Clinical Study Protocol

Title	Weekly subcutaneous semaglutide as adjunct to closed-loop therapy in type 1 diabetes care: a double-blind, cross-over, randomized controlled trial [SEMA-AP]
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Study site	Research Institute of the McGill University Health Centre Royal Victoria Hospital 1001, boulevard Décarie Montreal (Quebec) Canada H4A 3J1
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Sponsor	Research Institute of the McGill University Health Centre (RI-MUHC)

Version Tracker/Revision History

#	Date	Author	Description	REB Submission date Approval date	ITA Submission date Approval date	NOL Submission date Approval date
1.0	2021-FEB-20	Alessandra Kobayati	Original draft development	N/A	N/A	N/A
1.1	2021JUL-23	Melissa-Rosina Pasqua	Initial submission	2021-JUL-26 No approval - replaced by 1.2	2021-AUG-25 No approval - replaced by 1.2	2021-AUG-25 No approval - replaced by 1.2
1.2	2021-SEP-22	Melissa-Rosina Pasqua	Changes prior to approval by REB or Health Canada as requested by REB and Health Canada	2021-SEP-23 No approval - replaced by 1.3	2021SEP-30 Screening clearance 2021-OCT-07	2021-OCT-1 No approval - replaced by 1.3
1.3	2021-OCT-20	Melissa-Rosina Pasqua	Change recommended by REB to replace biobank with blood samples to be assessed for secondary use.	2021-OCT-25 No approval - replaced by 1.4	Had not yet been submitted	2021-OCT-25 No approval - replaced by 1.4
1.4	2021-NOV-9	Melissa-Rosina Pasqua	Clarification concerning acetaminophen use as per ITA, with addition of hydroxyurea use as exclusion criteria	2021-NOV-29 Awaiting ITA/NOL on 2021-DEC-08	2021-Dec-6 No approval - replaced by. 1.5	2021-Nov-29 Request for info 2021-Dec-20
1.5	2021-DEC-21	Melissa-Rosina Pasqua	As per Health Canada: addition of ECG testing, change in GFR threshold for inclusion, titration schedule	-	2022-Jan-18	2021-Dec-22 NOL 2021DEC24
1.6	2021-Dec-26	Melissa-Rosina Pasqua	Option of different pump (YpsoMed) to be used for Automated Insulin Delivery (replacing McGill Artificial Pancreas)	-	2022-JAN-18	2022JAN31 (CTA-N)
1.7	2022-Feb-14	Melissa-Rosina Pasqua	As recommended by ITA: Participants will continue on same system throughout study	-	2022FEB116 (changes requested)	2022FEB21 (CTA-N)
1.8	2022-JUNE-22	Melissa-Rosina Pasqua	More detail added to recruitment + ITA-requested change: Clarification of insulin pump catheter change	Approved 2022-AUG-02	iMAP 2022 JUL28 Euglide 2022AUG30	2022-JUN-28 (CTA-N)
2	2022-DEC-06	Melissa-Rosina Pasqua	Laboratory changes: TNF-alpha removed, CRP (not hsCRP) to be measured, NT-pro-BNP specified, lipase/ amylase clarified, frozen sample processing specified. Specified INSPIRE timing. Clarified as needed follow up wording.			

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1. Background & Rationales

Type 1 diabetes (T1D), which accounts for 5-10% of all cases of diabetes, is caused by autoimmune destruction of the insulin-producing cells of the pancreas (1). This often occurs in childhood, and necessitates life-long intensive insulin therapy. A goal of glycated hemoglobin (HbA1c) ≤ 7% is used to reduce the risk of micro- and macrovascular complications from chronic hyperglycemia (2–5). Unfortunately, achieving tight glucose control is limited by hypoglycemia (low blood sugar), which can cause a range of symptoms from impaired judgment to loss of consciousness. Throughout prior assessments in the United States and Canada, less than 25% of those with T1D are able to achieve target glycemic control (6,7).

One of the most pertinent breakthroughs emerging into commercial use is closed-loop insulin therapy (8). Closed-loop therapy is comprised of a continuous glucose monitor (CGM), an insulin pump, and an algorithm that is able to adjust subcutaneous insulin infusion based on glucose readings. Closed-loop therapy has demonstrated (compared to CGM and insulin pump, or "sensor augmented therapy") increased time spent in target blood glucose levels of 3.9 to 10 mmol/L , reduced hyper- and hypoglycemia, and reduced HbA1c levels (9–13). Unfortunately, it does not perfect glucose control; in one of the largest closed-loop trials lasting 6 months, almost half of those on closed-loop therapy still had HbA1c levels below target. One of the main barriers is post-prandial hyperglycemia, as nocturnal glycemia is well-controlled (14).

Closed-loop therapy alone also does not address major gaps in T1D care. There is a growing obesity epidemic in T1D (15–17), as well as a major gap in cardiovascular and renal protection compared to the recent pharmacological trials seen in type 2 diabetes (T2D) (18–21). Adjunctive therapies borrowed from T2D management have been used with variable efficacy and safety profiles (22).

Glucagon-Like Peptide-1 Receptor Agonists (GLP1-RAs) are a class of medications that have been extensively studied in T2D and weight loss management (20,21,23). GLP-1 is an intestinal hormone secreted by L cells which control glucose levels through reduced glucagon levels, increased insulin secretion, reduced beta cell apoptosis, increase satiety, and slowed gastric emptying (24). GLP1-RAs mimic this effect, and have shown to not only improve glycemic control in T2D, but the use of liraglutide, dulaglutide, and semaglutide have shown in randomized clinical trials to lead to weight loss, reduced cardiovascular events, and reduction in diabetic nephropathy (20,21,25–27). Of the GLP1RA's, semaglutide is the most potent in its weight loss and glycemic effects (28).

1.1 Prior GLP1-RA studies in T1D

The use of GLP1-RAs as adjunct has previously been used in T1D with variable effect, with agents studied being predominantly exenatide and liraglutide. Adjunct-One and Adjunct-Two were two large studies in participants with T1D with HbA1c 7 - 10% (and body mass index (BMI) > 20 kg/m^2) that resulted in weight loss and reduced HbA1c levels; there was a slightly more

pronounced effect in those with remaining C-peptide levels (29,30). The Lira-Pump trial included only those with T1D on pump therapy with BMI ≥ 25 (i.e. overweight and obese), and resulted in HbA1c reductions of 0.5%, total daily insulin dose reductions of 16%, and body weight reduction of 6.3 kilograms (31). Short studies have also been done using GLP1-RAs (liraglutide and exenatide) with closed-loop systems, which showed reductions in post-prandial hyperglycemia (32,33). Other studies have looked at the use of GLP1-RAs in islet cell transplantation and beta cell preservation in early diagnosis of T1D with mixed results (34,35).

Given the pathophysiology of T1D, the mechanism of GLP1-RA utility in T1D is still unclear. It may be related to remaining beta cell protection, weight reduction in the context of insulin resistance, improvement in gastric emptying to aid glucose absorption, reduced glucagon secretion, or change in eating habits. Given semaglutide was found to have more potent effects in T2D, its effects may then be more substantial in T1D.

1.2 Our prior studies using McGill's Automated Insulin Delivery (AID)

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 22 studies with more than 450 participants have been performed by our research group thus far (9,36–40). These studies use McGill's Automated Insulin Delivery (AID) system, which is a hybrid closed-loop system, meaning participants must include carbohydrate counting. 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).(9,41)

Multiple studies have been done using a bi-hormonal model with insulin and pramlintide, an analogue of the hormone amylin which is released by beta cells and improves glucose levels through increased satiety and delayed gastric emptying (42). Our most recent study, an inpatient study using the rapid insulin-pramlintide closed-loop system, revealed that compared to insulin-alone, the novel system increased percentage of time spent in target and reduced mean glucose (41). Despite the positive outcomes, barriers to the insulin-pramlintide closed-loop system include gastrointestinal symptoms, the need to use two pumps at once, and the lack of an approved formulation for the two hormones. However, pramlintide's mechanism of action are similar to GLP1-RA. It would be beneficial to have these similar effects with easier administration and the added benefits of cardiovascular and renal protection.

