SUCCESSFUL TRANSITION FROM INSULIN PUMP TO MULTIPLE DAILY INJECTIONS USING INSULIN DEGLUDEC IN ADULTS WITH TYPE 1 DIABETES (TRANSITION CLINICAL TRIAL)

INVESTIGATOR-SPONSORED STUDY PROPOSAL

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1. BACKGROUND AND SIGNIFICANCE:

Type 1 diabetes (T1D) is an autoimmune disease characterized by loss of insulin-producing pancreatic beta cells [1]. Patients with T1D require lifelong insulin therapy to maintain good glycemic control and reduce the risk for microvascular complications [2].

Despite many advances in insulin delivery methods, recent data from the Type 1 Diabetes Exchange Clinic Registry showed that only about 50% of people with T1D are using an insulin pump (continuous subcutaneous insulin infusion, CSII) as their insulin delivery method [3,4]. In addition, the overall frequency of pump discontinuation is 3%, being higher in adolescents (4%) and young adults (4%) than in young children (3%) or older adults (1%) [5]. Reasons behind pump therapy discontinuation, either after a short- or long- standing usage, can be different. The most commonly reported ones are issues with wearability, including problems with insertion, pump discomfort, skin reactions, adhesive problems, and interference with sports and activities. Other common ones included the feeling of anxiety, discontinuation recommended by health care practitioner, failure with glycemic control and pump working properly (i.e. infusion set failure) [5,6]. Moreover, many T1D patients on CSII treatment often go on a “pump vacation”, periods of the year during which the patient decides to temporarily go back on multiple daily insulin injections (MDI). Reasons for taking a pump vacation can be very different, the most common ones being related to esthetic reasons (i.e. during summer period at the seaside) and during holidays [7].

Insulin degludec is a new ultra-long acting insulin. To date, it is the only insulin analogue to self-associate into multi-hexamers upon subcutaneous injection, resulting in a soluble depot from

which it is slowly and continuously absorbed into the circulation [8-9]. In the pharmaceutical formulation, i.e. in the presence of phenol and zinc, the insulin degludec hexamers adopt a conformation where only one of the ends is available to interact with the side chain of another hexamer and thus forms stable di-hexamers. Upon diffusion of phenol following injection, the insulin degludec di-hexamers open at both ends and lead to the formation of multi-hexamers. The gradual diffusion of zinc from the ends of the multi-hexamers causes terminal insulin degludec monomers to slowly and steadily dissociate, resulting in a slow and gradual delivery of insulin degludec from the subcutaneous injection site into the circulation [8-10]. This is the major difference with insulin glargine which, following subcutaneous injection, forms microprecipitates that must re-dissolve prior to absorption and which renders its absorption inherently variable [8-10].

The longer duration of action and the lower day-to-day insulin degludec variability makes it an appealing choice when patients want to start multiple daily injections. In addition, when compared to insulin glargine, insulin degludec is associated with lower incidence of nocturnal and overall hypoglycemia in insulin requiring patients with diabetes [11].

However, differently from insulin glargine, the time needed from first dose of insulin degludec to reach steady state, defined as serum concentration exceeding 90% of the final plateau, is about 2 to 3 days, being at 60% of steady state within at day 1 and 85% at day 2 [12-13]. This results in an increased risk of hyperglycemia, during the initial 48-72 hours of CSII to MDI transition using insulin degludec.

Current CSII to MDI transition strategy is to stop CSII and initiate long acting insulin (such as glargine or detemir 1:1) from day 1 of stopping insulin pump [14-17]. However, the standard of care strategy has not been successful at the Barbara Davis Center for Diabetes, a leading T1D center in the world (unpublished observation), due to significant hyperglycemia during the first 48-72 hours of this transition. Hyperglycemia for initial 2-3 days makes transition from CSII to MDI difficult and frustrating for the patients. Therefore, there is a need to have a standardized approach to transitioning patients from CSII to MDI using insulin degludec.

Considering the lack of evidence and knowledge gap, this study is proposed to examine an investigational approach in contrast to the clinical standard of 1:1 dose conversion in an attempt to lower the incidence and/or duration of hyperglycemia after transition from insulin pump.

2. SPECIFIC OBJECTIVES:

The primary objective of this study is to evaluate the efficacy and safety of an alternative CSII to MDI transition strategy using insulin degludec compared to the standard of care in adults with T1D.

3. RESEARCH DESIGN AND METHODS:

3.1. Study Hypothesis

We hypothesize that, as compared to the actual standard of care transition strategy (1:1 dose conversion at the day of CSII to MDI transition), an alternative transition strategy will result in lower time spent in hyperglycemia without increasing the risk for hypoglycemia. The alternative strategy being (overlap transition strategy):

- Administration of insulin degludec at a 1:1 basal dose conversion dosage at day 0, with the concomitant use of the insulin pump for 48 hours from transition, where CSII basal rate

will be reduced by 50% during the first 24 hours from transition and by 75% during 24 to 48 hours from transition. CSII will be disconnected after 48 hours from transition.

3.2. Endpoints:

Primary and secondary endpoints will be analyzed from 1-week of blinded CGM use during randomization phase.

