EFFICACY AND SAFETY OF ONCE WEEKLY SEMAGLUTIDE IN ADULTS WITH OBESITY AND INADEQUATELY CONTROLLED TYPE 1 DIABETES USING HYBRID CLOSED-LOOP SYSTEM

Short title: **ADJUnct Semaglutide Treatment in Type 1 Diabetes (ADJUST-T1D)**

INVESTIGATOR-INITIATED STUDY

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1. BACKGROUND AND SIGNIFICANCE:

Due to complexity in managing type 1 diabetes (T1D) and hypoglycemia associated with intensive insulin therapy, only 30% of patients with T1D are able to achieve desirable glycemic goal; HbA1c <7% as recommended by the American Diabetes Association [1,2]. Moreover, the prevalence of overweight and obesity is increasing among patients with T1D [3,4]. Insulin resistance associated with obesity is also believed to be a contributing factor to inadequate glycemic control in T1D [5].

Hybrid closed-loop systems (HCL), also known as artificial pancreas, where an insulin pump delivers insulin dose based on continuous glucose monitor (CGM) glucose values by means of controller (mathematical) algorithm [6]. Studies with HCL have been shown to improve glycemic control and reduce hypoglycemia in children, adolescents, and adults with T1D [7,8,9,10]. The HCL systems are the most advanced diabetes management tools in the armamentarium of diabetes management. The use of the HCL system is increasing among patients with T1D and it is becoming a standard of care in the management of T1D. With increasing use of diabetes technologies such as CGM and the HCL and limitation of HbA1c in managing of diabetes, diabetes care is now moving from HbA1c centric to CGM-based metrics such as time-in-range (TIR; sensor glucose between 70-180 mg/dL), time-below range (TBR; sensor glucose <70 mg/dL) and time-above range (TAR; sensor glucose >180 mg/dL)[11-13]. Studies have also validated TIR as an outcome measure for diabetes clinical trials [14] and there is a strong inverse relationship between TIR and diabetes complications [15-21]. International consensus recommends TIR>70% with TBR of <4% as optimal glycemic control for most adults with T1D and type 2 diabetes [11].

There are three HCL systems currently available in the US; Medtronic 670 G/ 770G, Tandem Control IQ and Omnipod 5 [21-23]. On April 21, 2023, Medtronic 780 G was approved by the US FDA for management of T1D. Despite use of these most sophisticated diabetes technologies, not every HCL user with T1D is able achieve the recommended HbA1c or TIR goal [25-27]. This is mainly due to inability of the currently available HCL systems to control post-prandial glucose excursions [28]. Studies have shown improvement in glycemic control (HbA1c and time-in-range) due to mainly dramatic improvement in overnight glycemic control [8-10]. The daytime control

between adults with T1D using HCL system and controls using insulin pump and CGM is only modestly different [8-10].

Semaglutide is once a weekly glucagon-like peptide-1 receptor agonist (GLP-1RA). It has been approved for the management of type 2 diabetes and has been shown to improve glycemic control and is associated with significant weight loss without increasing hypoglycemia [29-31]. GLP-1RA have potential to improve glycemic control in existing HCL uses with inadequately controlled T1D by improving daytime (mainly post-prandial) glycemic control and also may reduce insulin requirement due to weight loss. Small pilot studies have documented improvement in mean glucose and time-in-range with short-term use of liraglutide in patients with T1D using HCL [32,33]. Moreover, liraglutide had no effect on plasma glucagon during mixed meal tolerance test [34] suggesting GLP-1RA may not blunt glucagon response during hypoglycemia. In addition, Semaglutide has been shown to improve cardiovascular and renal outcomes in patients with type 2 diabetes [35-38]. Since cardiovascular disease is the leading cause of death in people with T1D [39-40], there is an interest in exploring effect of GLP-1RA in patients with T1D. Further, as obesity is growing in prevalence among people with T1D, nonalcoholic fatty liver disease (NAFLD) is of concern in this population. Semglutide may improve biomarkers of NAFLD, including hepatic steatosis index (HSI) and fibrosis score (FIB-4), based on easily obtained blood markers. Further, assessment of NAFLD by magnetic resonance imaging corresponds well to livery biopsy data on steatosis and fibrosis. Magnetic resonance elastrography (MRE) can be used to assess liver stiffness, a measure of fibrosis, and proton density fat fraction (PDFF), a measure of steatosis.

Previous studies with the use of GLP-1RA in patients with T1D using HCL systems were limited by small sample size, and shorter duration (only for few days) [32,33], and therefore, unable to provide evidence for long-term efficacy and safety of GLP-1RA in patients with T1D using HCL systems. Semaglutide is a long-acting GLP-1RA with a once a weekly administration that makes it convenient for patients and shown to have high adherence rate in patients with type 2 diabetes [41]. Weight loss is more pronounced with semaglutide compared to liraglutide [42]. Therefore, we plan to evaluate efficacy and safety of semaglutide as an add-on therapy in adults with T1D who are inadequately controlled despite the use of HCL therapy.

2. SPECIFIC OBJECTIVE

Primary objective of the study is to evaluate improvement in a composite outcome (CGM-measured TIR>70% with TBR of <4% and reduction in body weight by 5% at 26 weeks with the use of once weekly semaglutide in inadequately controlled obese adults with T1D using FDA-approved HCL therapy.

3. RESEARCH DESIGN AND METHODS

3.1.Study Hypothesis

We hypothesize that a significantly higher number of adults with T1D randomized to receive semaglutide (30-40%) will be able to achieve the primary composite outcome compared to adults with T1D randomized to the placebo group (≤5%).

3.2 Endpoints

3.2.1 Primary outcome

Proportion of participants achieving composite outcome of time in range (TIR) 70-180 mg/dl >70% and reduction in body weight by 5% with time below range (TBR) <70 mg/dl of <4%.

3.2.2 Key secondary efficacy outcomes

HbA1c

TIR (70-180 mg/dL)

Mean glucose

TBR <70 mg/dL

Time in tight target range (70-140 mg/dl)

Change in Weight

Change in BMI

Time spent >180 mg/dL

Time spent >250 mg/dL

Standard deviation

Coefficient of variation

3.2.3 Key Safety outcomes

-SH events

-DKA events

3.2.4 Exploratory outcomes

Proportion with hbA1c <7%

Proportion with HbA1c <7.5%

HbA1c improvement from baseline to 26 weeks

HbA1c improvement of >0.4% from baseline

Proportion of participants achieving TIR >70%

Proportion of participants achieving TITR >50%

Proportion of participants achieving TIR >80%

Proportion of participants achieving TITR >60%

Number of TBR<70 events (event is defined as <70 mg/dL lasting for at least 15 minutes)

Number of TBR <54 events (event is defined as <54 mg/dL lasting for at least 15 minutes)

Change in TDD (Units per day)

Change in TDD (units/kg/day)

Proportion achieving weight loss ≥5%

Proportion achieving weight loss ≥10%

Proportion of achieving BMI <30 kg/m2

Proportion of achieving BMI <25

Change in systolic blood pressure

Change in diastolic blood pressure

Change in pulse pressure

Change in TG/HDL ratio

Change in Brach D

Change in cIMT

Change in femoral to carotid pulse wave velocity (m/s)

Change in ACR

Quality of life (Diabetes Dependent QOL)

CGM metrics (TIR, TITR, mean glucose, TBR, TAR >180, SD, CV) by daytime (6 AM to <11PM) and nighttime (11 PM to <6 AM)

