated with the Study

7.3.1 Empagliflozin

The mechanism of action of empagliflozin is inhibition of the sodium-glucose-linked cotransporter 2, which blocks reabsorption of glucose in the tubules of the kidney. This creates a glucosuric and diuretic effect. The following are known risks in order of likelihood:(27)

- Common risks (>10%)
    - Reduced need for insulin (and in doing so, possibly hypoglycemia)
- Less common risks (1 – 10%)
    - Increased urine output
    - Urinary tract infection
    - Genito-urinary fungal infection
    - Nausea
    - Dyslipidemia
    - Hypotension

- Rare risks (< 1%)
    - Ketoacidosis
    - Acute kidney injury
    - Hypersensitivity reaction, including urticaria, skin rash, angioedema
    - Dehydration
    - Necrotizing fasciitis
    - Severe urinary infection including: pyelonephritis, urosepsis
- Reported associations with SGLT2is
    - Canagliflozin was associated with increased risk of amputation in the CANVAS trial;(14) however no other study using SGLT2 inhibitors reported this link
    - Though empagliflozin is not associated with increased risk of fracture in various studies, canagliflozin and other SGLT2i's may increase bone resorption and decrease bone mineral density.(28)

7.3.2 Blood sampling

This is required to obtain blood laboratory values including HbA1c, creatinine, etc. Blood sampling is done through temporary intravenous access, which may result in localized pain, bleeding, or bruising at the puncture site. Participants may rarely feel dizzy or uneasy if they are prone to experience vasovagal responses from these procedures. Rarely, infection, thrombophlebitis or nerve damage may occur.

7.3.3 Glucose sensors and insulin infusion sets

Glucose sensors and infusion sets are both inserted subcutaneously. It is recommended to change insertion site every 3 days for an infusion set, and every 7 days for a glucose sensor. Both pose a risk of pain with insertion, continued irritation, and rarely, contact dermatitis if the patient has an underlying hypersensitivity to the adhesive. Rarely, use longer than suggested for the product may increase risk of local infection. Lack of insulin site change as recommended may increase risk of lipo-hypertrophy, which may then result in hyperglycemia.

7.3.4 Hypoglycemia

Hypoglycemia refers to a blood glucose less than 4.0 mmol/L that may induce sympathetic and neuroglycopenic symptoms; some patients, depending on presence of autonomic neuropathy or frequency of hypoglycemia, may not develop these symptoms. Severe hypoglycemia refers to an event of hypoglycemia which requires third party intervention, i.e. the participant is not able to treat hypoglycemia via fast carbohydrates or glucagon, which includes (but is not limited to) impaired level of consciousness, coma, or seizure.

Hypoglycemia is mitigated by the use of continuous glucose monitoring with alarm sets which are triggered by hypoglycemia. The threshold at which the alarm starts can be modified by the user. Review of hypoglycemia treatment will be performed at the initial clinic visit and if not in the participant's possession already, dextrose tablets and glucagon kit (from the emergency kit) will be offered for treatment of hypoglycemia.

7.3.5 Hyperglycemia (and associated conditions)

Mild hyperglycemia is any glucose level above 10 mmol/L, but severe hyperglycemia refers to excess glucose that results in symptoms of polyuria, polydipsia, and fatigue.

Diabetic ketoacidosis (DKA) refers to a low-insulin state where ketone bodies are produced, creating acidosis and severe electrolyte disturbances, which requires immediate attention. This may range from mild presentation where adjunctive insulin and a change in insulin catheter is needed, to severe life-threatening presentation where hospitalization is required for intravenous insulin therapy. DKA may be triggered by lack of insulin administration (compliance, catheter dehiscence, pump malfunction) or an underlying condition such as acute illness. Symptoms include nausea, vomiting, abdominal pain, and dehydration. The table below (created by the American Diabetes Association) demonstrates laboratory investigations suggestive of ketoacidosis:

	DKA (usual serum glucose > 13.8 mmol/L)			**HHS (serum glucose > 33 mmol/L)**
	Mild	Moderate	Severe	
Arterial pH	7.25 – 7.30	7.00 – 7.24	< 7.00	> 7.30
Serum HCO3 (mmol/L)	15 - 18	10 – 14.9	< 10	> 18
Serum ketone	Positive	Positive	Positive	Minimal if positive
Urine ketone	Positive	Positive	Positive	Minimal if positive
Serum osmolality (mOsmol/kg)	Variable	Variable	Variable	> 320
Anion gap	> 10	>12	> 12	Variable
Mental status	Alert	Alert to drowsy	Stupor to coma	Stupor to coma