Primary endpoint:

1. Time spent in CGM glucose levels >180mg/dl

Secondary endpoints:

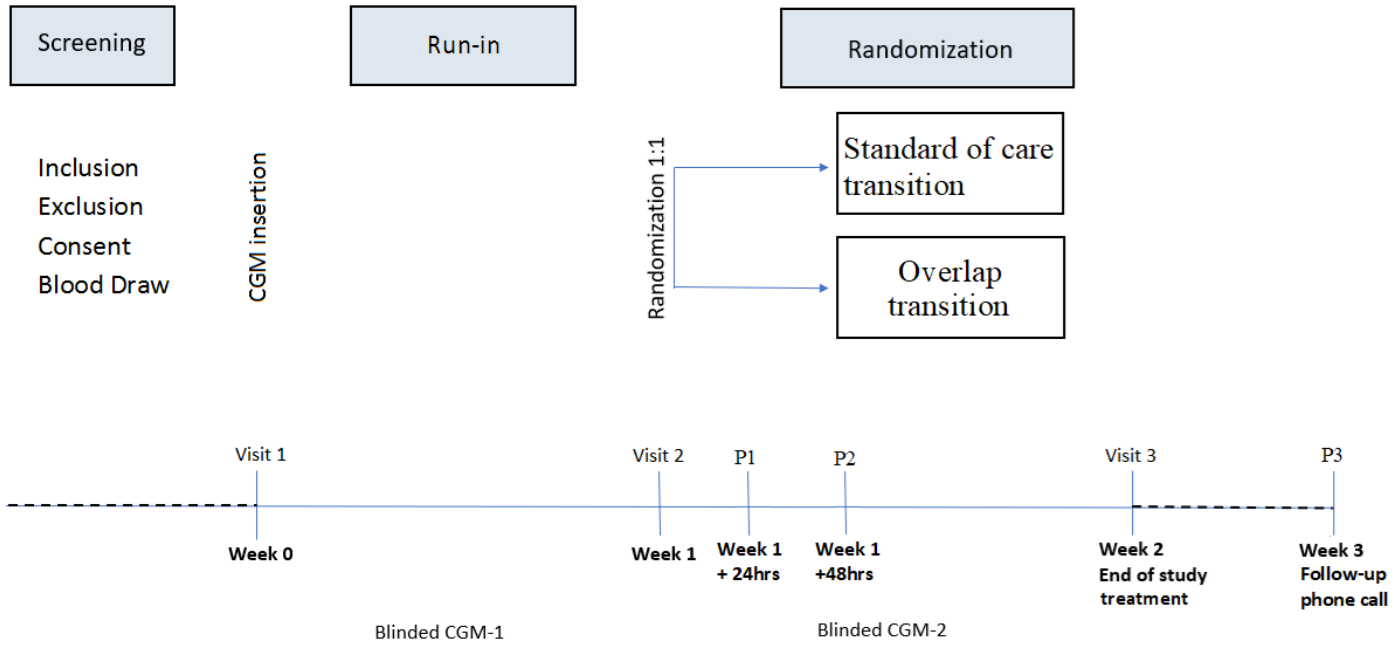
1. Time spent in CGM-measured "time-in-range"(glucose levels ≥70 mg /dl and ≤180 mg/dl)
2. Time spent in CGM-measured hypoglycemia < 70 mg/dl
3. Frequency of severe hypoglycemia as defined by the ADA (severe cognitive impairment requiring external assistance for recovery) and severe hyperglycemia (BG≥250 needing hospitalization)
4. Number of boluses (correction boluses) between groups during first 72 hours of randomization
5. Patient-Reported Outcomes (PRO) using validated questionnaires; insulin delivery satisfaction survey (IDSS) and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI: SHP) [18,19]

3.3. Study design:

- This is a 3-week, randomized control, open label, single center clinical trial with two study arms comparing the efficacy and safety of the 'standard of care transition' and an 'overlap transition' strategy

- The study consists of a screening phase, one week of run-in phase (blinded CGM monitoring), one week of the experimental protocol following randomization phase and one week of follow-up phase.
- Overall, the study will last 3 weeks that includes four clinical trial phases (**Figure 1**):
  - Screening phase (Week 0): After informed consent, inclusion and exclusion, blinded CGM will be inserted.
  - Run-in phase (Week 0 to end of week 1): Subjects will wear blinded CGM and continue to use CSII.
  - Randomization phase (Week 1 to week 2): Subjects will be randomly allocated to one of two transition protocols (1:1 randomization).
  - Follow-up phase (Week 2 to week 3): Subjects will return to their preclinical trial CSII regimen.

Figure 1: Study Design



3.4. Rationale for study design

The rationale behind the overlap protocol strategy is linked to insulin degludec pharmacokinetic and pharmacodynamics. Indeed, insulin degludec steady state concentration reaches 60% and 85% respectively at day 1 and 2, and 100% steady state is reached on day 3 from the first day of insulin degludec injection [12-13].

Therefore, 50% and 75% dose reduction proposed in the overlap transition strategy of the first 2 days will cover for the slow rise of insulin degludec concentration the first 2 days, and the 100% insulin pump discontinuation on day 3 will correspond to the time needed for insulin degludec to reach the steady state. This would reduce time spent in hyperglycemia post-CSII discontinuation.