AID setting adjustment. Defined any adjustment in settings by provider or patient per person over the study period by two groups (number of adjustments (N) during trial)

Change in basal insulin per day (Total basal insulin including autobasal delivery, units per day)

Change in basal insulin per day (units/kg/day)

Change in total boluses per day (frequency of boluses per day)

Achievement of primary outcome and key secondary outcomes by types of AID systems

Change in Carbohydrate intake per day (grams/day)

Change in total bolus insulin per day (units per day)

Change in total bolus insulin (units/kg/day)

Change in eGFR using CKD-EPI

Change in Fib-4 score

Change in HSI (hepatic steatosis index)

Change in MRI measured pulse wave velocity and longitudinal strain

Change in LDL-C

Change in TC

Change in TG

Change in HDL-C

Proportion with ACR <30 at 26 weeks

Proportion with change in ACR from >30 to <30

Achievement of primary outcomes by baseline BMI (BMI <35 vs >35)

Achievement of primary outcomes by baseline A1c (A1c <7.5% vs >7.5%)

3.3 Study design

- This will be a multicenter (four centers), double blind, parallel-group, randomized, placebo controlled clinical trial in obese T1D adults with suboptimal glycemic control despite 3 months use of FDA approved HCL technology. Study design is summarized in the Figure below.

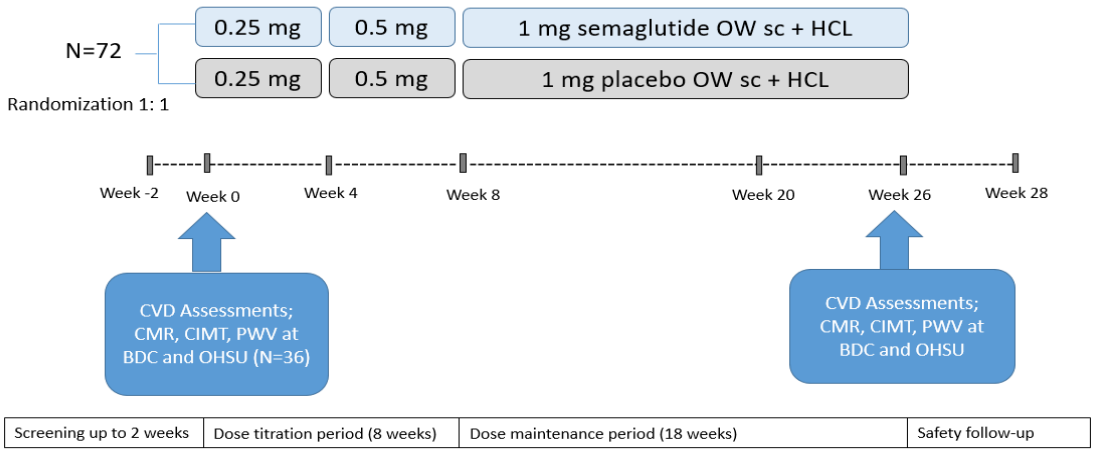

Figure: An illustration of study design

- All participants will be randomized using computer generated block randomization and stratified by clinic research center.
- There are up to 6 clinic visits and 3 phone call visits.
- CVD assessments will take place at Randomization and at the week 26 visit. Brachial distensibility will be measured using the Dynapulse Pathway device at all centers, and pulse wave velocity (PWV), augmentation index by radial artery tonometry, cIMT and CMR assessments, along with ectopic fat measures of abdominal and pericardial fat, will take place at the BDC and OHSU sites. CVD assessments will be completed at an early discontinuation visit if a study participant drops out.
- NAFLD assessments will be done in conjunction with CVD assessments, as part of the blood tests for all participants and as part of the MRI completed for participants at the BDC and OHSU.

3.4 Justification for study design

- HCL therapy is the standard of care managing T1D. Despite HCL use, not all patients with T1D are able to achieve recommended glycemic goals [25-27]. Moreover, prevalence of obesity is increasing in this population [3-4], which is associated with insulin resistance and poor glycemic control [5]. Therefore, adjunctive therapies such as GLP-1RA are needed in this population to improve glycemic control as well as improve weight management.
- We propose a randomized, placebo controlled clinical trial, as a well-designed RCT, will provide a high level of evidence for efficacy and safety of semaglutide in obese adults with T1D.
- We will have a 4 week titration period as recommended by the manufacturer. All subjects will be encouraged to titrate up to 1 mg a week. In case of intolerability, the dose will be titrated back to pre-tolerable dose and subjects will be encouraged to use max tolerable dose of at least 0.5 mg weekly.
- This will be a first clinical trial to provide efficacy and safety of semaglutide in suboptimal glycemic control despite on optimal therapeutic regiment in adults with T1D.
- We will try to screen subjects using different HCL systems (Medtronic 670/770 G/780G, Tandem control IQ and Omnipod 5).

- With increasing obesity and higher insulin resistance, cardiovascular risk is higher in people with T1D [43]. Semaglutide has been shown to reduce Major Adverse Cardiovascular Events (MACE) in patients with type 2 diabetes with high cardiovascular risk [35,44]. Therefore, it would be of interest to explore change in cardio-renal and NAFLD parameters over 26 weeks of treatment with Semaglutide in patients with T1D. Since enrolled patients are anticipated to have good glycemic control (due to HCL use) and because of the short duration of this clinical trial, we do not anticipate statistically significant differences in cardio-renal or NAFLD endpoints. However, these exploratory data would be useful for designing future clinical trials to reduce cardiovascular risk in people with T1D.

4. CLINICAL RESEARCH SITES

The study will be conducted at four US clinical sites. The Barbara Davis Center for Diabetes will be the lead primary site.

5. STUDY POPULATION:

5.1 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered "yes"

1) Age ≥18 and ≤ 65 years at screening
2) Patients with clinical diagnosis of T1D for at least 12 months
3) Patient is on FDA- approved hybrid closed-loop system for ≥ 3 months
4) Willing to use once weekly semaglutide
5) Willing to share devices (HCL system) data uploads
6) HbA1c >7.0% and <10.0%
7) Body mass index ≥30 kg/m^2
8) Has current glucagon product to treat severe hypoglycemia
9) Has current ketone meters to check ketones
10) Ability to provide informed consent before any trial-related activities

5.2 Exclusion criteria

1) Age <18 years and > 65 years
2) HbA1c ≤7.0 % or ≥ 10.0% at screening
3) Less than 12 months of insulin treatment