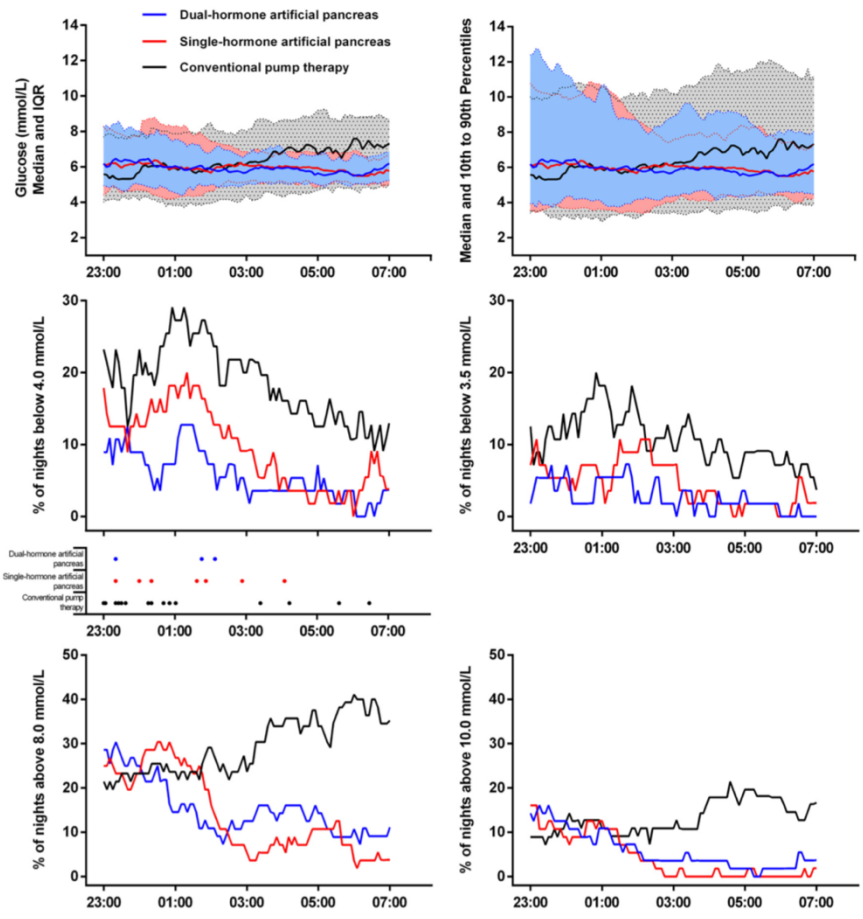

Figure 1. Taken from Haidar *et al.,* 2016 in JCEM. Glucose levels, percentage of nights in hypoglycemia (need for treatment indicated below) and percentage of nights in hyperglycemia in 28 participants with type 1 diabetes, using one of the three interventions: dual-hormone artificial pancreas (insulin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

2. Objectives, hypothesis, and design

2.1. Objectives

2.1.1 Primary objectives

The primary objective of our study is to assess the effect on time-in-target range (TIR) between 3.9 to 10.0 mmol/L of the following:

1) Semaglutide SC weekly at maximum tolerated dose in those with T1D on closed-loop therapy versus placebo with closed-loop therapy

2.1.2 Secondary objectives

The secondary objectives are to assess the following outcomes due to semaglutide SC weekly versus placebo on those with type 1 diabetes:

1) Glycated hemoglobin (HbA1c)
2) Anthropometric measurements: weight, body mass index, blood pressure

3) Total daily insulin requirements
4) Daily carbohydrate intake
5) Biochemical metabolic parameters such as lipid profile, cytokines, adipokines, biomarkers, urine albumin-creatine ratio (urine protein)
6) Change in C-peptide, glucagon, and paracetamol levels during a mixed meal tolerance test
7) Change in quality of life (such as fear of hypoglycemia, diabetes distress, treatment satisfaction, bowel symptoms) as assessed through questionnaires and semi-structured interviews

2.2 Hypotheses

2.2.1 Primary hypotheses

Semaglutide SC weekly at maximum tolerated dose in those with T1D on closed-loop therapy will increase TIR of 3.9 to 10.0 mmol/L compared to those using placebo.

2.2.2 Secondary hypotheses

Semaglutide SC weekly at maximum tolerated dose in those with T1D will result in the following, compared to placebo:

1) Reductions in HbA1c
2) Reductions in total daily dose of insulin used
3) Reductions in daily carbohydrate intake
4) Reductions in weight, body mass index, blood pressure
5) Improvement in lipid profile, cytokines, adipokines, biomarkers, urine protein

2.3 Design overview

This is a double-blinded, randomized, two-way crossover, outpatient trial. Each arm will start with 12 weeks of titration of study drug tolerance (semaglutide or placebo) and insulin doses; the first 11 weeks will be on the participant's routine insulin pump therapy, and the last will be on the closed-loop insulin system. This will be followed by 3 weeks of closed-loop therapy with the maximum tolerated dose of the study drug. There will be 2 weeks of wash-out prior to the next intervention. Laboratory and anthropometric measures will be done at the beginning as baseline, and then at the end of each intervention.

3. Study population

The trial will enroll 28 participants who meet the below criteria.

3.1 Inclusion criteria

1) At least 18 years of age
2) A clinical diagnosis of T1D 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 up to 11% (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 persons of child-bearing age (if sexually active) 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.

3.2 Exclusion criteria

1) Current or < 2-week use of another GLP1-receptor agonist
2) Less than 2 weeks use of any anti-hyperglycemic agent other than insulin
3) Planned or ongoing pregnancy
4) Breastfeeding individuals
5) 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
6) Severe diabetic ketoacidosis (DKA) within the last 6 months ("severe" referring to need to present to medical attention and requirement of intravenous insulin)
7) Prior history of acute pancreatitis, chronic pancreatitis, or gallbladder disease
8) Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2
9) Severe impairment of renal function with eGFR <30 mL/min/1.73 m^2 (using CKD-EPI formula), measured within the last 12 months
10) Clinically significant diabetic retinopathy or gastroparesis, as per the clinical judgment of the investigator
11) History of bariatric surgery within 6 months of screening
12) 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)
13) Prior adverse reaction to GLP1-RAs
14) Body mass index ≤ 21 kg/m^2
15) Regular use of hydroxyurea during the expected time of Dexcom G6 use, as this medication is known to cause inaccurate measurements (43)
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) Any demonstrate of difficulty in using the iAID system following training, as per investigator's judgment
19) Concern for safety of the participant, as per the clinical judgment of the primary investigator

Note that if any laboratory investigations required for screening are not available at the time of screening, conditional eligibility will be given so that baseline laboratory investigations can be performed at the initial admission visit. These baseline laboratory investigations can be used for inclusion/exclusion criteria.

3.3 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) Withdrawal of consent to participate or desire to no longer take part in the study
3) Pregnancy
4) The required use of medications listed in the exclusion criteria
5) Severe hypoglycemia or diabetic ketoacidosis requiring hospitalization
6) Acute pancreatitis or gallbladder disease
7) Appearance of clinically significant diabetic retinopathy that threatens vision
8) Severe hypersensitivity reaction
9) Decision by the study group to prematurely terminate the clinical trial

3.4 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 reasons 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 semaglutide) back to the participant's usual regimen.

4. Study centres and recruitment methods

The study will be conducted in Montreal, Quebec at the Centre for Innovative Medicine (CIM) of the Research Institute of the McGill University Health Centre (RI-MUHC). Enrolment will consist of 28 adult participants. Recruitment will predominantly take place among the clinic for adult T1D care seen by specialists in Endocrinology & Metabolism at the Royal Victoria Hospital, 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. Those who find the study through other means (e.g. the Clinical Trials website, CONNECT1D, REB-approved flyers, online platforms of diabetes organizations, other participants) will also be invited.