Table 1. Diagnostic criteria for DKA vs HHS as per the American Diabetes Association (2009).(29)

Hyperglycemic hyperosmolar state (HHS) is another syndrome which presents as persistent hyperglycemia > 33 mmol/L with severe dehydration in the absence of frank diabetic ketoacidosis (table 1); this is however more common in type 2 diabetes than type 1 diabetes.

Empagliflozin, as described, may also contribute to ketoacidosis in an unknown mechanism, but uniquely, the hyperglycemia is not as obvious as the excess glucose is excreted through urination. SGLT2i use poses an increased risk of DKA specifically in those with type 1 diabetes.(18,19,24) The doses used in our study have the lowest risk for ketoacidosis. Various studies have been performed to treat this unique form of ketoacidosis in type 1 and type 2 diabetes, an example being the STICH protocol for type 1 diabetes patients using an SGLT2i as adjunctive treatment (Figure 6).(17)

A)

TABLE 1. STICH PROTOCOL INVOLVING ADMINISTRATION OF INSULIN, CARBOHYDRATES, AND FLUIDS ONCE KETOSIS HAS BEEN CONFIRMED IN THE SETTING OF SGLT INHIBITOR USE IN COMBINATION WITH INSULIN FOR THE TREATMENT OF TYPE 1 DIABETES

Step 1	Verify ketosis by early symptoms as described above Identify conditions that might be causing ketosis[a] Test for ketones
Step 2	STICH protocol STop the SGLT inhibitor[b] + Inject bolus insulin + Consume 30 g carbohydrates + Hydrate
Step 3	Recheck ketones every 3–4 h
Step 4	Seek emergency medical care if ketosis does not resolve or if symptoms of DKA appear, including abdominal pain, nausea, vomiting, fatigue, and/or dyspnea

[a]Symptoms may start hours after last SGLT inhibitor dose (e.g., if SGLT inhibitor is taken in the morning, symptoms may begin in the evening).
[b]Patients should not take the SGLT inhibitor after ketosis is detected and not take another dose until ketones have resolved.
DKA, diabetic ketoacidosis; SGLT, sodium glucose cotransporter.

B)

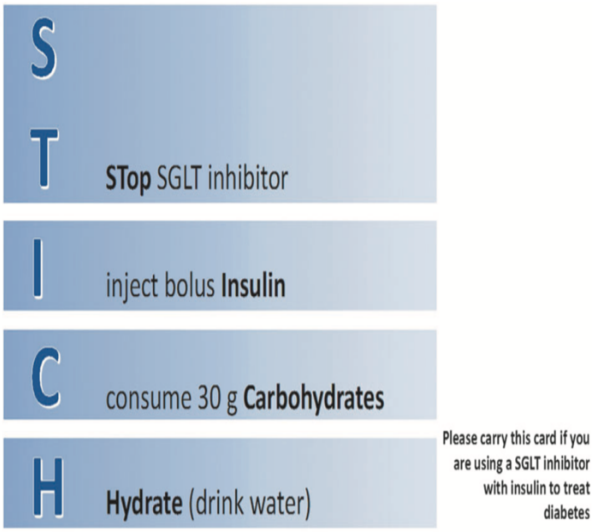


Figure 6(A-B). Description of the STICH protocol for patients with type 1 diabetes on SGLT2i's as adjunctive therapy to insulin.(17) (A) The recommended steps as described in the article for treatment and monitoring of ketones. (B) Sample wallet card (front) describing the STICH protocol to treat any possible ketoacidosis.

7.3.6 Genito-urinary and soft tissue infections

Empagliflozin increases the risk of genito-urinary infections (1 – 10%), in particular genital mycotic infections. There have also been reports of increased risk of soft tissue infection, particularly in the genital area, the worst being necrotizing fasciitis of the peritoneum, i.e. Fournier's gangrene (with a risk of < 1%). Increased amputations were previously reported with canagliflozin, (14) but this has not been reported with empagliflozin.