4) Use of unapproved insulin for HCL system. E.g. use of Fiasp in the Tandem Control-IQ system
5) Not willing to share the devices (HCL system) data uploads
6) Non compatible devices (e.g. pump, CGM or smart phones) for data transfer
7) Current use of multiple daily injection or inhaled insulin (Afrezza)
8) Patients with T1D using any glucose lowering medications other than insulin at the time of screening
9) Pregnancy, breast feeding, and positive pregnancy test during screening
10) Women of childbearing age wanting to become pregnant
11) Unwilling to use acceptable contraceptive methods (for both men and women) during the trial period
12) Current use (≥ 2 weeks of continuous use) of any steroidal medication, or anticipated long-term steroidal treatment (>4 weeks continuously), during the study period
13) Use of GLP-1RA or weight loss medications in the past 3 month
14) Clinical diagnosis/history of gastroparesis or gastric motility disorders
15) Serum triglycerides >500 mg/dL
16) Planning for bariatric surgery during the study period
17) eGFR below 45 ml/min/1.73 m^2 using CKD-EPI formula
18) History of severe hypoglycemia in the previous 3 months
19) History of diabetic ketoacidosis requiring hospitalization in the past 3 months
20) History of allergy to any form of insulin, GLP-1RA or its excipients
21) History of any form of pancreatitis
22) History of stroke, myocardial infarction in the past 3 months
23) History of congestive heart failure class III or IV
24) History of acute or chronic liver disease
25) History of malignancy requiring chemotherapy, surgery or radiation in previous 5 years
26) Personal or family history of multiple endocrine neoplasia type 2 (MEN-2) or familial thyroid carcinoma or non-familial medullary thyroid carcinoma
27) Have a pacemaker, metal implants, or aneurysm clips or weigh >330 lbs (exclusion only if doing MRI)
28) Use of investigational drugs within 5 half-lives prior to screening

29) Participation to other intervention trials during the study period
30) Any comorbidities or medical conditions such as severe psychiatric disorder that make a person unfit for the study at the discretion of the investigators

5.3 Rationale for inclusion/ exclusion criteria: Only patients using FDA approved HCL system will be included. Many patients with T1D uses do-it-yourself (DIY) system that are not FDA approved and they will be excluded for safety reasons.

5.4 Withdrawal criteria

- Participation in this research is voluntary. Subjects may withdraw at will at any time. When withdrawing from the study, the participant should let the research team know that he/she wishes to withdraw. A participant may provide the research team with the reason(s) for leaving the study but is not required to provide their reason.
- If subject is withdrawn after week-10, we will encourage participants to complete V6 (week-26) or complete V6A/P3A.
- Participants will be withdrawn from the study if they become pregnant, actively try to become pregnant, develop an allergic reaction to semaglutide or at the judgement of investigators due to safety concerns.
- After withdrawal, the participant will be given instructions on how to safely stop using study medications and, eventually, on how to correctly and safely return to the previous treatment regimen. Instructions are also given on who to contact if there are any questions or concerns that arise after study withdrawal.
- At the time of withdrawal, the research participant should let the research team know if he/she will allow the use of his/her health information and collected data by the researchers.

5.5 Subject replacement

Withdrawn subjects will not be replaced. However, re-screening is allowed within recruitment period at the investigator's discretion.

5.6. Reminders

To minimize loss to follow-up, reminders (text message, phone call or email) will be sent to participants prior to each clinic visits.

6. VISIT PROCEDURES:

- The details of the study visits and procedures are provided in the Table below. In brief, there are up to six in-person research visits and up to three phone call visits.
- Before screening takes place, subjects will be provided with written information about the trial and the procedures involved. Subjects will be fully informed, both orally and in writing, about their responsibilities and rights while participating in the trial, as well as about possible advantages and disadvantages when participating in this trial. Subjects will have the opportunity to ask questions and have ample time to consider participation. The informed consent process will take place before the screening visit. Before signing the informed consent, the investigator will make sure that the potential subject has full knowledge of the study processes, and the possibility to withdrawal at any time during the study.
- Subjects who wish to enroll in the trial must sign and date the informed consent form for the trial before participating in any trial-related procedures. All subjects will be provided with a copy of signed informed consent form.

Trial period	Screening	Randomization	Treatment period						Follow-up	End-of-treatment premature discontinuation	Follow-up premature discontinuation
Visit (V) or Phone (P)	V1	V2	V3[4]	P1	V4[4]	P2	V5	V6	P3	V6A[2]	P3A[3]
Weeks	-2	0	4	6	8	10	20	26	28		2 weeks from V6A
Window (days)	± 7	-	±3	±3	±3	±3	±7	±7	+7		+7
Subject-Related Information/ Assessments											
Informed consent	X										
Inclusion/Exclusion	X										
Randomization		X									
Screen fail/Withdrawal criteria		X	X	X	X	X	X	X		X	
Medical history/concomitant medications/ Demography	X	X	X	X	X	X	X	X		X	
Trial-related efficacy and safety measures											
Height/Weight/BMI/ Waist & Hip circumference	X	X	X		X		X	X		X	
CVD and NAFLD risk assessment[6]		X						X		X	
Device downloads (CGM and pump data)[1]	X	X	X		X		X	X		X	
Questionnaires[8]	X				X		X	X		X	
AE/SAE assessment including assessment for severe hypoglycemia and DKA	X	X	X	X	X	X	X	X	X	X	X
Laboratory											
HbA1c (Central)	X				X		X	X		X	
Lipid, CBC and CMP[7]	X	X			X		X	X		X	
Random urine albumin to creatinine ratio		X			X		X	X		X	
Pregnancy test (for premenopausal women)	X	X	X		X		X	X		X	
Fasting blood and urine collection (only for storage)		X			X		X	X		X	
Trial Material											
Drug accountability			X		X		X	X		X	
Drug Dispensing[5]		X	X		X		X				
Patient handouts/ reminders	X	X	X	X	X	X	X	X		X	

[1]patients own devices. [2]V6A to be scheduled at the discontinuation of the trial product; [3]P3A to be conducted for those who complete their V6A. [4]V3 and V4 can be done remotely if needed. [5]In a situation needing subsequent visit to be done remotely, you can dispense extra IMPs. [6] CVD risk assessment includes brachial artery distensibility, pulse wave analysis and velocity, cIMT and CMR, MRE and PDFF. Brachial artery distensibility at all 4 sites. Other cardiac measures at BDC and OHSU sites, initial MRI and cIMT can be done prior to V2 after eligibility has been determined. [7]At

screening, non-fasting plasma triglycerides and CMP will be measured. Randomization onwards, fasting lipids, CBC and CMP with be measured. [8] Questionnaires such as GOLD, QOL, physical activity measures.

6.1 Screening

- The subjects will be assigned a unique subject number, which will remain the same throughout the trial. The subject number will consist of 3 digits: first digit is site number (e.g. 1) followed by two digit subject number (e.g. 01).
- All subjects will undergo review of inclusion and exclusion criteria. If any inclusion criteria is answered 'no' or any exclusion criteria is answered 'yes', the subject is a screen failure, and no further assessment will take place.
- Patients will be told the importance of compliance of the pre-set study visit time schedules
- All subjects will be assessed and reeducated on diabetes self-management, appropriate and safe use of their own diabetes devices, and its trouble shooting, prevention and treatment of hypoglycemia and sick day management.
- All subjects must use appropriate insulin that is approved for their HCL system. For example, insulin Fiasp is not allowed to be used in Tandem Control-IQ HCL system.

6.2. Randomization

- Randomization visit will be done within 2 weeks from screening visit.
- Subjects will be randomized using computer generated randomization scheme to receive either semaglutide or placebo (1:1 randomization). Patients or investigators will be blinded to either treatment modalities.
- A pre-designated study personnel will be in-charge of allocating study drugs and keeping track of study drug distribution across all the sites.
- A Directions For Use (DFU) will be provided by Novo Nordisk and will be given to each patient at the first dispensing visit (dosing details in Section 6.3)

6.3. Semaglutide dose, titration, and insulin adjustment

- Starting dose of semaglutide is 0.25 mg subcutaneously once a week.
- All patients will be provided with verbal and written education on the use of semaglutide pen
- Dose will be titrated after 4 weeks to 0.5 mg/ week and after 8 weeks to 1 mg/week. In case of intolerance to the medication, the dose can be scaled back. All patients will be encouraged to use maximally tolerable dose up to 1 mg/week.