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.

5. Study drugs, devices, and materials

5.1 Study drugs

Table 2.

Investigational drug name	Dose and formulation	Blinding and preparation
Semaglutide	0.25mg (0.19ml), 0.5mg (0.37ml), 1.0mg (0.74ml) injected subcutaneously once per week, colorless solution	Liquid formulation prepared in blinded vials with an expiration date of 30 days (from the date of preparation) by the MUHC Research Pharmacy. Injection needles will be provided to self-administer solution subcutaneously in the abdomen, thighs or upper arms once a week
Placebo (saline)	0.19ml, 0.37ml, 0.74ml, injected subcutaneously once per week, colorless solution	Liquid formulation prepared in blinded vials with an expiration date of 30 days (from the date of preparation) by the MUHC Research Pharmacy. Injection needles will be provided to self-administer solution subcutaneously in the abdomen, thighs or upper arms once a week

5.1.1 Storage and handling

Participants will be instructed to store the vials of study drug (placebo and semaglutide) in the refrigerator at 2-8℃, though the vials can remain at room temperature once removed from refrigeration for up to 56 days. Participants may either keep the vial refrigerated or place it at room temperature (and away from direct sunlight) prior to each injection.

5.1.2 Drug accountability

Research personnel at the RI-MUHC pharmacy will complete a drug-dispensing log with enrolment ID, dispensing date and method, return date for each drug dispensation. Participants will also be asked to record dose administration (or any possible missed dose) with time and date in a drug log. Participants will be asked to communicate immediately to the research personnel if there are any missed dose > 24 hours or accidental additional/subtracted dose.

5.2 Study devices and materials

Table 2

Insulin pump by Tandem Diabetes Care *or* YpsoMed Diabetes Care, and associated materials	This is the choice of continuous subcutaneous insulin infusion (CSII) administering compatible 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. The participant's study pump and supplies will either be from Tandem Diabetes Care or YpsoMed Diabetes Care; the participant will continue on the same brand of pump and appropriate corresponding AID system for the duration of the study.
Dexcom 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. No calibration is required. During the titration, CGM will be used. If the participant does not have their own form of CGM, Dexcom G6 will be given.
Study Smartphone	The main algorithm for the closed-loop system is set on this device via the AID application. The smartphone, pump, and sensor communicate via Bluetooth. Each study participant is given one smartphone.
Freestyle Precision Neo meter with glucose and ketone test strips	Participants may use their own capillary point-of-care glucose and ketone measuring devices throughout the study. In the event the participant does not have a glucose and/or ketone meter, participants will be given a Precision Neo meter with ketone and glucose test strips. If a participant has already a Precision ketone and glucose measuring device (such as Precision Neo, Freestyle Libre or Freestyle Lite), capillary blood glucose and ketones will be provided. Though Dexcom G6 does not require calibration, point-of-care glucose testing may be required to ensure accuracy in the case of symptoms not corresponding to CGM glucose level. Ketone levels should also be tested in the setting of acute illness, nausea and vomiting, or glucose > 16 mmol/L more than 2 hours.
Emergency kit	The kit includes fasting-acting glucose tablets, insulin syringes, and intranasal glucagon. This will be given to all participants.

5.2.1 Automated Insulin Delivery

Automated Insulin Delivery (AID) 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 G6)
2) A mobile application on a study smartphone
3) An insulin pump

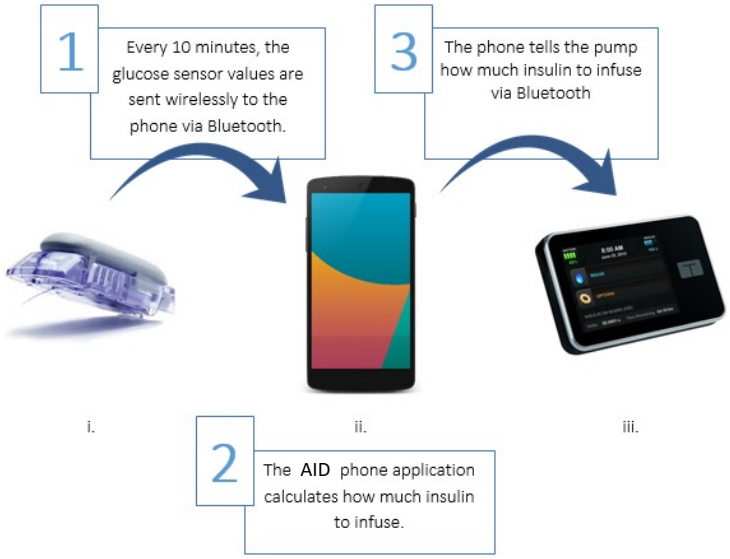

Figure 2. Depiction of McGill's Automated Insulin Delivery.

For the ability to manipulate insulin administration via Bluetooth connection, the research team's own insulin pumps are required. The algorithm is unique to our own research team, therefore it can be adjusted accordingly, therefore no commercial systems will be used in the study. The application is certified only for these pumps and the Dexcom CGM.

6. Trial Design

6.1 Study timeline

This is a double-blind, randomized, controlled, crossover, outpatient study comparing semaglutide SC weekly at maximum tolerated dose compared to placebo. Further details on investigations performed and follow-ups are described below.

The overall study length for each participant will be 32 weeks each.

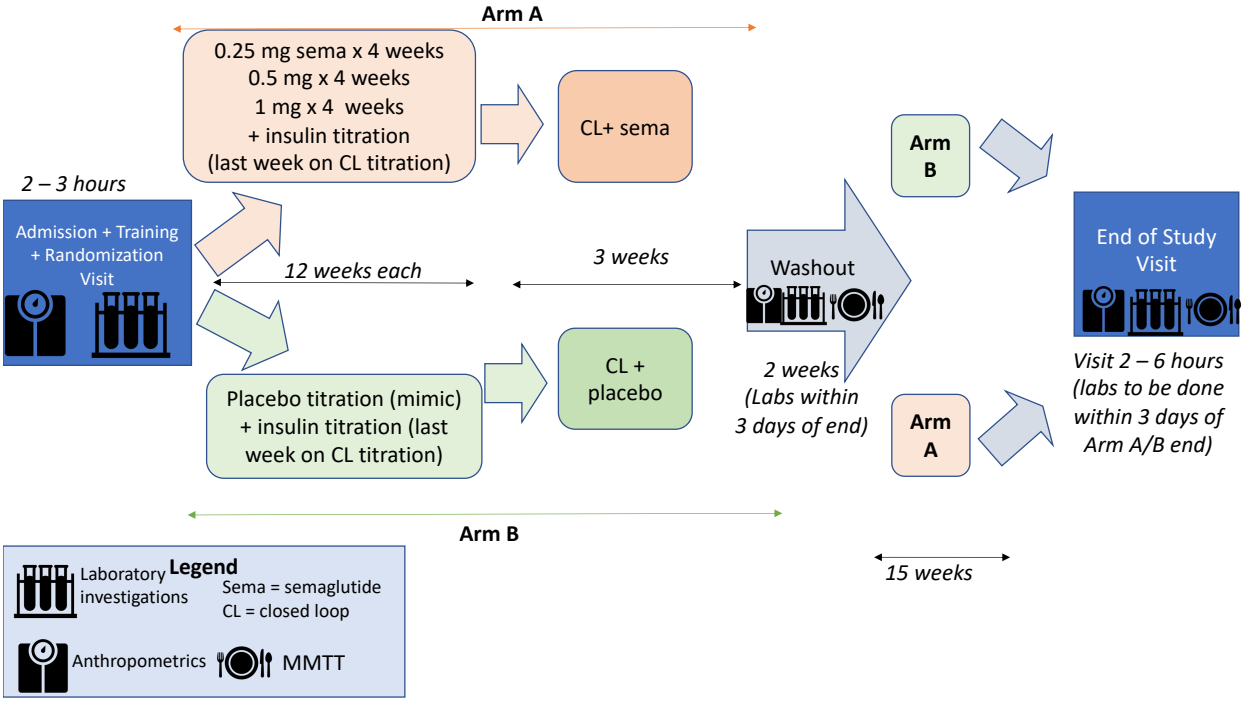

Figure 3. Timeline of study interventions for each participant.