7.3.7 Dehydration

Increased urinary frequency and urine volume is commonly seen with SGLT2i's due to their mechanism of action, at a risk of 1 – 10%. In severe cases where a participant is not able to remain hydrated, there is a risk of dehydration, and subsequently if left untreated, low blood pressure and dizziness. Acute kidney injury may occur in the context of severe dehydration; the risk is increased if there is already existing kidney disease. Most of these cases can be avoided with adequate hydration, and in severe cases, can be treated by intravenous fluids.

7.3.8 Risks related to the MAP system

7.3.8.1 Disruption in communication between the insulin pump device and iMAP:

- If Bluetooth communication is disrupted between the two devices, the application will automatically attempt to reconnect. If this is not successful after 20 minutes, the system will revert to a mode of open-loop insulin basal administration (i.e. administration of pre-programmed basal rates). If Bluetooth connection is lost during bolus delivery, participant will be alarmed by the system and manual bolus may be required.

7.3.8.2 Error in glucose sensor accuracy:

- The MAP uses Dexcom G5 or G6 for continuous glucose monitoring, that requires twice per day minimum calibration for accurate measurement. If the interstitial glucose measurement

performed by the CGM is inaccurate, insulin recommendations by iMAP will be suboptimal. If there is a major discrepancy between CGM measurements and point-of-care glucose testing by capillary glucose (see table below), participant will be prompted to re-test for calibration with a separate measurement in 30 minutes. If the second calibration demonstrates ongoing error, open-loop mode will commence. Participants will be asked to contact the research team if sensor error persists 30 minutes post calibration, as this may be due to sensor malfunction and may require sensor replacement.

For BG <=7.5:	**For BG >7.5**
sensorError= |(BG - bgSensor)| Sensor error threshold = 2.0mmol/L	sensorError = |(BG - bgSensor)|/ BG Sensor error threshold = 27%

- Participants will also be recommended to **avoid acetaminophen.** Taking medications containing acetaminophen may falsely raise the sensor readings, causing the MAP System to deliver more insulin than required.

7.3.8.3 Disruption in communication with the glucose sensor

- If Bluetooth communication of the CGM to the rest of the MAP system is lost for more than 60 minutes, the insulin pump system will revert back to open-loop mode. Closed-loop insulin delivery will restart once CGM communication has been re-established.

7.3.8.4 Smartphone malfunction or shut-down

- If there is any malfunction with the study phone preventing access to iMAP (e.g. insufficient battery), open-loop mode will commence within 20 minutes.

7.3.8.5 Software error

- Any termination of the iMAP software for any reason will result in reversion to an open-loop mode of insulin delivery.

7.4 Pregnancy

Empagliflozin has not been previously tested in pregnancy, therefore it is a Category C class medication in pregnancy. Furthermore, glycemic management during pregnancy requires tighter-than-average regulation and should be followed by a specialized multi-disciplinary team. Given the risks, any female participant who has menses is at risk of pregnancy (see prior definitions) and must be on appropriate contraception throughout the study and will be counselled on the risks of pregnancy in the study. If a participant feels she may be pregnant, she should stop the study medication and contact the study group immediately for confirmation (i.e. pregnancy test) and will be withdrawn from the study if positive. Serum beta-HCG (via blood test) will be measured at the Initial Clinic Visit in female participants with ongoing menses to biochemically rule out pregnancy. Females who are post-menopausal or who have undergone removal of the uterus and/or ovaries will be exempt from taking a pregnancy test.

8 Statistical Analysis

All study outcomes will be compared between placebo vs. empagliflozin 2.5 mg, as well as placebo vs. empagliflozin 5 mg. Wherever applicable, outcomes will be calculated for 24 hours, daytime (6h00 – 24h00), and nighttime (24h00 – 6h00).