- At randomization, and during drug titration (week 4 and week 8), study investigator or designated study personnel must review HCL settings, adjust it per the guidance provided in the Appendix A, and provide appropriate education to minimize hypoglycemia. HCL adjustment will be recorded in the study database (Redcap).
- To achieve desirable glycemic control (>70% TIR and <4% TBR), HCL settings may be adjusted by the investigators per the guidance provided in the Appendix C after patient has reached the maximum tolerable dose (after week 10 or P2 study visit). HCL adjustment will be recorded in the study database (Redcap).

6.4. Clinic and phone visits

- All study procedures must be conducted as mentioned in the procedure table above.
- In a situation where an in-person visit cannot be possible, research visits (V3 and V4) can be conducted remotely. A study procedure manual will be provided to all sites.
- If a subject is withdrawn after week-10, participants will be encouraged to complete V6 (week-26) or complete V6A/P3A

6.5 Un-blinding

- The subject randomization list and IMP dispensation details will be stored at the BDC. Subject number will be matched with IMP assigned to the subject.
- The designated independent personnel unblinded to the study drugs (Sarit Polsky, MD) will perform any un-blinding of study participants.
- Un-blinding can be performed under the following circumstances:
    - Treatment of an individual in a medical emergency where knowledge of the treatment allocation is required.
    - Treatment of an individual for an AE.
    - In the event of a SUSAR.
    - In the event that the participant's study medication is accidentally taken by a member of their household e.g. a child.
    - If required by the DSMB committee or regulatory agencies.

7. STATISTICAL PLAN

7.1 Preliminary data for sample size calculation

In SUSTAIN 1, 4 and 5 clinical trials, Semaglutide 0.5 mg and 1 mg per week for 30 weeks in patients with type 2 diabetes resulted in 2.5-4.5 kg, and 3.5-6 kg weight loss compared to baseline [44-46]. 30-40% of patients with type 2 diabetes with baseline BMI between 30-35 kg/m^2 achieved weight loss of >5% using Semaglutide 0.5 mg weekly compared to comparator and 45-60% had weight loss >5% using Semaglutide 1 mg weekly compared to comparator [47]. Based on this data, we conservatively estimated that 30% of patients with T1D using HCL and randomized to semaglutide with BMI >30 kg/m2 will achieve >5% of weight loss at 26 weeks from baseline. None of the clinical trials in T1D demonstrated weight loss with the use of HCL therapy [8-10] and therefore, we don't expect adults with T1D using HCL and randomized to placebo to lose >5% of body weight.

Our previous real-life study of adults with T1D using Medtronic 670 G had mean percent TIR of 67%±1.2% after 3 months of using HCL. In our clinical experience of using semaglutide in adults with T1D with mean HbA1c of 7.7±1.4 at baseline had drop in HbA1c to 7.2±1.1 after 3 months (unpublished data). Each 5% improvement in TIR approximates reduction in HbA1c by 0.3-0.4% [48, 49] and therefore, based on our preliminary data, we expect that greater percentage of adults with T1D randomized to semaglutide would have improvement in TIR by at least 5% than adults with T1D randomized to placebo. Moreover, most adults with T1D using HCL system have TBR <4% and GLP-1 analogs have not found to increase TBR. Therefore, we expect that >75% of adults with T1D on HCL and randomized to either semaglutide or placebo would have TBR <4%.

7.2 Sample size calculation

Using the Fisher's exact test at an alpha level of 0.05, a sample size of 32 per group (intention to treat analysis) completing the study is expected to have power close to 80% to detect a 30% difference in the proportion of participants achieving the composite outcome if the proportion in the control group is 5%. If the proportion in the control group is 3%, then our power level is over 80% to detect a difference between groups of at least 29%, as shown in the table below.

Power analysis for proportion of participants meeting primary composite outcome between two groups

Treatment group	Control group	Power
35%	5%	78.4%
30%	5%	64.2%
25%	5%	47.1%
20%	5%	29.5%
35%	3%	85.9%
30%	3%	74.5%
25%	3%	59.0%
20%	3%	41.0%

Power and Sample Size for secondary endpoints:

Power calculations for key secondary outcomes were conducted using PASS v24.02. Differences in each variable from baseline will be calculated and compared by treatment group. We determined the detectable mean group difference for each secondary outcome, assuming the null hypothesis of no difference between the means. With a sample size of 32 per group, we have 80% power to detect mean differences as shown in the table below, assuming the SD shown in the table.

Outcome	SD	Detectable difference for comparison of means
HbA1c (%)	0.7	0.5
TIR (%), TITR, TAR>180	15	10.7
Mean Glucose (mg/dL)	18	12.8
TBR <70 (%)	3	2.1
Weight (Kg)	25	8.07
BMI (kg/m^2)	4	2.8
Glucose SD (mg/dL)	10	7.1
Glucose CV (%)	5	3.6

7.3 Evaluability of subjects

- We will prepare two data sets for the analysis.
- Per-Protocol (PP) analysis set: All exposed subjects who complete the 26-week trial without significantly violating the main aspects of the protocol. The Per-Protocol set will be used for sensitivity analyses.
- Intention to treat (ITT) analysis set: All randomized subjects exposed to at least one dose of trial product. ITT data set will be used for efficacy and safety analysis.

7.4 Analyses plan

Analysis plan is detailed in a separate statistical analysis plan. All statistical analysis plans were finalized prior to the completion of the study and analysis of any data.

8. DATA HANDLING AND RECORD KEEPING

8.1 Data management

- Colorado Multiple Institutional Review Board (COMIRB) will serve as the IRB for the Barbara Davis Center. The other sites will use their own IRB.
- The data and specimens obtained from the subject will be identified by subject number.
- The principal investigator will retain all data generated during the study. Data management is the responsibility of the investigator.
- All electronic data from all four sites will be stored at the BDC, in a de-identified manner, which are secured by the University of Colorado servers. The data will be accessible only by the study team and if transfer of data needed, appropriate measures, including encryption of data files will be used to ensure security and subject confidentiality.
- The records will be stored securely and kept for minimum of 9 years per the Standards Operating Procedures (SOP) of the University of Colorado (https://research.cuanschutz.edu/comirb/home/guidance-and-policies)

8.2 Source data

- Source documents will be kept with the site investigators per local regulatory requirements. Source data must be available to the study monitors or regulatory agencies such as US FDA whenever asked for.
- All source data must be entered in the study data database electronically.

9. ETHICS

- The trial will be conducted in compliance with this protocol, ICH GCP, the University of Colorado COMIRB research policy, local site regulatory agencies, and in accordance with the Declaration of Helsinki.
- The clinical trial protocol, consent form and appropriate study documents will be submitted to COMIRB for the approval before the start of any study related activity.

- Once the protocol is approved by COMIRB for the BDC and the IRBs for the other sites, the study team will be allowed to contact potential subjects.
- Before any trial-related activity, the investigator/study team will give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.
- The subjects will be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.
- The investigator will ensure the subject is given ample time to come to a decision whether to participate in the trial.
- A voluntary signed and personally dated informed consent will be obtained from the subject before any trial-related activity.
- The process of informed consent process will occur in a clinical research place. The subject will sign the informed consent process in the presence of the investigator and witness. The confidentiality and HIPAA will be handled per the University of Colorado and local site regulatory research policies.