6.2 Randomization and allocation concealment

Block randomization using random block size of 4, 6, or 8 will be performed by a separate research team member. This separate research member will create 2 envelopes: one for the investigator that includes the coded vials to be used for each arm of the study, and another that reveals which vial is which molecule. The first envelope will be given to the investigator at the time of the initial admission visit when randomization is to occur; this is to be kept with participant documentation. The second envelope will be placed (by the researcher who performs randomization) in separate documentation storage to be used after study completion or in the event of an emergency.

6.3 Blinding

This study will be double-blinded: the participant's study drugs will be vials that only include a code, and do not reveal if the medication is semaglutide or placebo. The investigator will only know the code to be able to dispense vials, but will not know the molecule being administered. Both types of vials will be created by the RI MUHC research pharmacy, where the pharmacist is unblinded.

Unblinding would occur in the event of a serious adverse event or in any other situation where it is pertinent for the participant's well-being to know if the participant was on the study drug. Prior to this, discussion will be held with the primary investigator for approval. This will be

done by one of the members of the team not involved in allocating medication. Only the study drug in question for that participant will be reviewed.

6.4 Anthropometric investigations

Anthropometric measurements (except for height) will be taken at the Admission Visit, within 3 days of the end of the first intervention, and at the End of Study Visit (which will be within 3 - 7 days of the last intervention). Body mass index will be calculated for each visit based on weight as well. The following will be measured through the following instruments.

Table 3

Body weight	A digital scale will be used to measure in kilograms.
Height	Height will be measured by a metal scale mount (or measuring tape if the other not available). This measurement will be used for body mass index measurements. Unlike the other measurements, it will only be taken at the admission visit.
Waist circumference	Measuring tape will be used to measure waist circumference at the top of the ischial crests as a landmark. The measurement will be taken in centimetres when the participant exhales.
Hip circumference	Measuring tape will be used to measure hip circumference at the largest circumference around the buttock area; this will be taken in centimetres.
Blood pressure	An electronic sphygmomanometer will be used for blood pressure measurement above the brachial artery. The patient should have sustained from smoking for 30 minutes, and emptied bladder prior. The participant should not be talking or cross their legs during the exam. The mean of 3 measurements will be taken.
Heart rate	Heart rate will be taken by the same electronic sphygmomanometer as the blood pressure; the average heart rate will be taken as well.
Calculated measurements	Body mass index and hip: waist ratio will be calculated from the above measurements.
Electrocardiogram	An electrocardiogram (ECG) will also be performed due to risk of PR prolongation as describe in the product monograph (44).

6.5 Laboratory investigations

5 mL of serum via intravenous catheter will be taken at the same visits at anthropometric measurements (i.e. Admission Visit, end of first intervention, at End of Study Visit). The description and rationale for each investigation is described below. Note the study is not necessarily powered for changes in these parameters, but are exploratory in this setting.

Table 4

Blood	
Glycated hemoglobin (HbA1c)	Baseline and change in average glycemic control within the last 3- 4 months
Liver profile	At the MUHC, this includes bilirubin, alanine aminotransaminase (ALT), alkaline phosphatase (ALP). Screen and assess for change in possible cholestatic disease or liver disease (in particular non-alcoholic fatty liver disease).
Lipid profile	At the MUHC, includes total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides. Screen and assess for change in dyslipidemia, in particular triglycerides and HDL-c (markers of metabolic syndrome) and LDL-c (clinically important for cardiovascular protection)
Creatinine	Screen for and assess for change in renal function that may limit study drug use.
Random (non-fasting) blood glucose and C-peptide	Screen for beta-cell activity at the admission visit. Prior studies have looked for effect of beta cell preservation on GLP1-RAs (35), and Adjunct-One noted amplified glycemic effect in those with remaining C-peptide levels (29). Random (non-fasting) C-peptide in prior studies has demonstrated to correlate with fasting C-peptide levels and the 90 minute mixed-meal tolerance test (45).
Brain Natriuretic Peptide (NT-pro-BNP)	Screen for and assess for change in surrogate cardiovascular marker (46), given cardiovascular benefit seen in T2D in SUSTAIN6 trial (21).
C-reactive protein (CRP), ferritin	Screen and assess for change in markers of inflammation, influenced by metabolic syndrome (47,48). Though metabolic syndrome is not key to T1D diagnosis, there are those with T1D who have concomitant metabolic syndrome. This is to assess for any possible metabolic effect influenced by this phenomenon.
Lipase	Screen for pancreatic inflammation with lipase and other relevant testing (adverse effect of GLP1-RAs).
Interleukin(IL)-6	This is an adipokine linked with metabolic syndrome, seen previously to be influenced by GLP1-RA (47,49).
Thioredoxin-interacting protein (TXNIP)	TXNIP is a protein whose expression is increased in diabetes (50). TXNIP downregulation has been linked with protective effects of the beta cell and organs susceptible to diabetes complications (50). Prior GLP1-RAs (exendin-4) have was shown to decrease TXNIP expression (50). TXNIP can be measured in serum and correlates with diabetes status and nephropathy (51).
Fructosamine	Fructosamine is a measurement of glycosylated proteins, in particular albumin, which reflects glucose control within the last 2 - 3 weeks (52). This will be used to compare more recent glucose control, similarly to glycated hemoglobin.
Urine	

Albumin: creatinine ratio (uACR)	Screen and assess for change in diabetic nephropathy, in particular given renal outcome results from SUSTAIN6 (21).
Pregnancy screen	An additional safety parameter to rule out pregnancy.
Mixed-Meal Tolerance Test (MMTT)	**Description** The mixed meal tolerance test is considered one of the goal standards for assessing beta cell activity in T1D (45,53,54). It has also been previously used to assess for mechanistic of action of GLP1-RAs in prior trials (31,55). See Section 7.8.1 for details. 14 participants (7 female and 7 male) will participate.
Glucagon	Glucagon is a counterregulatory hormone of insulin produced by the alpha cells of the pancreas; levels inappropriately rise post-prandially in those with T1D (56–58). GLP-1 is known to suppress glucagon (24), and GLP1-RAs have shown to suppress glucagon with use in T1D previously (33,59,60). Glucagon will be measured during the mixed-meal challenge and area-under-curve (AUC) will be used for secondary endpoints.
C-peptide	Will be measured as area-under-curve.
Serum glucose	Will be measured as area-under-curve.
Paracetamol	Given that gastric emptying rate is the rate-limiting step for paracetamol metabolism, this will be used to estimate changes in gastric emptying. Area-under-curve will be assessed.

6.5.1 Laboratory measurement

The majority of the laboratory investigations will be performed at the laboratory at the McGill University Health Centre. Serum glucose measurements during the MMTT may be done through point-of-care testing (YSI Life Sciences). TXNIP and glucagon measurements will be done via kit assays; TXNIP measurements will be done by chemiluminescence (Novus, NBP2-68134), and glucagon will be measured by ELISA (Millipore, EZGLU-30K). Processing of these samples will be done as recommended by manufacturer. TXNIP analysis will be done with the collaboration of the laboratory of Dr George Fantus. Plasma collection and storage for secondary use will be done at the timepoints of laboratory testing via centrifugation for 15 minutes at 1000 x g, and storage within 30 minutes at ≤- 20^{o}C. This will be to further assess the hypotheses of the protocol or to further examine findings that were explored from the results of this study.