8.1 Study Endpoints

8.1.1 Primary endpoints

- Time in target range (3.9 to 10 mmol/L)

8.1.2 Secondary endpoints

8.1.2.1 Glycemic level as per CGM readings

1) Percentage of time spent in the following ranges of glucose levels
    a. Between 3.9 and 7.8 mmol/L
    b. Below 3.9, 3.3 and 2.8 mmol/L
    c. Above 7.8, 10, 13.9, and 16.7 mmol/L
2) Mean glucose level
3) Standard deviation of glucose levels as a measure of glucose variability
4) Percentage coefficient of variation of glucose levels
5) Proportion of participants with TIR between 3.9 - 10.0 mol/L $\geq$ 70%

8.1.2.2 Quality of life measures

1) Average scores between interventions for the following questionnaires
    a) Type 1 Diabetes Distress Scale
    b) Hypoglycemic Fear Survey – II
    c) INSPIRE questionnaire for adults

8.1.2.3 Other secondary endpoints

1) Total daily insulin dose
2) Average point-of-care ketone level per intervention
3) Rise in ketone level between interventions

8.1.3 Safety endpoints

The following will be evaluated for all interventions:

1) Number of episodes of severe hypoglycemia (as defined previously)
    a. Requiring emergency room visit
    b. Requiring hospitalization
    c. Not requiring medical attention
2) Number of episodes of diabetic ketoacidosis
    a. Requiring emergency room visit
    b. Requiring hospitalization
    c. Not requiring medical attention
3) Number of infections
    a. Genito-urinary
    b. Other infections
4) Forms of dehydration, defined as drop in blood pressure, dizziness, increased thirst or urination, or symptomatic feeling of dehydration
5) Gastro-intestinal side effects

8.2 Sample Size and Power Calculations

The power calculations aim to compare the effects of the following interventions on the primary endpoint (time in target range), made at the $\alpha = 0.05$ significance level:

i) placebo vs. empagliflozin 2.5 mg;
ii) placebo vs. empagliflozin 5 mg.

Sample size was calculated based on the smallest clinically significant difference, which we assume as 6.25% (i.e. 90 min per day) of time in target range. The standard deviation of the paired differences in the percentage of time in target range is assumed to be 10% from our previous studies.(7,8,11) Given these parameters, and with an aim for power of 80%, a sample size of 23 patients was calculated using the sample size formula for paired t-test. However, to accommodate uncertainty within the power calculation, 25 participants will be recruited.

8.2.1 Level of significance

5% significance threshold will be used to assess statistical significance. No formal correction will be applied for the secondary comparisons.

8.2.2 Statistical analysis

A linear mixed effect model will be used to assess the effect of these treatments on the described endpoints. An approximate normal distribution will be examined from residual values from the regression model. If there are any major outliers in the values, a transformation or non-parametric analysis will be performed. Carry-over effects will be tested via hypothesis of no sequence effect.

This type of analysis will also be used to assess the results of individual survey items and composite scores to account for the types of interventions and their sequences. Reverse scoring will be used in the direction of greater worries or higher treatment satisfaction. Descriptive analysis will also be done for survey ratings, for e.g. percentage of patients that check off "disagree", "agree", etc. Pearson correlation and analysis of variance will be used to assess for any correlation with participant characteristics (e.g. sex, age, duration of diabetes).

9 Ethical and Legal consideration

9.1 Good clinical practice

This study will be performed as per good clinical practice, as described in the International Conference of Harmonisation (ICH) E6: Guideline for Good Clinical Practice (1 May 1996), in agreement with the Declaration of Helsinki and regulations met locally, by the Institutional Research Board of Advarra at the Clinique Médicale Hygea, and by McGill University.

9.2 Delegation of investigator's duties

The primary investigator will ensure the following:

- That all study members of the research team are qualified, informed of the protocol and study treatments and its subsequent changes, and the overall function of the trial
- That the timeline of the study is respected
- That co-investigators and other personnel are delegated appropriate duties

9.3 Participant's Informed Consent

A participant will only be included in the study if informed consent has been obtained. At the initial visit, reading material concerning details of the trial (including possible risks) will be given to the participant; this will also be discussed verbally to the participant by the study member at the visit. Both the study member and the participant will sign and date the document of consent. The original copy of this document will be kept with the study team, and a copy will be given to the participant. Only after consent has been contained will the rest of the study be continued. A letter will be sent concerning the study to the participant's primary physician undertaking care of their diabetes. Consent may also be withdrawn as per Section 3.2.

9.4 Confidentiality

Confidentiality will be respected as per routine practice as mandated by the Royal College of Canada. Participant's personal identifiers, including names, date of birth, and address, will be concealed, and replaced by a study number. This will be used to record participant's results as used by the investigator and team members; these results will be stored on a protected computer as per regulations of the Institutional Review Board of the clinic and McGill University.