Rationale for blinded CGM: Since the primary outcome is time spent in hyperglycemia (CGM glucose >180 mg/dl), it is necessary to have CGM during randomized phase. Real-time CGM would interfere with the primary and secondary outcomes as patients will have ability to see CGM glucose trend and adjust insulin accordingly. Therefore, blinded CGM would be appropriate for this research protocol. In addition, the time in range (and percentage of hypoglycemia) also depends on person' ability to manage diabetes and therefore, baseline CGM will provide the data about time-in-range and time spent in hyper-and hypo-glycemia. The information from blinded CGM during run-in-phase will be useful for analysis of primary and secondary outcomes that will be adjusted for baseline CGM glucose metrics. Blood glucose fluctuations are greatest during the first week of insulin pump to MDI transition and therefore, 1 week CGM period is enough for comparison of primary and secondary outcomes between the groups.

4. CLINICAL RESEARCH SITES

The study will be conducted at a single site, Barbara Davis Center for Diabetes.

5. STUDY POPULATION:

We plan to enroll 34 participants with the expectation that 30 will be randomized and complete the study.

5.1. Inclusion criteria

1) Age ≥18 years and ≤ 65 years
2) Patients with T1D diagnosed for at least 12 months
3) Point-of-care HbA1c levels between ≥6.5% and ≤ 8.5%
4) Patients on CSII (any insulin pump) for at least past 6 months
5) Willing and able to wear a blinded CGM during the time of study period
6) Willing to perform self-monitoring of blood glucose (SMBG) at least 4 times a day
7) Ability to provide informed consent before any trial-related activities
8) Not willing to or plan any travel out of Colorado during the 3 weeks of study period
9) Willing to use insulin degludec in the morning once a day

5.2. Exclusion criteria

1) Age <18 years and > 65years
2) HbA1c >8.5 % at screening
3) Less than 12 months of insulin treatment
4) Patients on 670G or Tandem Control IQ (Medtronic and Tandem Hybrid Closed-loop systems) and not willing use manual mode during the study period
5) Patients with T1D using any glucose lowering medications other than insulin
6) Pregnancy, breast feeding, and positive pregnancy test during screening

7) Women of childbearing age wanting to become pregnant or not using adequate contraceptive measures
8) Current or recent (< 2 weeks prior to visit 1) use of any steroidal medication, or anticipated steroidal treatment, during the study period
9) eGFR below 45 ml/min/1.73 m^2 using MDRD formula
10) History of severe hypoglycemia in the previous 3 months
11) History of diabetic ketoacidosis (DKA) requiring hospitalization in the past 3 months
12) History of allergy to any form of insulin or its excipients
13) History of allergy to adhesives
14) Unwilling to use blinded CGM during the study period
15) Unwilling to perform SMPG at least 4 times a day
16) Known history of alcohol abuse or illicit drug use within 6 months prior to screening
17) Use of investigational drugs within 5 half-lives prior to screening
18) Participation to other study trials during the study period
19) Elevated liver enzymes (AST and ALT) 3 times the upper limit of normal
20) Hypoglycemia unawareness defined as GOLD score ≥4 [20]
21) Any comorbidities or medical conditions that make a person unfit for the study at the discretion of the investigators
22) Anticipated travel across different time zones (difference greater than 4 hours) or anticipated change in physical activities or diet at the discretion of the investigators.

5.3. 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.
- Participants will be withdrawn from the study if they become pregnant, actively try to become pregnant, develop an allergic reaction to insulin/adhesives, severe episodes of hypoglycemia/hyperglycemia, or at the judgement of investigators due to safety concerns, such as abnormality in laboratory exam results.
- 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 insulin 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.

5.4. Subject replacement

Subject replacement will occur only if withdrawal occurs before the one-week randomization phase. Subjects will not be replaced during the one-week randomized phase.

5.5. Rationale for study population

In anticipation of screening failure or withdrawal or anticipated issues due to covid-19 pandemic, we plan to screen up to 40 subjects to have 30 complete the clinical trial.

6. VISIT PROCEDURES:

6.1. Visit 1, week 0, day0, screening and blinded CGM insertion

- Subjects will attend a screening visit (Visit 1, week 0) in order to assess eligibility for the study.
- 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 has full knowledge of the study processes, and the possibility to withdrawal at any time during the study.
- Subjects who wish to participate in the trial must sign and date the informed consent form for the trial before any trial-related procedures. All subjects will be provided with a copy of signed informed consent form.
- At screening, the subjects will be assigned a unique subject number, which will remain the same throughout the trial. The subject number will consist of 6 digits (the first 4 digits indicating the protocol number and the last 2 digits are unique for the subject).
- 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 in pre-set study visit time schedules. This will be true for both visits done at the BDC and phone call visits. After screening visit (visit 1, day 0), they will be asked to come at the BDC at visit 2 (day 7±1) and visit 3 (day 14±1). Furthermore, they must be compliant with phone call 1 (Week 1+24 hours; visit 2+24 hours), phone call 2 (Week 2+48 hours; P1+24 hours) and phone call 3 (day 21±1)
- Point of care HbA1c and spot urine pregnancy test (for women in reproductive age group) will be done at the time of screening. A non-fasting blood will be drawn for complete metabolic panel (CMP).
- If any clinical pathological condition is detected at physical examination, the investigator can decide, at his/her discretion, to withdraw the patient from the study.
- For laboratory results such as CMP, "results pending" will be selected at Visit 1, week 0.
- Please refer to Table 1 for a description of items to be performed at the screening visit.
- All subjects will undergo GOLD questionnaire to exclude patients with hypoglycemia unawareness. Subjects with hypoglycemic unawareness defined as a GOLD score of ≥ 4 [18] will be excluded.
- All subjects will be assessed for ability to perform SMBG. Participants will be required to perform at least 4 SMBG daily using their own glucose meter; with at least one being in a fasted state, one pre-prandial and one 2-3 hours post-meal glucose value. In addition, participants will be required to check their blood glucose level if they have symptoms of hyperglycemia or hypoglycemia. We expect hyperglycemia during first 48-72 hours after randomization in group1 (standard of care transition). Therefore, SMBG requirements are

necessary to select appropriate patients for this clinical trial for safety reasons. However, SMBG data will not be analyzed for primary or secondary endpoints.