6.6 Questionnaires

Participants' quality of life will be measured by the following validated questionnaires (note all of these have been used in prior projects within the research group):

1) Type 1 Diabetes Distress Scale for adults: a validated 28-item questionnaire to assess distress concerning management, eating, and hypoglycemia for type 1 diabetes (61)
2) Hypoglycemic Fear Survey – II: a validated 33-item questionnaire (62)

3) INSPIRE questionnaire for adults: a validated 22-item questionnaire assessing the following for those on insulin pumps: INsulin delivery Systems, Perceptions, Ideas, Reflections and Expectations) (63)
    - Note because this one reflects automated insulin delivery, it will not be used at the admission visit
4) The Diabetes Bowel Symptom Questionnaire: A validated questionnaire used to assess gastro-intestinal symptoms specifically in type 1 diabetes (64)
5) Diabetes Treatment Satisfaction Questionnaire (DTSQs): An 8-item validated questionnaire (65)

Participants will fill out the questionnaires at the admission visit, and after each intervention. All questionnaires will be collected at the End-of-Study Visit.

7. Study procedures

7.1 Visit schedule

Table 5

			First Intervention						Second Intervention			
	Admission Visit [a] (Day 1)	Training Visit [b,c] (Day1+)	Drug insulin titration (Weeks 1-11)	AID training [b] (Visit 2)	AID Run-in (Week 12)	AID (Weeks 13 - 15)	Visit 3 (± 3 days end of Week 15)[a]	Washout (Weeks 16 - 17)	Drug and insulin titration (Weeks 18-28)	AID Run-in (Week 29)	AID (Week 30-32)	Visit 4 End of Study Visit (Week 32)[b]
Consent & Eligibility	X											
Medical History	X											
Full physical exam	X											
Anthropometrics (BP, HR, Weight, Height, BMI, WC) ECG testing	X						X					X[a] (3 days end of Week 32
Basic Laboratory Investigations [b] Blood: HbA1c, liver profile, lipid profile, creatinine, blood glucose, C-peptide, NT-pro-BNP, CRP, ferritin, lipase+ Urine: uACR, pregnancy screen[c]	X						X					X[a] (3 days end of Week 32
Extensive investigations (serum) TXNP, IL-6 Mixed meal tolerance test (for the first consenting 7 females and males)							X					X[a] (3 days end of Week 32
Remote monitoring (contact by email, text, or telephone)			Days: 7, 21, 32, 56, 63, 77 (± 2 days)	1 of last 3 days of Week 11	Days: 4, 7 (±2 days)	Days: 14 ± 2		Day 7 ±4	Days: 7, 21, 32, 56, 63, 77 (± 2 days)	Days: 4, 7 (±2 days)	Days: 14 ± 2	

[a] Must be done in person

[b] Choice of in-person or remotely by teleconference (for AID training, only offered to those who are familiar with prior AID studies)

[c] May be done at same time as Admission Visit

[d] Blood glucose and C-peptide should be done non- fasting. If the participant is hypoglycemic at time of laboratory investigations, the investigations will be done after correction. This should be done prior to study drug administration.

[e] If participant of childbearing potential

BMI = body mass index, BP = blood pressure, HR = heart rate, LFTs = liver profile, WC = waist circumference

7.2 Admission 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.

Table 6

General procedures	- Explanation of the study and answering of questions - Assessment of inclusion and exclusion criteria (if the participant fails this section, they can be re-assessed after 3 months) - Signing of consent form
Medical history	- Complete past medical history, both of their T1D and other medical conditions - Current diabetes care (frequency of glucose checks, recent difficulties in glycemic control, history of DKA, etc.) - Current diabetes regimen, doses and average carbohydrate count, 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 and heart rate - Height and weight - Waist and hip circumferences - Routine cardiovascular, respiratory, and abdominal examination - Foot and peripheral vascular exam - Signs of lipo-hypertrophy in areas of insulin catheter sites - An electrocardiogram (ECG) to assess heart rate and PR interval
Blood and urine laboratory investigations	5 mL of serum via intravenous catheter will be taken to measure the investigations. A urine sample will also be required. See Table 5 for details of investigations taken.
Questionnaires	Participants will be given time to fill out quality of life questionnaires (except INSPIRE, which will only be done after each intervention)
Randomization	Randomization and allocation will be assigned.
Emergency kit	An emergency kit (see Section **Error! Reference source not found.**) 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

7.3 Training visit

The training visit may be done the same day as the admission visit or on a different day given travel and time constraints.

The participant will receive the following training. AID training and training on its components (Dexcom CGM, insulin pump) will be done at a later date.

Table 7

Routine diabetes care	Revision of hypo- and hyper-glycemic management, driving safely with diabetes, safe injection practices, sick day management, and ketone management. A ketone management algorithm will be given. Participants will be expected to download their pump using their respective uploading software.
Semaglutide SC weekly training	The participant will be taught the titration schedule, how to administer the study drug, how to store, and how to record doses. A drug log and symptom log will be given for them to fill each time the drug is used. Proper insulin titration on their own insulin pump while on the study drug (and the schedule of follow ups) will also be discussed. Along with the discussion of risks and benefits of semaglutide in the consent form, participants will be taught to identify the symptoms of nausea and vomiting, acute gallstone disease, and acute pancreatitis. The study drug will be given for Intervention 1 will be given once training is successfully completed.
Dexcom G6 (if required)	If the participant does not use CGM in their usual diabetes care, Dexcom will be given. Training will be given at the session concerning how to insert, use, and upload to the appropriate software.

7.4 Semaglutide/ placebo titration period (Weeks 1 - 12)

Titration of the study drug will be over a span of 12 weeks (i.e. the 1-week AID run-in is the 12th week), with each dose/volume increment every 4 weeks. If there are intolerable symptoms, the participant will be asked to resume the last tolerated dose. Follow-ups by remote monitoring will occur on the following days: Day 7, 21, 32, 56, 63, 77 (± 2 days of each for flexibility). Given the long half-life of the drug and long time for steady state, there will be no prophylactic setting reductions unless preferred by the investigator to prevent hypoglycemia (for example, if the participant already has hypoglycemic events). If the participant requires impromptu assistance or if increased surveillance is recommended at the discretion of the investigators, the research personnel responsible for medical care (i.e. insulin titration, side effects) will be available 24/7.

7.5 AID training (Visit 2)

Within 3 days of the end of Week 11, training will be done on the AID system and its constituents. Supplies and tools will be given during training.

Table 8

Dexcom G6 CGM	Training on the Dexcom G6 sensors, transmitter, and reader will be performed.
Insulin pump (Tandem Diabetes Care or YpsoMed Diabetes Care)	Training on the insulin pump, including reservoir and catheter site insertion, will be done. The participant's latest parameters will be programmed. The participant's study pump and supplies will either be from Tandem Diabetes Care or YpsoMed Diabetes Care; the participant will continue on the same brand of pump and appropriate corresponding AID system for the duration of the study.
Artificial Insulin Delivery application	Training on the smartphone platform will be provided. The User Guide will also be given to the participant.

7.6 Closed-loop therapy (Run-In)

The first week on the AID will occur during the 12th week of the titration. Remote follow-up will occur on Day 4 and Day 7 (± 2 days) during Week 12, and as needed at the discretion of the participant and investigators. CGM and pump data will be automatically uploaded via wireless connection to our database for analysis. A separate researcher will create the graphs.

7.7 Closed-loop therapy (3 weeks)

The participant will continue their maximum tolerated dose of study drug and the AID for 3 weeks. Remote follow-up to review glucose data will be performed on Day 14 ± 2 and as needed. The CGM data used for primary and secondary endpoints will be based on these 3 weeks and the AID training week (a total of 4 weeks).

7.8 Laboratory and anthropometric measurements (Visit 3)

Participants will be required to perform laboratory investigations and anthropometric measurements (done by the research team) within 3 days of the end of the 4 weeks on closed-loop therapy. This can be done during the period of closed-loop therapy or during the washout period.