9.5 Approval of the clinical study protocol and amendments

An application will be sent to the clinic's Institutional Review Board for assessment and approval prior to start of the study. If any changes are made to the study protocol, the IRB will be informed and the study will continue once the amendment has been approved. The primary investigator will keep track of all communication with the IRB.

9.6 Record retention

The study will follow guidelines as per ICH where all information will be collected and kept securely for 25 years.

10 Data Safety and Monitoring Board

10.1 Roles and Responsibilities

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the study team. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The primary responsibilities of the DSMB are to 1) periodically review and evaluate the study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial.

10.2 Membership

The membership of the DSMB should reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. For this trial, the DSMB is composed of two adult endocrinologists that are independent of the study.

10.3 Conflict of Interest

No member of the DSMB should have direct involvement in the conduct of the study. Furthermore, no member should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Letters of invitation to prospective DSMB members will include the following: "Acceptance of this invitation to serve on the Low Dose Empa trial, protocol 2021-6542 DSMB confirms that I do not have any financial or other interest with any other organizations involved in the study that constitute a potential conflict of interest."

10.4 Meetings

The DSMB will meet:
(1) After the first 10 participants are finished their interventions.
(2) After P011 to P025 have finished their interventions.
(3) After any serious adverse event.

Items reviewed by the DSMB include:

- Individual and cumulative data for evidence of study-related adverse events;
- Individual and cumulative data for evidence of efficacy;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The DSMB should conclude each review as to whether the study should continue without change, be modified, or be terminated.

Recommendations regarding modification of the design and conduct of the study could include:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study because of serious concerns about subjects' safety, inadequate performance, or rate of enrollment.

10.4.1 Meeting Format

The recommended meeting format consists of two sessions: Open Session and Closed Session:

(1) **Open session**: issues relating to the general conduct and progress of the study are discussed including adverse events, demographic characteristics of enrollees, and protocol compliance. The principal and/or co-investigators and/or the study coordinator should be in attendance in order to present results and respond to questions.
(2) **Closed session**: Grouped and individual safety data and efficacy data are reviewed at this session. This final session involves only DSMB members to ensure complete objectivity as they discuss outcome results, make decisions, and formulate recommendations regarding the study.

10.4.2 Decisions

After a thorough discussion of DSMB members' opinions and rationale, the final recommendations of each DSMB member should be solicited during the Closed Session. All decisions must be a consensus. If a consensus is not reached, the IRB will be notified.

10.4.3 Study Reports

It is the responsibility of the PI to ensure that the DSMB is apprised of all new safety information relevant to the study. The DSMB should receive all protocol revisions and may receive other documents relating to the study. Reports are prepared by a member of the study team and distributed to the DSMB at least three days prior to the meeting. The data presented in the reports must reflect both the need for the fullest possible information on study results and the need to assure reliability and accuracy of the information included. The reports will include individual and cumulative data as well as any adverse events.

10.5 Reports from the DSMB

1. **Verbal Report**: At the conclusion of a DSMB meeting, the DSMB should discuss the findings and recommendations with the study team.
2. **Summary Report**. The DSMB will approve written minutes that identify topics discussed by the DSMB and describe its individual findings, overall safety assessment, and recommendations. The rationale for recommendations will be included when appropriate. Minutes will generally not include information that was discussed in the Closed Session. Additional reporting (e.g., IRB) is the responsibility of the study team.
3. **Immediate Action Report**: The DSMB will notify the study team of any findings of a serious and immediate nature or recommendations to discontinue the study. Appropriate study staff will be notified immediately, including the PI and co-PIs. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to the study team in writing within 48 hours. This written should include DSMB member's rationale for their recommendations.

11 Adverse events

11.1 Adverse events

An adverse event is any unintended effect of either a medication or medical device, that may vary from mild discomfort to severe illness. This includes medication overdose, exacerbation or worsening of a known illness, or development of new symptoms that relate to a separate mechanism of the medication. Pertaining to a medical device, this also includes malfunction that may result in over-medication or under-medication that may cause deleterious effects to the patient. Section 7.3 describes potential risks of the medications and devices being used, that may result in an adverse event.