- All subjects will go through a quick review on diabetes self-management, including:
  - Recognition of carbohydrates in commonly eaten foods
  - Ability to count the carbohydrate content in typical portions of simple foods
  - Ability to interpret a nutrition label for carbohydrate content
  - Preventing and treating hypoglycemia using carbohydrate-containing food and/or glucagon
- All subjects will be instructed NOT to make any changes in the basal and bolus pump settings during run-in phase unless necessary for safety reasons (i.e. episodes of severe hypoglycemia or hyperglycemia) at discretion of investigators. If any therapy change will be necessary, it must be recorded.
- Dexcom G6 will be inserted either on abdomen or upper arm depending on patient's preference and blinded at screening to analyze baseline CGM glucose metrics. The participants will not be able to see glucose values from the blinded CGM. All the subjects will be trained on function modalities of the blinded CGM. Dexcom G6 does not require calibration.
- Patients on Medtronic 670 G (Medtronic hybrid closed-loop system where insulin pump delivers automatic basal rate based on Medtronic Guardian CGM glucose) will be instructed to use only pump (the Auto/ hybrid closed-loop mode will be disabled) because automatic insulin delivery can alter the primary objective of the study.

- Patients using real time (rt) personal CGM (e.g. Freestyle Libre, Dexcom G4, Dexcom G5, Medtronic Guardian Connect) will be screened for the study; however, they are not allowed to use rt-CGM during the 2 weeks of the study (run-in-phase and randomization). They can use rt-CGM during third week of the study while transitioning back to their own insulin pump.

6.2. Screening Failure

Screening failure form must be completed. Resampling/ rescreening is not allowed if person failed any of inclusion or exclusion criteria except for the laboratory criteria, where one-time rescreening will be permitted at discretion of the investigator.

6.3. Visit 2, Week 1, Day 7±1, Randomization visit

- Blood glucose meter download and review of SMBG.
- Subject's blinded CGM will be removed and downloaded.
- Review of previous CMP lab data with patient.
- Look for any local skin reaction at the site of previous CGM.
- If glucose meter or CGM download shows a glucose value <54mg/dl, patient will be asked if they experienced symptoms of hypoglycemia, if any assistance was required, and if there were circumstances that possibly contributed to or resulted in hypoglycemia.
- Reporting of AE/ SAE if any
- Exclusion criteria (after review of CMP laboratory and glucose meter data):
    - AST/ALT > 3 times the upper limit of normal

- eGFR <45 ml/min/1.73 m^2 using MDRD formula
- Abnormal laboratory results or allergic reaction at CGM site, which at the view of investigator makes subject unsafe to continue the study. In that case, the investigator has to explain the reason of his choice to the patient.
- Non-compliance defined as SMBG less than 4 times a day for at least 4 out of 7 days and use of CGM less than 5 out of 7 days during the run-in-phase

- If no exclusion criteria was met, and the patient is still willing to continue the study, randomization process can start.
- Second, blinded CGM (Dexcom G6) will be inserted.
- Subjects will receive 1 pen of insulin degludec U-100 and 1-2 pen of insulin aspart U-100 depending on calculated insulin requirement during randomization phase.
- Diabetes self-management training including treatment of hypoglycemia and hyperglycemia will be reassessed.
- Subjects will be trained on the use of insulin pen and administration of correct dose of insulin degludec U-100 in the morning once a day and correct dose of insulin aspart U-100 based on carbohydrate ratio and correction factor.
- <u>Randomization</u>

  Subjects will be randomized equally into one of the two possible treatment arms.
  - <u>Group 1 (standard of care)</u>: subjects will stop using CSII on the randomization day, and will start insulin degludec injection (1:1 dose conversion) once a day in the morning.

- Group 2 (overlap transition): Subjects will receive insulin degludec in full dose (1:1 dose conversion) at randomization, and CSII basal rate will be reduced by 50% during the first 24 hours of the transition and by 75% during 24 to 48 hours of the transition. CSII will be discontinued on day 3 of the transition.