10. STUDY DRUGS AND MATERIALS:

Patients will be using their own insulin, and diabetes devices (HCL system and related supplies)

Study medications

- Injection semaglutide 1.34 mg/mL
- Injection placebo (Clinic variant of marked product*)

Packaging and labelling of study medication(s)

- The BDC will receive study medications from Novo Nordisk A/S.
- BDC pharmacist/designated person will distribute the drugs/placebo to other sites.
- All sites will be provided guidance (study procedure manual) on medication packaging, labelling, storage and distribution.
- All subjects will be provided written and verbal education on taking study medications appropriately.

Storage and drug accountability of study medication(s)

- All the study medication (including placebo) will be assumed as semaglutide and stored according to the approved label.

- The temperature log will be monitored at the site and any temperature fluctuation will be reported as deviation.

Auxiliary supply

- Pen needles will be provided to all subjects.

11. CONCOMITANT ILLNESS(ES) AND MEDICATION(S)

- Concomitant illness is any illness that is present at the start of the trial *(i.e. at the first visit)*.
- Concomitant medication is any medication other than the trial product(s) that are consumed during the trial.
- Details of all concomitant illnesses and medication will be recorded per protocol. All sites will be provided with source documents and instructions on recording concomitant illnesses and medications.

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* The clinic variant of the cartridge is produced with an army green closure cap compared to a dust green closure cap in the marketed Ozempic® product. Ozempic® are marketed in different pen variants for different intended dosing regimens. The push button and cartridge holder are light grey, and the pen can be found in both a 1.5 ml and 3 ml variant, dependent on the country. The clinical pen can be found in one variant to support 0.25mg, 0.5mg and 1mg doses in a 1.5 ml variant. The push button and cartridge holder are light brown. Neither closure cap nor the pen is in contact with the product and the differences in colours have no impact on the stability of the product.

12. ADVERSE EVENTS

12.1 Definition

Adverse event (AE)	Any untoward medical occurrence associated with the use of a drug whether considered drug related or not. AE can be unfavorable symptoms, sign (abnormality on physical exam or laboratory findings) or disease temporarily associated with the use of products whether or not related to the products.
Serious adverse event (SAE)	An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: ▪ Results in death, or, ▪ Is life-threatening, or, ▪ Requires inpatient hospitalization or prolongation of existing hospitalization, or, ▪ Results in persistent or significant disability/incapacity, or, ▪ Is a congenital anomaly/birth defect, ▪ Is a medically important event that may not result in death, be life threatening or require hospitalization may be considered an SAE when - based on appropriate medical judgement -they may jeopardize the subject and may require medical or surgical

	intervention to prevent one of the outcomes listed in the definition of SAE Suspected transmission of an infectious agent should be considered as an SAE.
Adverse Drug Reaction (ADR)	An Adverse Reaction is an Adverse Event for which the causal relationship between the Product and the Adverse Event is suspected
Serious Adverse Reaction (SAR)	An Adverse event that fulfills both the criteria for a Serious Adverse event and the criteria for an Adverse Reaction.
Medical event of special interest (MESI)	A MESI is an event, which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria. –Medication errors concerning trial products: – Administration of wrong drug – Wrong route of administration, such as intramuscular instead of subcutaneous – Accidental administration of a lower or higher dose than intended, however the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the investigator, although not necessarily did happen. Overdose and missed insulin injection resulting in severe hypoglycemia or hyperglycemia are considered as AE or SAE depending on severity.
Suspected Unexpected Serious Adverse Reactions (SUSAR)	An unexpected adverse reaction (UAR) is an adverse reaction that is not consistent with the product information in the summary of product characteristics (SPC, i.e.US prescribing information). The current version or any updated if available during the clinical trial for US prescribing information for study drugs will be used as SPC. If UAR is severe enough to define as SAE is called as SUSAR.
Technical complaint	A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

12.2 Reportable AE for Hypoglycemia and Hyperglycemia/Diabetic Ketoacidosis

- *Hypoglycemia*: Hypoglycemia is common in people with T1D. Only severe hypoglycemia defined as "hypoglycemia event requiring medical assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions" is reportable adverse event. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose

measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- *Hyperglycemic events/Diabetic Ketoacidosis (DKA)*: Hyperglycemic event is only reportable as an adverse event when one of the following four criteria is met:
    1) The event involved DKA, as defined by the Diabetes Control and Complication Trial (DCCT) and described here:
        - Hyperglycemic events are classified as DKA if the following are present (meeting all 4 criteria)

            a) Symptoms such as polyuria, polydipsia, nausea or vomiting
            b) Serum ketones >1.5 mmol/L or large/moderate urine ketones
            c) Either arterial PH <7.30 or venous PH <7.24 or serum bicarbonate <15
            d) Treatment provided in a health care facility
    2) Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
    3) Blood ketone level ≥ 1.5 mmol/L and communication occurred with a health care provider at the time of the event
    4) Blood ketone level ≥ 2.5 mmol/L even if there was no communication with a health care provider

12.3 Non-reportable adverse events

- Hypoglycemia or hyperglycemia events not meeting above criteria are not required to be reported as an adverse event

- Patients' own devices (e.g. insulin pump, CGM, BG meters) related issues and skin issues arise from the use of these devices (such as skin rash due to adhesive or infusion site issues) are not reportable unless the event meets the definition of an SAE.

12.4 Reporting of adverse events

- All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period.
- Once an AE is identified, assessment for severity (mild, moderate or severe), causality (probable, possible or unlikely) and outcome of an AE (recovered, recovering, recovered with sequelae, not recovered, fatal or unknown) must be provided. Probable is defined as good reason and sufficient documentation to assume a causal relationship. Possible is defined as a causal relationship is conceivable and cannot be dismissed. Unlikely is defined as the event is most likely related to etiology other than the trial product.
- Since patients are using their own diabetes devices, we do not intend to collect device issues. However, if a device issue results in SAE, it must be reported.
- The investigator is responsible for reporting all AE to their IRB within five business days once they are aware of AE.
- All non-severe and severe AE will be followed until the end of the study
- Subjects must be instructed to notify the investigator immediately if they become pregnant. If a subject becomes pregnant during the study, the subject will be dropped from the study and followed until birth for pregnancy outcomes. Pregnancy will be reported as an AE (or SAE if fulfills the criteria of SAE). The sponsor-investigator is responsible for reporting pregnancy to Novo Nordisk and reporting will occur within same timelines described below. Pregnancy complications will be recorded as an AE and if the infant has a congenital abnormality or birth defect, it will be reported and notified to the IRB
- Site investigators are responsible to notify their IRB within 24 hours once they are aware of an SAE.
- Sponsor-Investigators will be responsible for notifying COMIRB, DSMB, the FDA and Novo Nordisk of an AE/SAE within the stipulated time frame of each of the agencies.
- Sponsor-investigator will report to NovoNordisk all SAEs, SUSARs and SADRs within 15 days of the sponsor-investigator becoming aware of such adverse events. The Sponsor-Investigator will provide the following information to NovoNordisk: study name, patient initials, sex, age, event (probable diagnosis), drug name (Semaglutide/placebo) and

reporter identification (name or initials) in addition to a description of the AE events such as causality and outcome.