During the study, adverse events will be recorded in the following manner:

- Active surveillance through each intervention questionnaire
- Active surveillance via planned remote visit through the study team
- Passive surveillance, where any participant may report (remotely or in person) to the study team

Adverse events will be recorded as follows, from the time of signed consent to the end of the study (including wash-out period):

- Record of the date of onset of symptoms
- Severity of the symptoms (from discomfort to any need for hospitalization)
- Causality (i.e. relation to the study drug itself or the insulin pump system)

The team will report to the primary investigator for any adverse events. If the adverse event is severe enough that the participant's health is significantly compromised, withdrawal from the study will be discussed.

Furthermore, if any adverse event were to occur during the study, the patient will continue to be followed up after cessation of the study to ensure improvement and resolution, either in person or remotely (i.e. telephone, email, etc.), depending on the symptom itself and as per the primary investigator.

11.2 Classification of specific adverse events

The following adverse events are specific to the treatments of the study. Below are described how these adverse events will be dealt with during the study.

11.2.1 Hypoglycemia and hyperglycemia

Given the intensity and complexity of treatment of insulin therapy in type 1 diabetes, hypo- and hyperglycemia are common. Different therapies may influence the frequency and severity of these events for each participant. See Sections 7.3.4 and 7.3.5 for more details.

The iMAP system, given its autonomy in administration of insulin, and possibility of hardware malfunction, may result inadvertently in either hypoglycemia (if excess insulin is given in respect to the patient's status activity and oral intake) or hyperglycemia (if not enough insulin is given, or if there is hardware malfunction).

Empagliflozin may also influence glycemic control, though more likely hypoglycemia if the same amount of insulin is given for excess glucose that will be removed through urination.

To mitigate this, treatment of hypo- and hyperglycemia will be discussed at the initial visit; for any significant or persistent hyperglycemia, assessment of ketoacidosis will be recommended (see Section 11.2.2). Remote visits during the beginning of each intervention will ensure to discuss any excess hypo- or hyperglycemia. Significant events of hypo- and hyperglycemia will be screened after each intervention, after which further discussion with a healthcare professional of the team will be held. In the event of any severe hypoglycemia, a visit from the team will be held as soon as possible.

Any significant episodes or recurring episodes causing impairment to the participant will be reported to the IRB and regularity authorities. Note that non-severe hypo- and hyperglycemia will not be reported as adverse events.

11.2.2 Ketoacidosis

Any malfunction causing lack of insulin delivery can increase the risk of DKA in a patient with type 1 diabetes. SGLT2i use in type 1 diabetes patients poses an addition unique risk.

To ensure safety during the trial from severe hyperglycemia, DKA, and HHS, the following will be performed:

- Instructions on how to treat hyperglycemia and assess for ketoacidosis will be performed at the initial visit.
- Continuous glucose monitoring will enable the participant to be alerted concerning hyperglycemia (the threshold set by the participant) as soon as possible, therefore any action is not delayed.
- Regular point-of-care ketone measurements daily
- Participants will be instructed to measure ketones if CGM measures above 16 mmol/L for more than 1 hour.

11.2.3 Local skin reactions

Adverse events related to local skin reactions range from mild reactions (local irritation, discomfort, mild bleeding, bruising, remaining indentation from site insertion) to dermatitis or lipo-hypertrophy (see section 7.3.3). Though rarely would a soft tissue infection occur, the most life-threatening would be toxic shock syndrome, which is a systemic inflammatory response to Staphylococcus or Streptococcus soft tissue infection causing multi-organ damage; case reports of this have been reported in the past.(30) This would only occur in the case of improper hygiene and a severe lack of recommended site change (recommended to be every 3 days).

To prevent this, safe and clean insertion site technique is reinforced at the initial clinic visit. Recommendations will be given for change in pump catheter site every 3 days and change in sensor site every 7 days (note this is routine practice for any patient on insulin pump therapy). Any other mild reactions will be discussed at remote visits.

Only skin reactions requiring medical attention (i.e. infection or concern for such, pain causing inability to go about daily activities, and any need to go to the emergency room) will be reported as adverse events. Various ways to safely reduce risk of inflammation will be discussed in the case of contact dermatitis.

11.2.4 Infection and soft tissue ischemia

As previously discussed in Section 7.3.1, there is an increased risk of infection with SGLT2i use, in particular genito-urinary, but also soft-tissue infections, the worst (and extremely rare) being necrotizing fasciitis. There is also an increased risk of ketoacidosis in those with type 1 diabetes who have an acute illness.(29) Increased risk of amputation was only reported in the CANVAS trial,(14) but nonetheless due to this report, surveillance is heightened for other agents.