7.8.1 Mixed meal tolerance test (MMTT)

A MMTT will be in the first consenting 7 female and 7 male participants (for a total of 14 participants). It will be performed immediately after each intervention, preferably the same day as the post-intervention laboratory and anthropometric measurements (within 3 days of intervention end). See Section 6.5 for more details of measurement.

Before the test:

- Participants will be asked to continue using the McGill Artificial Pancreas, to be started minimum the evening before the MMTT, with a target glucose at 7 mmol/L.
- Participants will need to fast overnight.
- Upon arrival, the participant is to be weighed; if other anthropometrics are to be done, they can be done at this time as well.

During the test (a total of 4 hours):

- The glucose level should be between 3.9 and 11.5 mmol/L per CGM data prior to start of the study (if hypoglycemia, the participant can correct and wait 4 hours, or if hyperglycemic, can wait for the AID to reduce glucose levels)
- An intravenous catheter is to be inserted and remain there throughout the examination.
- The first blood draw will be at time 0 (upon catheter insertion), where glucagon, C-peptide, paracetamol and glucose will be drawn; other laboratory investigations (see Table 5) can be done at this time.
- The mixed meal, i.e. Boost® (Complete Nutritional Drink High Protein, Nestlé Health Science) will be consumed at 6 mL/kg within 5 minutes. 1500 mg of paracetamol will be added to the drink as well.
- For time 0 - 120 minutes:
    - Blood draws will be done at 30, 60, 90, and 120 minutes for glucose, C-peptide, paracetamol, and glucagon.
    - No pre-meal insulin bolus is to be administered; however, basal insulin via the McGill Artificial Pancreas will be continued.
    - No pre-meal insulin bolus is to be administered; however, basal insulin via the McGill Artificial Pancreas will be continued.
- For time 120 - 240 minutes:
    - Paracetamol will be drawn at 180 and 240 minutes.
    - The participant can correct their glucose as per usual care, and carry on with usual diabetes care.
    - No restrictions on physical activity.
- Reasons for premature cessation of test:
    - Concern for diabetic ketoacidosis (nausea, vomiting, abdominal pain with ketone level ≥ 0.6 mmol/L per point of care testing)
    - Hypoglycemia with glucose < 3.8 mmol/L
    - Withdrawal of consent from participant
    - Acute illness or increased risk as perceived by investigator

After the test

- Venous cannulation is removed.

If the MMTT is done during the intervention, then that day's CGM data will be removed from data used to calculate primary and secondary endpoints.

Glucagon measurements will be processed and stored for measurement at a later date; these are to be processed, frozen and stored in a similar fashion to other laboratory tests (see Section 6.5.1).

7.9 Washout (2 weeks)

The participant will be asked to stop the research medication for 2 weeks. Prior to the washout period, the research personnel will give instructions (as per their clinical judgement) on how to safely go back to the participant's usual diabetes care. Due to the long half-life of semaglutide, there will be no automatic prophylactic changes in pump settings. However, if the participant had significant changes in pump settings during the last 4 weeks that may result in hypoglycemia, the research personnel will err on the side of caution and hypoglycemia reduction. The participant will be given the second drug at this visit.

If the participant does not use CGM in their usual diabetes care, Dexcom use will be recommended to aid with hypoglycemia reduction.

On Day 7 (± 4 days), the research personnel will contact the participant to assess for any side effects off the study drug and any change in glycemia. A quick and informal review of CGM data will be assessed to reduce the risk of hyperglycemia (> 13.9 mmol/L) and hypoglycemia (< 3.9 mmol/L).

7.9 Second intervention

Drug titration over 12 weeks, AID run-in over 1 week, and the 3 weeks of AID use will be repeated with the following study drug as described previously.

7.10 End of Study Visit (Visit 4)

The last visit will take place within 3 days of the end of 4 weeks of using the AID and study drug. Final laboratory investigations and anthropometric measurements will be taken. All study materials (questionnaires, logs, study drug bottles, diabetes care) will be returned. A semi-structured interview will be performed to assess items that may not be captured through questionnaires. This will include the participant's overall experience the study, use of the closed-loop therapy, the study drug, and elements of T1D care that they are important to them. The interview will be audio-recorded with permission of the participant, and transcribed at a later date. Ongoing consent during the recording process will be obtained.

7.11 Post-study follow-up

Participants will ask to continue their usual follow-up with their own diabetes care team. However, a remote follow-up 1 week (± 3 days) will be done to informally ensure there are no adverse effects from the study.

8. Risk and Risk Mitigation

8.1 Semaglutide dose rationale

The doses of semaglutide SC weekly used (0.25 mg, 0.5, 1 mg) in the the study are the same as those that are commercially available and have been used in the SUSTAIN trials (21,66–69). The approach of using maximum tolerated dose is also used previously (23). Though there is a long half-life to the drug, prior cross-over designs have successfully been used at 3 - 7 weeks of washout (70,71). The dose titration is as reflected in the product monograph (44).

8.2 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.

8.2.1 Concomitant and prohibited medications

- Concomitant medications that require observation (72)
    - Drugs that may enhance hypoglycemic effects: alpha-lipoic acid, androgens, directing acting antiviral agents (specifically for treatment of Hepatitis C), guanethidine, maitake, monoamine oxidase inhibitors, pegvisomant, prothionamide, quinolones, salicylates, selective serotonin reuptake inhibitors, other anti-hyperglycemic agents (metformin, DPP4 inhibitors, sulfonylureas, SGLT2 inhibitors, acarbose)
    - Glucocorticoids: Potential for significant hyperglycemia
    - Drugs that may diminish hypoglycemic effects: ritodrine, thiazides
    - Other agents to be aware of:
        - Levothyroxine: serum concentration of supplemental thyroid hormone levels may be modified in conjunction with semaglutide
        - Sincalide: effect may be diminished due to impact of gallbladder motility

8.3 Risks associated with the study

8.3.1 Semaglutide

The following side effects are reported in those who have used the drug primarily for T2D, as well as off-label use (72). Similar effects are assumed to be seen in T1D. The risks are divided by frequency as a percentage.

Table 9

> 10%	1 - 10%	< 1%	Not defined
Abdominal pain	Abdominal distension	Acute pancreatitis	Anaphylaxis, angioedema
Nausea	Cholelithiasis	Discomfort at injection site	Increased heart rate
	Constipation	Dizziness	Increased serum lipase and amylase
	Decreased appetite	Fatigue	Increase in PR interval on ECG
	Diabetic retinopathy*		
	Emesis		
	Eructation (i.e. belching)		
	Flatulence		
	Gastritis		
	Gastroesophageal reflux		
	Hypoglycemia		

* Increase in diabetic retinopathy, particularly in proliferative diabetic retinopathy, was seen in SUSTAIN6 (21). Subsequent analysis revealed there is increased risk with existing diabetic retinopathy, and rapid decrease of hyperglycemia (73).

Semaglutide was found in rodent studies to increase thyroid C cell hyperplasia and C cell tumours (72). Because of this, semaglutide is contraindicated in patients with personal or family history of medullary thyroid cancer and Multiple Endocrine Neoplasia 2 (high risk for medullary thyroid cancer development).

8.3.2 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.

8.3.3 Glucose sensors and insulin infusion sets

Glucose sensors and infusion sets are both inserted subcutaneously. It is recommended to change insertion site every 2 - 3 days for an infusion set, and every 10 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.

8.3.4 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.

8.3.5 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 10. Diagnostic criteria for DKA vs HHS as per the American Diabetes Association (2009).(74)

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.

8.3.6 Risks related to the AID system

8.3.6.1 Disruption in communication between the insulin pump device and AID:

- 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.