The insulin degludec initiation and CSII basal reduction over 72 hours has been summarized in Table 2;

Table 2: CSII changes and MDI initiation by randomization groups

Randomization	Treatment Change	V2 (Day 7±1)	P1 (V2+24 hours)	P2 (P1+24 hours)
Group 1(n=15) Standard of care	CSII	Discontinuation		
	Insulin degludec	Once a day in the morning (1:1 dose conversion)		
	Insulin aspart	Based on carbohydrate ratio and correction factor		
Group 2(n= 15) Overlap transition	CSII	50% basal rate reduction	75% basal rate reduction	Discontinuation
	Insulin degludec	Once a day in the morning (1:1 dose conversion)		
	Insulin aspart	No insulin aspart injections as patients will be using boluses through insulin pump	No insulin aspart injections as patients will be using boluses through insulin pump	Insulin aspart injections based on carbohydrate ratio and correction factor

- Insulin degludec dose conversion guidance:

- On the day of randomization, CSII will be downloaded and information on average basal insulin for the last 3 days, carbohydrate ratio and correction factor will be recorded.
- The average basal insulin for last 3 days will be used to calculate insulin degludec U-100 starting dose. For example; average basal insulin during last 3 days of CSII is 20 units/day, the insulin degludec U-100 starting dose will be 20 units/day. The dose will be rounded up or down as needed. E.g. if patient's total daily dose is 32.4 units, it will be rounded to 32 units

per day. All subjects will be instructed to use insulin degludec once a day in morning only. The first dose of insulin degludec will be given in the clinics at Visit 2.

- The dose of insulin aspart will be based on patient's own carbohydrate ratio and correction factor. Carbohydrate ratio is defined as the number of carbohydrates covered by each unit of rapid acting insulin. Correction factor (aka insulin sensitivity factor) is defined as how much one unit of rapid acting insulin will drop blood glucose. For example; a patient with carbohydrate ratio of 1:15 and correction factor of 1:50 >150 will take 3 units if preprandial blood glucose is ~200 mg/dl for 30 grams of meal (2 units for 30 grams of carbs + 1 unit for correction). Subjects randomized to group 2 will be instructed to start insulin aspart 48 hours after randomization; i.e. when they disconnect their insulin pump.
  - It is likely that patients randomized to standard-of-care group may experience hyperglycemia during first 48-72 hours. Therefore, both groups will be given a diary (**Appendix 1**) to record any correction made during the randomization phase to count extra insulin injections needed to correct blood glucose during first 72 hours.

6.4. Phone call 1 [P1, week 2, visit 2+24hrs] and phone call 2 [P2, week 2, P1+24hrs]

- As a safety measures, there will be 2 phone calls 24 and 48 hours after randomization, respectively.
- Phone call 1 (P1) will be done 24 hours (±6 hours in case if patient does not respond to first phone call) after visit 2.
- Phone call 2 (P2) will be done 24 hours (±6 hours in case if patient does not respond to first phone call) after P1.
- All subjects will be asked/assessed for

- Any episodes of severe hyperglycemia requiring hospitalization or hypoglycemia requiring third person' assistance. These events will be recorded as SAE and insulin dose modification will be done at discretion of the investigator for safety reasons.
- Correct insulin dose and administration will be reassessed.
- Maintenance of glucose and insulin injection dairy.
- Any skin reaction at CGM site.

- For Group 2 (overlap transition):
  - Instructions to change in basal rate (75% basal reduction) will be done at P1
  - Instructions for CSII discontinuation and initiation of insulin aspart based on carbohydrate ratio and correction factor at P2

6.5. Visit 3, week 2, day 14±1: end of treatment

- Blood glucose meter download and review of SMBG.
- Subject's blinded CGM will be removed and downloaded.
- Look for any local skin reaction at the site of CGM insertion.
- Subjects will return all the remained study-related products (CGM device components, insulin degludec and aspat pens, and any auxiliary supplies)
- Report any AE/SAE if any.
- Subjects will be transitioned back to their preclinical trial insulin pump regimen. The same basal and bolus settings will be used as of preclinical trial insulin pump settings. However, there may be changes made to basal and bolus insulin doses depending on blood glucose control during the study period at the discretion of investigators. To reduce the risk of

hypoglycemia, subjects will be advised to set a 50% temporary basal insulin rate for 24 hrs following insulin degludec transition.

6.6. Phone call 3, week 3, day 21±1: follow-up phone call and end of the study

- The intention of phone call 3 is to make sure that subjects are not experiencing major hypoglycemia or hyperglycemia events. The study coordinator will make a phone call to assist subjects if they require insulin dose adjustments. AE/ SAE will be recorded, if any, during third week of clinical trial. However, they would not be a part of statistical analysis.

6.7. Table 4: study visit outline

Period	Screening and Run-In-Phase	Randomization			End of treatment	Follow-up
Visits	V1	V2	P1	P2	V3	P3
Day/time from last visit	0	7	V2 + 24hrs	P1 +24hrs	14	21
Time window		±1 day	±6hrs	±6 hrs	±1 day	±1 day
Subject related info/assessment						
Informed consent	X					
Inclusion/exclusion criteria	X					
Screen fail/withdrawal criteria	X	X				
Demography and medical history	X					
Diabetes history	X					
GOLD questionnaire	X					
IDSS, and WPAI questionnaire	X	X			X	
Concomitant illnesses	X					
Review of current medications	X					
Vital signs	X					
BMI	X					
Physical examination	X					
Report AE/SAE	X	X	X	X	X	X
Trial material/steps						
Dispensation of study drugs	X	X				
SMBG and DSM education	X					
Glucose and insulin diary		X	X	X		
Blinded CGM insertion/training	X	X				
Blinded CGM removal/download		X			X	
SMBG profile	X	X				
MDI initiation and training		X				
Randomization		X				
Transition back to CSII					X	
Compliance check		X				
Blood Draw	X				X	
POC A1c, urine pregnancy test*	X					
CMP (blood sampling)	X					

V1, V2, V3 stand respectively for visit 1, 2 3; P1, P2, P3 stand respectively for phone call 1, 2, 3
SMBG; self-monitoring of blood glucose, BMI; body mass index, DSM; diabetes self-management education, POC; point-of-care.
*pregnancy test only for women in reproductive age.