At the initial clinic visit, participants will be screened for any recurrent or chronic infections or peripheral vascular disease and will be excluded from the study (see exclusion criteria) if applicable.

Participants will be trained to immediately stop taking the study medication and to monitor for ketones during acute illness. The participant is to seek medical attention for ketoacidosis or for any acute infection worse than a mild viral upper respiratory tract infection. A prescription of clotrimazole 1% will be prescribed for each patient, to be filled out on an as-needed basis. The participant is to seek immediate medical attention for any sudden onset numbness, pain, or lack of blood flow to any limb.

All of these adverse events (whether mild or severe) will be recorded during the study, and will be screened for with the end-of-intervention questionnaires. If any severe infection requiring antibiotics or acute limb ischemia occur, then the patient will be withdrawn from the study as they cannot concomitantly be on the study medication.

11.2.5 Dehydration

Given the mechanism of action of SGLT2 inhibitors, increased urinary frequency is a common side effect. In the extreme setting, this may result in dehydration and drop in blood pressure. Rarely, this could result in acute kidney injury.

These symptoms will be screened for actively after each intervention. During the initial clinic visit, participants will be advised about this effect and encouraged to stay hydrated. Adverse events related to the above will be activated recorded by the questionnaire and end of visit survey.

11.2.6 Phlebotomy

At the initial visit, blood samples will be taken for baseline biochemistry. This is a small amount of blood, with most common side effects being temporary discomfort, and bruising or redness at site of venipuncture. Some patients may have more severe psychological discomfort, and rarely can develop a vasovagal response. An adverse event will only be recorded if it is deemed severe by the primary investigator as per their clinical judgment.

11.2.7 Closed-loop system device failure

Possible malfunctions are described in Section 7.3.8. Included in these adverse events is the need for any study personnel to override the MAP system due to any troubleshooting to avoid other adverse events. Any MAP system failure will be recorded as a Technical Adverse Event (TAE) via a special form. These will be recorded in addition to the other standard adverse events.

11.3 Severity (intensity) and causality of adverse events

A rough classification system will be used to describe the severity/intensity of adverse events in the study. These are classified by medical judgment. They are described as follows:

- Mild: Discomfort is apparent but daily activities are not disrupted
- Moderate:
    - Discomfort disrupts daily activities
    - Need to seek medical attention in an ambulatory or clinic setting (e.g. urinary tract infection)
- Severe: Any medical occurrence that is beyond discomfort which includes any of the following:
    - An event that is life-threatening
    - Need to present to the emergency department
    - Requires inpatient hospitalization
    - Results in permanent disability
    - Results in death
    - Results in a possibility birth defect or obstetrical-related adverse event (if patient became pregnant inadvertently during the time of the study)

Once the adverse event occurs, causality by any agent in the study will be determined through medical judgment via temporal relationship, pattern of reaction, and confounding factors.

11.4 Reporting serious adverse events

11.4.1 Responsibilities of the principal investigator

The principal investigator is responsible ultimately for adverse event evaluation. These roles include:

- Classification and evaluation of the adverse event that is recorded by the study team
- Relationship to the study, and need for further protocol re-evaluation
- Review of any possible factor in the study that could have caused the adverse event to find a potential way to reduce the risk to others
- Documentation of the above analysis
- Report to the research ethics board and regulatory authorities within 10 days of observation of this problem
- Determination of the need to update risk analysis and other preventative measures, i.e. update of the protocol

11.4.2 Definition of a Serious Adverse Event (SAE)

A *serious adverse event (SAE)* is any adverse event that is labelled as severe, as described in Section 11.3, which includes any reaction that is life-threatening, requires admission to hospital, or would result in death, permanent disability, or congenital malformation.

If an SAE occurs, it will be reported immediately to the local IRB (as per their local guidelines). If a drug (e.g. empagliflozin) or a device (e.g. any MAP system components) is suspected, SEA will also be reported to CTA or ITA division of Health Canada, respectively, within the timeframe defined in the guidelines.

When an SAE occurs, medical attention and follow up by the study team will continue until the SAE has resolved, even after cessation or completion of the trial. This is to record the course of the medical condition to ensure safety in other patients.

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