- Follow-up of adverse events: Investigator must provide adequate medical care to study subject for any study-related adverse events including clinically significant laboratory values related to the study and medical care of the subjects should be provided regardless of their insurance status. AE classified as serious or possibly/probably related to trial drug must be followed until the subject has been recovered and all queries have been resolved. For cases of chronic conditions follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered". All other adverse events must be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.

13. Individual subject stopping criteria

Study drug administration may be stopped for any of the following reasons:

1) Two or more episodes of severe hypoglycemia as defined in the section 13.2
2) Two or more DKA events not related to device malfunction. Definition of DKA is detailed in the section 13.2
3) Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study

14. Criteria for suspending or stopping the study

Greater than 10 cases of severe hypoglycemia or greater than 5 cases of DKA that are not due to device malfunction. These criteria are based on exceeding the average incidence of severe hypoglycemia (11.8%) and DKA (4.8%) in patients with T1D as reported in the Type 1 Diabetes Exchange Clinic Registry [50].

15. Data Safety Monitoring Board (DSMB)

A DSBM consisting of three members (two clinicians and one statistician) will independently monitor the study, including adverse events and study drug or device issues with potential to impact participant safety. A meeting will be held at the beginning of the study, and every six

months between the study teamsBDC and IU investigators) and the DSMB to review any adverse events. Following each safety review, a summary of recommendation from the DSMB will be collected.

16. Precautions/over-dosage

Inappropriate medication dose can cause severe hypoglycemia or hyperglycemia. The education on recognition of hypoglycemia or hyperglycemia and its treatment will be provided at screening and as needed during the study.

17. Risks and Discomforts

a) Blood Drawing Risks

The risks of drawing blood from a vein include temporary discomfort from the needle stick (common), bruising (common), excessive bleeding (unlikely), lightheadedness (rare), infection (rare), and fainting (rare).

b) Study procedure related discomfort

The participant may feel some discomfort during height, weight, waist measurement and blood pressure measurements. All care will be taken to reduce discomfort.

c) Side-effects related to semaglutide

Semaglutide is a long-acting glucagon like peptide-1 (GLP-1). The most common adverse reactions, reported in ≥5% of patients treated with semaglutide are nausea, vomiting, diarrhea, abdominal pain, and constipation. Nausea/ vomiting can sometimes lead to dehydration and acute kidney injury. Semaglutide causes a delay of gastric emptying and has the potential to influence the absorption of concomitantly administered oral medications, so caution should be exercised. Acute and chronic pancreatitis have been reported in clinical studies. Hypersensitive reactions have also been reported. Semaglutide is contraindicated in patients with a history or family history of medullary thyroid cancer and in patients with multiple endocrine neoplasia type 2 (MEN-2)

d) Risk of Hypoglycemia (Low Blood Sugar)

As with any person with diabetes who uses insulin, there is always a risk of having low blood sugar (hypoglycemia). GLP-1RA such as semaglutide is known to improve insulin action and

therefore, may increase risk for low blood sugar. Symptoms of low blood sugar can include sweating, jitteriness, and not feeling well. There is also the possibility of fainting or seizures (convulsions), brain damage, or death with a very low blood sugar. Since we will be closely monitoring participants during this study, a serious low blood sugar is less likely to occur in any study participant. Even if a low blood sugar does occur, it usually goes away quickly with treatment (carbohydrates) that raises the blood sugar. A severe low blood sugar may require that a participant get an injection of glucagon and/or have emergency services to help raise his/her blood glucose level. Hypoglycemia risk mitigation plan is discussed in the Appendices.

e) Risk of Hyperglycemia (High Blood Sugar)

Hyperglycemia usually does not cause many obvious symptoms, but participants may become thirsty, fatigued, or have a higher level of sugar in their urine. In severe cases of hyperglycemia, diabetic ketoacidosis (DKA) or coma may occur. Hyperglycemia leading to DKA can lead to renal failure (kidney failure), cardiac arrhythmia (irregular heartbeat), myocardial infarction (heart attack), rhabdomyolysis (muscle breakdown), and even death. A serious effect from hyperglycemia is not expected to occur in any study participant, as we will be monitoring blood glucose levels frequently.

f) Psychosocial Questionnaires

Answering questionnaires about thoughts, concerns, and distress related to diabetes and general quality of life assessments may result in undesired thought processes and/or emotions. These feelings may be transitory, recurrent, or permanent though most risks are minimal/transitory.

g) Cardiac magnetic resonance imaging – during the MRI exam, some participants may experience claustrophobia and discomfort, due to being enclosed in a small tube. In order to minimize the risk of this occurring, potential participants will be screened for claustrophobia or prior issues undergoing MRI and excluded if they have experienced claustrophobia or had other negative experiences with MRI. In addition, participants will be excluded if they have a pacemaker, metal implants or aneurysm clips.

h) Unknown Risks

In any study, there may be additional risks that we do not know about at this time. This is not likely but is always a possibility. If we become aware of any new risks, participants will be told about them. They will be able to decide if they want to continue to participate in this study. If a treatment or procedure has increased risks because it was not done according to study procedures due to error, participants will be informed, and the necessary steps will be taken to care for them.

i) Confidentiality

There is a risk of a breach in confidentiality. Thus, a confidential subject database will be established to maintain study data. Data will be entered into REDCap (Research Electronic Data Capture). REDCap is an internal secure, computerized database system at the University of Colorado Denver. This system allows data entry, survey/questionnaire building, data exportation to statistical packages, and is HIPAA compliant. Each subject will be assigned an identification number, which will be used to code and identify all of that subject's records. This will avoid the continual use of subject names. REDCap surveys can be sent to study participants via e-mail for direct input into the database. All study data will be locked in the PIs' offices and all relevant computer study files will be input on staff computers, which are password protected and contain encryption software. Data storage will be on a secured server maintained by the University of Colorado. The server is backed up nightly and a copy of the back-up file is kept off site in a secure facility. Data access will be limited to study personnel. Study results may be presented in the form of posters, abstracts, oral presentations, or publications at academic meetings or in journals. In all forms of study result reporting, subject identification will not be disclosed. A study subject may access his/her protected health information at any time by requesting said information in writing of the investigator. The investigative team has been trained in IRB and HIPAA compliance issues and will maintain confidentiality and protect health information. The above-stated procedures have been highly effective in preventing breaches of patient confidentiality for the prior and current research studies in which the PI has been and continues to be involved.