6.8. Assessments for Safety:

The following safety assessments will be performed;

- Time spent in CGM measured hypoglycemia (< 70 mg/dl) and time spent in hyperglycemia (≥250 mg/dl)
- AE/SAE
- Documented hypoglycemic episodes
- Height, weight, vitals and physical examination
- Baseline laboratory assessment
- Hypoglycemia unawareness assessment (using GOLD questionnaire)
- Pregnancy test at screening

6.9. Assessments for Efficacy:

The assessment for efficacy is time spent in CGM glucose time-in-range (min/ 24 hours, 70-180 mg/dl) during the 7 days of randomization period.

7. EVALUABILITY OF SUBJECTS:

The data for a subject with minimum of 5 out of 7 days of blinded CGM prior to randomization and 5 out of 7 days of blinded CGM after randomization will be evaluable and included for the analysis of primary and secondary objectives.

8. STATISTICAL CONSIDERATIONS:

8.1. Sample size calculation

In a study by Garg and colleagues, the subjects with T1D on MDI and blinded CGM for first 4 weeks of the study spent average of 8.8 hours/day (~528 min/ 24 hours) in CGM defined glucose above 180 mg/dl [21]. Similarly, in the recently published DIAMOND study, subjects on MDI using CGM experienced average of 601 minutes (~10 hours/ day, IQR; 467-793 min) per 24 hours

514 of time spent in hyperglycemia [22]. We assume that subjects in standard of care group would
515 have more hyperglycemia than subjects in overlap transition group. Therefore, the expected CGM
516 hyperglycemia is ~ 650 minutes/24 hours in standard of care and ~ 500 minutes/24 hours in
517 overlap transition group with the differences in CGM glucose by150 minutes/day between the
518 groups.
519 This study is powered based on the primary endpoint, which is time spent in CGM-measured
520 glucose levels >180mg/dl (hyperglycemia). We have based the sample size on minimal relevant
521 differences between the two treatment groups, using a Type I error rate of 5% and a Type II error
522 rate of 20%. We hypothesize that the primary endpoint, time in minutes spent with glucose levels
523 >180 mg/dl, will be higher in the standard treatment group than in the experimental group (overlap
524 transition group), but we will use a two-sided test to assess differences in hyperglycemia by
525 treatment group. We hypothesize a standard deviation (SD) for time spent in hyperglycemia of
526 140 minutes (2.3 hours, or ~10% of the day) based on data from our clinic and previous
527 publications. We will have 80% power to detect a difference of 148.4 minutes (just under 2.5
528 hours) between groups, which is a clinically meaningful difference in time spent hyperglycemia,
529 with a sample size of 15 participants completing the study per group (total N=30). We have also
530 calculated the detectable difference for larger SD estimates, in case the SD in the study population
531 is larger than in our clinic in general, and for 90% power. The effect sizes detectable with a final
532 sample size of 15 patients per group at 80% and 90% power are 1.06 and 1.23, respectively, for all
533 endpoints.
534
535

SD	Detectable difference (minutes)	Effect size	Power
140 min	148.4 min	1.06	80%
160 min	169.6 min		80%
180 min	190.8 min		80%
140 min	171.7 min	1.23	90%
160 min	196.2 min		90%
180 min	220.8 min		90%

Detectable differences in secondary CGM endpoints, including time in range (70-180 mg/dl) and time spent hypoglycemic (<70 mg/dl) have also been considered in our power analysis.

Parameter	SD	Detectable difference (minutes)	Power
Time in range (70-180 mg/dl)	160 min	169.6 min	80%
Time in range (70-180 mg/dl)	180 min	190.8 min	80%
Time in range (70-180 mg/dl)	200 min	212.0 min	80%
Time spent hypoglycemic (<70 mg/dl)	45 min	47.7 min	80%
Time spent hypoglycemic (<70 mg/dl)	60 min	63.6 min	80%
Time spent hypoglycemic (<70 mg/dl)	75 min	79.5 min	80%

8.2. Statistical Methods

The proposed study includes two groups, one undergoing standard treatment and the other using a novel protocol of overlapping doses when transitioning from pump to MDI. Primary and secondary endpoints were described earlier.

Study participants will be randomized using block randomization, but no stratification will be used since this is a small, single center trial.

Our primary outcome is time spent hyperglycemic (CGM glucose values >180 mg/dl), which we will compared between randomized treatment groups (standard of care vs. novel overlap protocol)

during the transition from pump to MDI. We hypothesize that the time spent hyperglycemic will be reduced in the experimental group, using the novel overlap protocol, when compared to the standard treatment group. This hypothesis will be tested using a student's t-test to compare univariate differences between the standard care group and the experimental group for each of the outcomes. Secondary endpoints include time in range (70-180 mg/dl), time spent hypoglycemic (<70 mg/dl), frequency of severe hypoglycemia, number of correction boluses, and patient reported outcomes as defined on the page 7 of the protocol. Secondary endpoints will be examined using student's t-test to compare these outcomes univariately between the standard care and experimental groups. In a sensitivity analysis, CGM metrics will be evaluated in the first 72 hours vs entire 1 week as we expect that differences in hyperglycemia and time-in-range will be more pronounced between the two groups in the first 72 hours. For both primary and secondary endpoints, linear regression analysis will be used to examine outcomes by treatment group while adjusting for potential residual confounders, such as age and sex, which may not be fully addressed by randomization. All testing will be two-sided. The analysis will be conducted as an intention-to-treat analysis.