8.3.6.2 Error in glucose sensor accuracy:

- The AID uses Dexcom 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 AID 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 doses of acetaminophen/paracetamol larger than 1 gram every 6 hours,** which is more higher than maximum dose recommended by the manufacturer (43,75)**.** Taking medications containing acetaminophen at high doses

may falsely raise the sensor readings, causing the AID system to deliver more insulin than required.
- Hydroxyurea is a known interfering substance that may cause falsely elevated glucose values; Dexcom G6 use is not advised with concomitant use of this drug as per the manufacturer. This is encompassed in exclusion criteria, and participants will be asked to update research personnel on change in medications throughout the study.

8.3.6.3 Disruption in communication with the glucose sensor
- If Bluetooth communication of the CGM to the rest of the AID 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.

8.3.6.4 Smartphone malfunction or shut-down
- If there is any malfunction with the study phone preventing access to theh AID (e.g. insufficient battery), open-loop mode will commence within 20 minutes.

8.3.6.5 Software error
- Any termination of theAID software for any reason will result in reversion to an open-loop mode of insulin delivery.

8.4 Pregnancy
Semaglutide has not been previously tested in pregnancy, though studies in animals showed some potential toxicities (44). The Food and Drug Administration had not released a specific category class for this drug, but it is recommended to not use during 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 participant who is at risk of pregnancy (see prior definitions) must actively avoid pregnancy throughout the study and will be counselled on the risks of pregnancy in the study. If a participant feels they may be pregnant, they must 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 3 times throughout the study in those at risk to biochemically rule out pregnancy. Those who are post-menopausal or who have undergone removal of the uterus and/or ovaries will be exempt from taking a pregnancy test.

9. Data Safety Monitoring Board (DSMB)
9.1 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.

9.2 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.

9.3 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 SEMA-AP trial, protocol number [*Research Ethics Board number here*] 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."

9.4 Meetings

The DSMB will meet:
(1) After P01-P06 (i.e. participants # 1 through 6) are finished their interventions.
(2) After P07 to P014 have finished their interventions.
(3) After any serious adverse event that is deemed potentially related to the intervention.

Items reviewed by the DSMB include:

- Individual and cumulative data for evidence of study-related adverse events;
- Individual and cumulative data of glucose outcomes data;
- 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.

9.4.1 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.

9.4.2 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 Research Ethics Board will be notified.

9.4.3 Study reports

It is the responsibility of the Primary Investigator 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.

9.5 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., Research Ethics Board) 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.

10. Statistical analysis

- All glycemic outcomes based on CGM data will be compared between the 4 weeks on the AID using placebo vs. semaglutide (at maximum tolerated dose). Wherever applicable, outcomes will be calculated for 24 hours, daytime (6h00 – 24h00), and nighttime (24h00 – 6h00)
- Mean values of TXNIP and IL-6 will be compared between each intervention
- For any analyses done for the MMTT, area-under-curve will be compared between each intervention
- All other measurements performed after each intervention will be compared to the baseline performed at the initial study visit

10.1 Study endpoints

10.1.1 Primary endpoints

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

10.1.2 Secondary endpoints

10.1.2.1 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, 3.0 mmol/L
    c. Above 7.8, 10, and 13.9
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 ≥ 70%
6) HbA1c

10.1.2.2 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
    d) Diabetes Bowel Syndrome Questionnaire
    e) Diabetes Treatment Satisfaction Questionnaire

10.1.2.3 Anthropometric measures

1) Blood pressure

2) Heart rate
3) Weight
4) Body mass index
5) Waist circumference
6) Waist-to-hip circumference

10.1.2.4 Laboratory measures

1) Lipid profile, specifically: LDL-cholesterol, HDL-cholesterol, triglycerides
2) NT-pro-BNP
3) Inflammatory investigations: CRP, ferritin, IL-6
4) uACR
5) TXNIP
6) Mixed-meal tolerance test
    a. Glucagon (area-under-curve)
    b. C-peptide (area-under-curve)
    c. Paracetamol (area-under-curve)

10.1.2.5 Other endpoints

1) Total daily insulin dose
2) Units per kilogram
3) Average daily carbohydrate count (as recorded from bolus calculator through pump)

The semi-structured interview's analysis will be based predominantly on qualitative rather than quantitative data assessment, though some statistical analysis may be performed on prevalence of themes that arise during the coding of transcripts.

10.1.3 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) Gastro-intestinal side effects
    a. Nausea
    b. Emesis
    c. Abdominal pain
    d. Changes in pancreatic enzymes, or liver profile tests

e. Gallbladder disease
f. Acute pancreatitis

10.2 Sample size and power calculations

The power calculations aim to compare the effects of placebo vs. semaglutide (at maximum tolerated dose) on closed-loop therapy on the primary endpoint (time in target range), made at the α = 0.05 significance level.

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 (36,37,41). 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 for 20% drop-out, 28 participants will be recruited.

10.2.1 Level of significance

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

10.2.2 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). A separate analysis will be used to assess if glycemic changes are linked with C-peptide levels (taken at admission visit) or weight reduction by end of intervention.

The semi-structured interviews taken at the end of the study, after recording, will be transcribed and then coded by research personnel for themes using an inductive-deductive approach via encoding software (MAXQDA, version 22.1.1 for Macbook, or latest version at time of analysis). There may be statistical analysis performed for prevalence of themes, but the assessment is ultimately qualitative in nature.

11. Ethical and legal considerations

11.1 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 Research Ethics Board of the McGill University Health Centre.

11.2 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

11.3 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. Consent can be withdrawn at any time by the participant.

11.4 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 securely in paper format as per regulations of the Research Ethics Board of the McGill University Health Centre.

11.5 Participant compensation

All study materials (both non-perishable and perishable) will be provided to participants. Given their time dedication, participants will be given $975: $25 for each in-person visit (initial study visit, examination after Intervention 1, and end of study visit), and $450 for each intervention completed. This amount was decided based on prior studies and was felt reasonable from other participants.

11.6 Approval of the clinical study protocol and amendments

An application will be sent to the Research Ethics Board of the McGill University Health Centre for assessment and approval prior to start of the study. If any changes are made to the study

protocol, the amended protocol will be submitted to Health Canada and the IRB will be informe. The study will continue once the amendment has been approved. The primary investigator will keep track of all communication with the Research Ethics Board.

11.7 Record retention

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

12. Adverse events

12.1 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 participant.

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

- Active surveillance through the DSMB
- 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.

12.2 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.

12.2.1 Hypoglycemia

Given the intensity and complexity of treatment of insulin therapy in type 1 diabetes, hypoglycemia is common. Different therapies may influence the frequency and severity of these events for each participant.

The AID 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).

Semaglutide 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 hypoglycemia will be reviewed at the training visit. Real-time continuous glucose monitoring allows for alarms (as per participant preference) so participants are notified if hypoglycemia is occurring. Remote visits during the beginning of each intervention will ensure to discuss any excess hypoglycemia. Significant events of hypoglycemia 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 (i.e. hypoglycemia requiring intervention by a third party due to altered mental status), immediate attention by medical personnel of the research group will be taken. CGM data, pump settings, and the cause will be reviewed. Revision by the primary investigator will confirm if the participant should be withdrawn from the city (as per their clinical judgment.

Any significant episodes or recurring episodes causing impairment to the participant will be reported to the Research Ethics Board and regulatory authorities. Note that non-severe hypoglycemia will not be reported as adverse events.

12.2.2 Hyperglycemia and affiliated conditions

Hyperglycemia is also a common feature of diabetes. Different therapies may influence the frequency and severity of these events for each participant.

A review of proper diabetes care (e.g. not overtreating hypoglycemia, meal bolus with carbohydrate counting) will be reviewed at the initial training visit, and brought up if need be throughout the study.

The most concerning consequences of hyperglycemia (which is a lack of balance between glucose and insulin) is diabetic ketoacidosis (DKA). Any malfunction causing lack of insulin delivery can increase the risk of DKA in a patient with T1D. Hyperosmolar hyperglycemic state (HHS) is rare but still possible in T1D.