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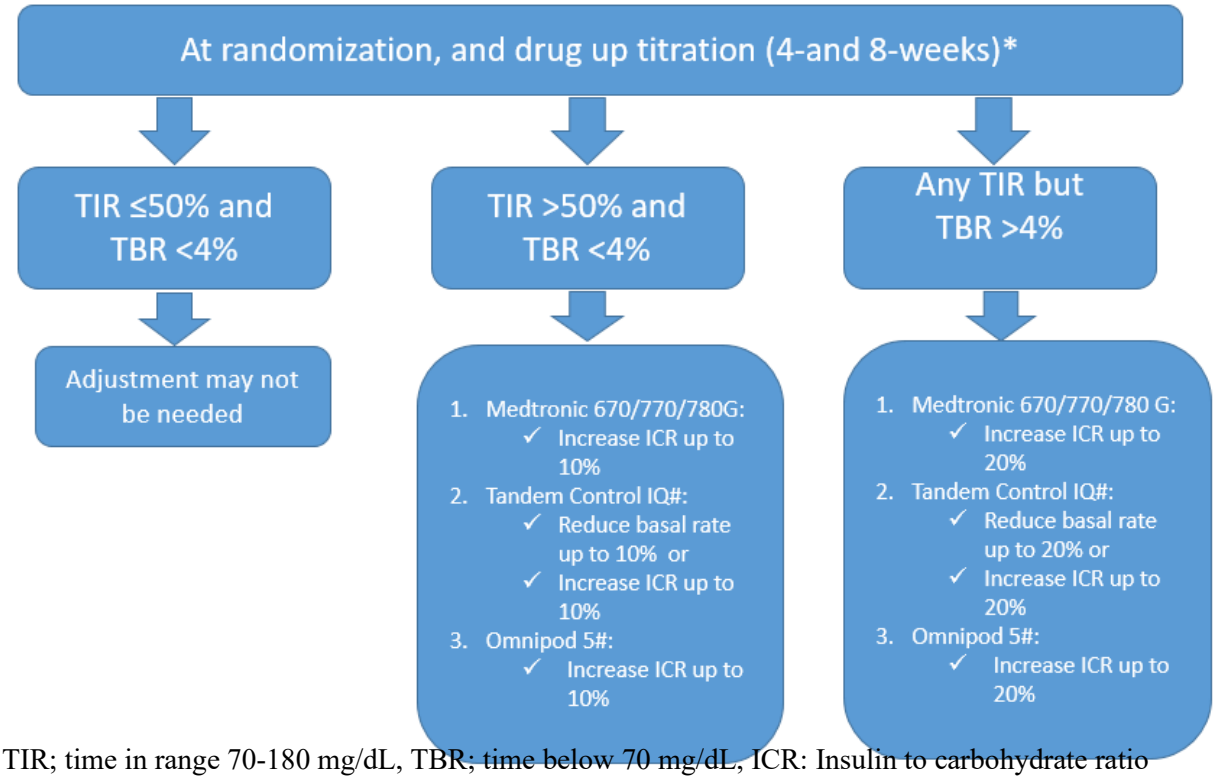
Appendix A: General Guidance on HCL setting adjustments during drug up titration

- Investigators must train subjects on diabetes self-management principles including hypoglycemia recognition, prevention, and treatment. This includes HCL specific training on hypoglycemia and hyperglycemia prevention and trouble shooting
- At randomization and week 4 and Week 8, based on baseline glycemic control (time in range) and risk of hypoglycemia (time below range), investigators should adjust the HCL settings. The general guidance is provided below.



TIR; time in range 70-180 mg/dL, TBR; time below 70 mg/dL, ICR: Insulin to carbohydrate ratio

TIR; time-in-range 70-180 mg/dL, TBR; time below 70 mg/dL, ICR: Insulin to carbohydrate ratio

*Each individual with type 1 diabetes is different in terms of response to GLP-1RA and risk for hypoglycemia. This is a general guidance and Investigators should adjust settings necessary to reduce the risk for hypoglycemia based on patient-related factors and clinical experience.

#If needed, investigators can reduce the correction factors up to 10% (TIR>50% and TBR <4%) or 20% (TBR>4%) in addition to changes in basal rate or ICR. Moreover, investigators may recommend patients to use temporary manual mode, exercise mode/temporary target if above changes are not sufficient to

mitigate hypoglycemia risk. For Omnipod 5 and Medtronic 780G, investigators may also adjust target glucose.

Appendix B: Guidance on the functionality of the hybrid closed-loop systems

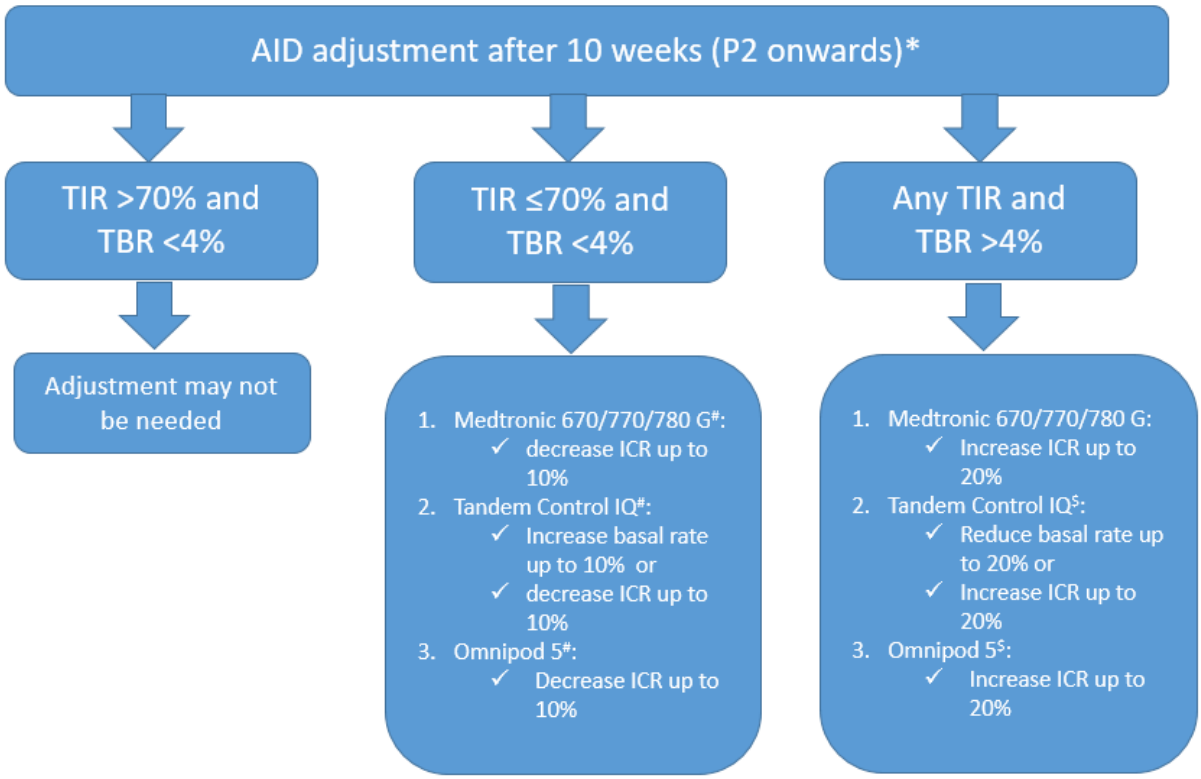
	Medtronic 670/770G	**Medtronic 780G**	**Tandem Control IQ**	**Omnipod 5**
How it works	Automated basal insulin delivery every 5 minutes based on total daily dose from the past 2-6 days	Automated basal insulin delivery every 5 minutes based on total daily dose	Automated basal insulin delivery that increases or decreases patient' programmed basal rate based on CGM glucose trends	Automated basal insulin delivery every 5 minutes based on total daily dose from the last pod change (2-3 days)
Algorithm target glucose level/range	120 mg/dL (fixed)	3 target options: 100, 110 and 120 mg/dL	112.5-160 mg/dL (fixed)	110-150 mg/dL (adjustable in increment of 10 mg/dL)
What you can adjust? **(modifiable settings in HCL)**	Insulin: Carb ratio Active insulin time	Insulin: Carb ratio Active insulin time	Basal rate Insulin: Carb ratio Correction factor	Insulin: Carb ratio Active insulin time Correction factor
Auto bolus feature	No	Yes, every 5 minutes based on algorithm calculations.	Yes, automated boluses every 1 hours (60% of calculated bolus) if needed. If patient takes bolus by him/herself, auto	No

			bolus clock resets to 60 minutes from the patient's manual bolus.	
Additional features on closed-loop mode	Temp target (during exercise or stress): increases the glucose target to 150 mg/dL	Temp target (during exercise or stress): increases the glucose target to 150 mg/dL	Exercise: Increase the glucose target to 140-160 mg/dL Sleep: changes the target to 112.5 to 120 mg/dL but stops auto bolusing during this mode.	Activity: changes the target to 150 mg/dL

All physicians will be trained on basic functionality of HCL, adjustable settings and trouble-shooting guidance per manufacturer instructions. For more information on comparisons of various HCL system, click this link- https://www.bdcpantherdiabetes.org/device-comparison

Appendix C: General Guidance on HCL setting adjustments after Week 10

Glycemic goal for the most patients with T1D is TIR >70% and TBR <4%. Investigators are encouraged to review HCL settings and adjust if patient is not within the glycemic goal.