9. DATA HANDLING AND RECORD KEEPING:

- All data generated during the study will be retained by the investigator. Safety events will be reported to Colorado Multiple Institutional Review Board (COMIRB) in a timely manner as described under "Adverse Events".
- Data management is the responsibility of the investigator. All paper and electronic data will be saved in a de-identifiable manner. The data will be stored on BDC computers 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 10 years per the Standards Operating Procedures (SOP) of the University of Colorado [23]. [http://www.ucdenver.edu/research/Research%20Administration%20Documents/COMIRB-Policy-and-Procedures-Document.pdf]

10. <u>ETHICS:</u>

- The trial will be conducted in compliance with this protocol, ICH GCP, the University of Colorado COMIRB research policy and in accordance with the Declaration of Helsinki [23-25].
- 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 the COMIRB, the study team will contact potential subjects from the BDC Adult clinic.
- Before any trial-related activity, the investigator 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 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 room located on level 1, Barbara Davis Center for Diabetes Adult Clinic. 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 research policy.

11. STUDY SCHEDULE:

Trial registration: 4 weeks

Trial will be registered at Clinicaltrials.gov as soon as the study is funded.

Colorado Multiple Institutional Review Board (COMIRB): 2-3 months

The protocol, consent form, and appropriate trial materials will be submitted to COMIRB for approval.

Planned duration of recruitment period: 7 months

Study duration from screening to the end of the study per subject- 3 weeks

Data cleaning and Statistical analysis: 2 months

Data presentation and publications: 6-12 months

12. STUDY DRUGS AND MATERIALS:

12.1. Study medications(s) / device(s)

Insulin:

- Insulin degludec 100 units/ ml prefilled-pen
- Insulin Aspart 100 units/ml prefilled-pen
- Insulin degludec and Aspart will be provided by NovoNordisk.

Blinded CGM:

- Dexcom G6 that will be blinded for the display. We would like to use Dexcom G6 as it does not require calibration and is most accurate CGM [26] amongst all marketed CGM. Freestyle Libre is relatively inexpensive compared to Dexcom G6; however, Libre takes 12 hours to warm- up and provide CGM values. The first 12 hours of CSII to MDI transition is crucial for primary outcomes.
- Instructions to use Dexcom G6

Insulin pump and pump related supplies would be patients own. Similarly, patients will use their own blood glucose meter for SMBG.

12.2. Packaging and labelling of study medication(s)

All the subjects will be provided sufficient study products including insulin pens, and pen needles. Direction of use of insulin pen will be provided as outlines in the protocol.

Documentation of the study drugs/devices will be documented for each subject in accordance with drug and device standard operating procedure of the Barbara Davis Center for Diabetes and the University of Colorado Denver.

12.3. Storage and drug accountability of study medication(s)

The drug (Insulin degludec and Aspart) will be stored according to approved label. The temperature log will be monitored at the site and any temperature fluctuation will be reported as deviation.

Subjects will be provided educational material(s) on direction of use of insulin and the storage. Subjects will be instructed to store insulin in outer carton to protect from the light and cap should be kept on the pen when not in use. Each insulin pump should be used within 26 days from the day of opening.

CGM (sensor and transmitters) will be stored per manufacturer' recommendation.

12.4. Auxiliary supply

The following will be supplied to study participants for the duration of clinical trial;

Needles for insulin pen, lancets, instruction for the use of insulin pens, instruction of CGM use and calibration.

13. 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).* For each concomitant illness, date of onset, date of resolution or continuing, at a minimum, should be recorded.

Concomitant medication is any medication other than the trial product(s) that are consumed during the trial, including the screening and run-in periods. The information collected for each concomitant medication includes, at a minimum, dosage, start date, stop date or continuing, and indication.

Details of all concomitant illnesses and medication will be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication must be recorded at Visit 6 at the time of randomization. If the change influences the subject's eligibility to continue in the trial, the investigator may withdraw the subject from the clinical trial.

14. ADVERSE EVENTS:

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, 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.

Few examples (but not limited) of AEs are clinically significant worsening of concomitant illness, a new illness, clinically significant radiological or laboratory abnormalities suggesting a disease or organ toxicity.

The following three definitions are used when assessing an AE:

- **Severity assessment**
  - **Mild** - no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** - marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** - considerable interference with the subject's daily activities; unacceptable.
- **Causality assessment**

  The following terms are used when assessing the relationship between an AE and the relevant study product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to etiology other than the study product.
- **Final outcome of an AE**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.

- **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
- **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
- **Unknown** - This term is only applicable if the subject is lost to follow-up.

Serious adverse event

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.

Non-serious AE

Any AE that does not fulfill the definition of SAE.

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.