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.
- Participants will be instructed to measure ketones if CGM measures above 16 mmol/L for more than 2 hours and no descent, in any acute illness, or symptoms of ketoacidosis (nausea, vomiting, abdominal pain).

The following will be specific adverse events of interest during the study:

- Point of care ketone levels above 1.5 mmol/L
- Ketone-related events requiring presentation to medical attention
- Diabetic ketoacidosis as previously defined.

12.2.3 Local skins 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. 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.(76) This would only occur in the case of improper hygiene and a severe lack of recommended site change (recommended to be every 3 days). Local skin reactions to the injection of semaglutide or placebo may also occur.

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.

12.2.4 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.

12.2.5 Gastrointestinal symptoms, gallbladder disease and pancreatitis

Mild gastrointestinal symptoms such as abdominal discomfort, nausea, and vomiting have been previously reported. Of the more severe gastro-intestinal adverse events are gallbladder disease (ranging from biliary colic to cholangitis, a life-threatening sepsis of an impacted gallstone) and acute pancreatitis.

The following will be considered adverse events of specific interest:

- Abdominal discomfort
- Nausea
- Vomiting
- Diabetic retinopathy (de novo or progression)
- De novo gallbladder disease of any kind (revision of the principal investigator will be required if withdrawal from the study is required)
- Acute pancreatitis: if this occurs, withdrawal from the study will occur

12.3 Technical adverse events

Possible malfunctions are previously described. Included in these adverse events is the need for any study personnel to override the AID system due to any troubleshooting to avoid other adverse events. Any AID 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.

12.4 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.

12.5 Reporting serious adverse events

12.5.1 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 (though this may be delegated to MD co-investigator)
- 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

12.5.2 Definition of a serious adverse event (SAE)

A *serious adverse event (SAE)* is any adverse event that is labelled as severe, 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. semaglutide) or a device (e.g. any AID 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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Appendix A: Ketone Management

Please be aware of the risks of diabetic ketoacidosis and the need to assess for this in the event of any of the following:

- Glucose level above 16 mmol/L for more than 1 hour
- Symptoms of hyperglycemia (increased urination, extreme thirst, fatigue, blurry vision)
- Symptoms of ketones (nausea, vomiting, abdominal pain)
- Sudden illness (such as infection)

If any of the above occur, you must do the following:

1) Measure blood sugar by finger-prick to confirm CGM reading
2) Measure blood ketone levels immediately (and follow the table below)
3) Confirm there is no damage or malfunction to the cartridge, catheter, or insertion site
4) Drink at least 250 mL (or 1 cup) of water every 30 minutes. Avoid drinks with sugar or caffeine.
5) Follow the below recommendations, depending on the ketone level obtained

If glucose is above 16 mmol/L, do the following depending on the described ketone level:	
Less than 0.6 mmol/L	1. Calculate bolus estimated by the smartphone AID application and administer via the insulin pump 2. Do not skip meals. Try to have at least 30 g of carbohydrates at next meal 3. Repeat blood glucose and ketone levels in 2 hours after bolus administration 4. If glucose remains elevated and/or ketone levels rise (but are less than 0.6 mmol/L), change infusion site and continue to monitor 5. If ketones rise above 0.6 mmol/L, follow instructions below
0.6 to 1.5 mmol/L	1. Contact your study lead as soon as possible. 2. Calculate bolus estimated by the smartphone AID application and administer rapid acting insulin via insulin pen or syringe. During closed loop setting, disconnect from pump and bolus the same amount so that pump is aware of insulin-on-board. 3. Check that insulin in use from original was stored appropriately and not expired. 4. Insert a new infusion catheter, with new insulin cartridge and tubing. Fill with a new vial of insulin if there are any concerns from the prior vial. 5. Examine the original pump catheter, tubing, and cartridge for any kinks or blockages. If any identified, notify your study lead. 6. Recheck blood glucose by finger-prick and ketones 2 hours after the injection

	7. If glucose remains high and ketones remain above 0.6 mmol/L, further treatment will be discussed with your study lead. You may need to go to the hospital.
Above 1.5 mmol/L	1. Contact your study lead. 2. Calculate bolus estimated by the AID application and administer 1.5x the calculated dose with rapid acting insulin via insulin pen or syringe (e.g. if 2 Units is suggested, give 3 Units instead). During closed loop setting, disconnect from pump and bolus the same amount so that pump is aware of insulin-on-board. 3. Check that insulin in use from original was stored appropriately and not expired. 4. Insert a new infusion catheter, with new insulin cartridge and tubing. Fill with a new vial of insulin if there are any concerns from the prior vial. 5. Examine the original pump catheter, tubing, and cartridge for any kinks or blockages. If any identified, notify your study lead. 6. It is possible if this persists, you may need to go to emergency department.

If glucose is below 16 mmol/L but symptoms of ketoacidosis are present (e.g. nausea/vomiting/abdominal pain), this may be euglycemic ketoacidosis (high ketone levels with a normal blood sugar). Do the following depending on the described ketone level:	
Less than 0.6 mmol/L	1. **If food can be kept down without vomiting:** Eat 30 g of carbohydrates and bolus for this and any correction via the pump 2. Repeat blood glucose and ketone levels in 2 hours after bolus administration 3. If glucose and/or ketone levels rise (but are less than 0.6 mmol/L), change infusion site and continue to monitor 4. If ketones rise above 0.6 mmol/L, follow instructions below
0.6 to 1.5 mmol/L	1. Contact your study lead as soon as possible. 2. **If food can be kept down without vomiting:** Calculate correction bolus and meal bolus for minimum 30 g of carbohydrates estimated by the AID smartphone app and administer rapid acting insulin via insulin pen or syringe. During closed loop setting, disconnect from pump and bolus the same amount so that pump is aware of insulin-on-board. Eat the carbohydrates after administering. 3. **If food cannot be kept down:** administer any possible correction bolus applicable as estimated by the AID as #2 without carbohydrate bolus.

	4. Check that insulin in use from original was stored appropriately and not expired. 5. Insert a new infusion catheter, with new insulin cartridge and tubing. Fill with a new vial of insulin if there are any concerns from the prior vial. 6. Examine the original pump catheter, tubing, and cartridge for any kinks or blockages. If any identified, notify your study lead. 7. Recheck capillary blood glucose and ketones 2 hours after the subcutaneous injection 8. If glucose remains high and ketones remain above 0.6 mmol/L, notify study physician
Above 1.5 mmol/L	1. Contact your study lead immediately. 2. **If food can be kept down without vomiting:** Calculate carbohydrate bolus for minimum 30 g estimated from the AID, and 1.5 times any correction bolus (e.g. if 2 Units for carbohydrates, and 2 Units for correction, administer [2 + 2x1.5] = 5 Units. Administer rapid acting insulin via insulin pen or syringe. During closed loop setting, disconnect from pump and bolus the same amount so that pump is aware of insulin-on-board. Eat carbohydrates after administering. 3. **If food cannot be kept down:** administer any possible correction bolus applicable as estimated by the AID as #2 without carbohydrate bolus. 4. Check that insulin in use from original was stored appropriately and not expired. 5. Insert a new infusion catheter, with new insulin cartridge and tubing. Fill with a new vial of insulin if there are any concerns from the prior vial. 6. Examine the original pump catheter, tubing, and cartridge for any kinks or blockages. If any identified, notify your study lead.

If an event where this protocol is required, all actions, symptoms, and measurements of ketone and glucose levels should be recorded.

Please note: This algorithm is based on protocols (the STICH and STOP-DKA protocols) created by experts to help patients to treat ketones while using SGLT2 inhibitors (67,77), and is also based on routine pump care for type 1 diabetes. This algorithm has also been used in many of our previous studies, and was reviewed by a doctor (Dr Pasqua). However, it is not in itself a validated algorithm and does not replace the need to contact qualified research personnel in the event of an emergency.