TIR; time in range 70-180 mg/dL, TBR; time below 70 mg/dL, ICR: Insulin to carbohydrate ratio

*This is a general guidance and Investigators should adjust settings necessary to reduce the risk for hypoglycemia and improve glycemic control based on patient-related factors and clinical experience

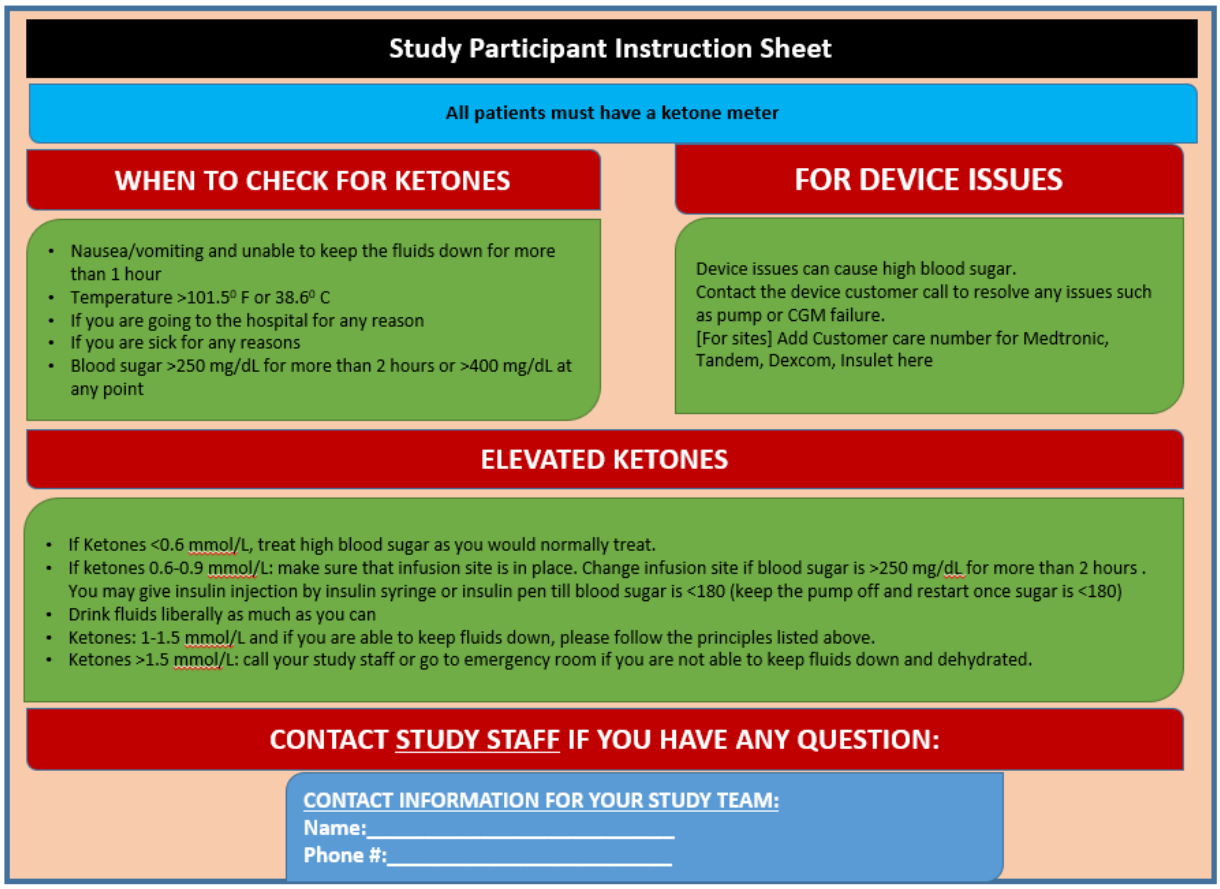
#If needed, investigators may strengthen correction factor (for Tandem Control IQ or Omnipod 5) or active insulin time (for 670/770G).

$ Reduce the correction factors up to 10% (TIR>50% and TBR <4%) or 20% (TBR>4%) in addition to changes in basal rate or ICR. Moreover, investigators may recommend patients to use temporary manual mode, exercise mode/temporary target if above changes are not sufficient to mitigate hypoglycemia risk.

Appendix D: General guidance on the management of hypoglycemia

- Follows the guidance provided in the Appendix A-C to adjust HCL settings during drug up titration to minimize the risk for hypoglycemia.
- Each subject must have glucagon product with them as a part of the standards of diabetes care. Subject and their caregiver (if any) must be trained on the use of glucagon product.
- Subject should be advised to follow treatment for hypoglycemia. if glucose <70 mg/dL, take 15 grams of carbs (or less as HCL may have insulin suspension for anticipated hypoglycemia) and repeat glucose after 15 minutes till glucose is >70 mg/dL
- If patient experience severe hypoglycemia, it should be reported as AE or SAE (if criteria for SAE are met). HCL setting should be adjusted to prevent another episode of hypoglycemia

Appendix E: Guidance on the checking for ketones



Study Participant Instruction Sheet

All patients must have a ketone meter

WHEN TO CHECK FOR KETONES

- Nausea/vomiting and unable to keep the fluids down for more than 1 hour
- Temperature >101.5^0 F or 38.6^0 C
- If you are going to the hospital for any reason
- If you are sick for any reasons
- Blood sugar >250 mg/dL for more than 2 hours or >400 mg/dL at any point

FOR DEVICE ISSUES

Device issues can cause high blood sugar.
Contact the device customer call to resolve any issues such as pump or CGM failure.
[For sites] Add Customer care number for Medtronic, Tandem, Dexcom, Insulet here

ELEVATED KETONES

- If Ketones <0.6 mmol/L, treat high blood sugar as you would normally treat.
- If ketones 0.6-0.9 mmol/L: make sure that infusion site is in place. Change infusion site if blood sugar is >250 mg/dL for more than 2 hours . You may give insulin injection by insulin syringe or insulin pen till blood sugar is <180 (keep the pump off and restart once sugar is <180)
- Drink fluids liberally as much as you can
- Ketones: 1-1.5 mmol/L and if you are able to keep fluids down, please follow the principles listed above.
- Ketones >1.5 mmol/L: call your study staff or go to emergency room if you are not able to keep fluids down and dehydrated.

CONTACT STUDY STAFF IF YOU HAVE ANY QUESTION:

CONTACT INFORMATION FOR YOUR STUDY TEAM:
Name:_____
Phone #:_____