Reportable Device Issues

AE and Unexpected Adverse Device Events (UADE) arising from the use of blinded CGM (Dexcom G6) will be reported irrespective of severity, except in following cicumstances:

The following device issues are anticipated and will not be reported unless the criteria for AE reporting described above are met

- Component disconnections
- CGM sensors lasting fewer than 7 days
- CGM tape adherence issues
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement that don't meet criteria for AE reporting

Safety Monitoring Officer

A safety-monitoring officer (Aaron Michels, MD) will independently monitor the study, including adverse events and study drug or device issues with potential to impact participant safety. A monthly meeting will be held between study team and the safety officer to review any adverse events. Following each safety review, a summary recommendation from the safety monitoring officer will be collected.

Reporting and follow-up 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.

During each contact, the trained professional research associate will ask the subject about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?". All AEs will be recorded by the investigator on an AE form. SAE will be recorded within 24 hours of the investigator's first knowledge of the SAE.

The investigator is responsible for reporting all AE to COMIRB within five business days per the University of Colorado Denver policy (http://www.ucdenver.edu/research/Research%20Administration%20Documents/Unanticipated-Problem-Reporting-Policy.doc). All non-severe and severe AE will be followed by till the end of the study and will be reported to the COMIRB.

If a subject becomes pregnant during the study, the subject will be dropped from the study and followed until the pregnancy outcomes. Pregnancy will be reported as AE (or SAE if fulfills the

criteria of SAE) and it will be reported to the study sponsor (NovoNordisk). Pregnancy complications will be recorded as adverse events and if the infant has a congenital abnormality or birth defect, it will be reported and notified to the COMIRB and the sponsor.

All SAE and SUSAR will be reported to NovoNordisk within 15 days from the investigator becoming aware of such adverse events. The following information will be provided to the sponsor; study name, patient identification (e.g. initials, sex, age), event (preferably a diagnosis), drug name, reporter identification (e.g. Name, or initials), causality, and outcome.

14.1. Precautions/over-dosage

Insulin over or under dose can cause severe hypoglycemia or hypoglycemia. All subjects will be explained on the insulin dose and instructed on insulin pen use as a precautionary measures. The education on recognition of hypoglycemia or hyperglycemia and its treatment will be provided at screening and as needed during the study.

14.2 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) Fingerstick Risks (for A1c and finger stick glucose monitoring)

It may hurt when the lancet goes into a participant's finger but not for long. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of an infection is less than 1 in 1,000 people.

c) Related to CGM

Wearing sensors can cause adverse skin reactions such as pain at the site sensor insertion. The adhesive pads may cause skin erythema for 1 to 2 days or more. An allergic reaction to 1 or more parts of CGM devices may occur which can be mild, moderate, or severe (rare). In rare cases, an infection at the sensor site may occur. In rare cases, the sensor or needle may break inside the body and would require a minor surgical procedure to remove it. We will also screen out individuals with a history of serious skin reactions to adhesives.

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). 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.

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) 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.

h) 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.

15. <u>PUBLICATION PLAN:</u>

We plan to present the data at ADA and/or EASD depending on the time of completion of the analysis. The study will be published in a peer-reviewed scientific journal. The data will be publically assessable through clinicaltrial.gov. Authorship of publications will be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors.

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Appendix 1: Glucose and Insulin Dose Diary

Glucose and Insulin dose Logbook

Study protocol no-
Study personnel name and contact-
Phone- email

Subject ID:_____ Date:_____ Day:_____

Time	12am	1	2	3	4	5	6	7	8	9	10	11	12p	1	2	3	4	5	6	7	8	9	10	11
BG Readings																								

Carbs (Grams)																								
Carb boluses																								
Correction bolus																								
Total Insulin Aspart dose																								

Additional Details:

	Breakfast				**Lunch**				**Dinner**			
Time	*Food Description*	*amount*	*Carb gms*	*Time*	*Food Description*	*amount*	*Carb gms*	*Time*	*Food Description*	*amount*	*Carb gms*
	Morning Snacks				**Afternoon Snacks**				**Evening Snacks**		

952 **Table: Summary of protocol changes and rationale.**

Revisions	Rationale
Email address change (page 1)	Due to domain change at CU Anschutz, email address of the protocol PI was changed
Exclusion criteria 4. (page 10)	Tandem Control IQ is a HCL system that is approved by the US FDA for T1D in December 2019. Therefore, it is added in the exclusion criteria.
Section 5.5 (page 12). Total number of patients required for screening are increased from 34 to 40.	Due to covid related institutional closure and restrictions, we lost data for 1 patient, 1 patient withdrew from study and 4 screen failed, we increased screening sample size to have 30 patients complete the entire study to have adequate power.
Insulin degludec dose conversion guidance (page 18).	A line is added to have clarification that if total insulin dose in last 3 day is rounded for calculation of insulin degludec. E.g. is patient's total daily dose is 32.4, it is rounded to 32.0 and if 32.7, it is rounded to 33.0 units per day.
Sample size calculation (Page 24 and 25)	Typographical errors were corrected on page 24 and 25.
Statistical Methods (Page 26)	Sensitivity analysis of CGM metrics in the first 72 hours vs entire 1 week is added. This is because we expect the differences in hyperglycemia to be more pronounced in the first 72 hours.
Secondary endpoint 4: there was a typographic mistake (page 7)	As stated on page 19, we intended to collect correction boluses information during first 72 hours only.

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