Protocol Title

Transition from Basal/Bolus to Once-weekly Subcutaneous Semaglutide and Basal Insulin in Patients with Type-2 Diabetes Mellitus (TRANSITION-T2D)
A Prospective Randomized Controlled Trial

INVESTIGATOR-SPONSORED STUDY PROPOSAL

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TABLE OF CONTENTS

1. BACKGROUND AND SIGNIFICANCE:

Patients with type-2 diabetes mellitus (T2D) are often overweight or obese. In order to obtain adequate glycemic control, many of these patients require intensive therapy with multiple daily injections of insulin (referred to as MDI, basal/bolus regimen), using a rapid-acting/bolus insulin at each meal in combination with a once- or twice-daily long-acting/basal insulin. Unfortunately, intensive insulin therapy can result in undesired weight gain, which may, in part, result in further insulin resistance. In addition, weight gain may adversely affect the control of comorbid health conditions (hypertension, hyperlipidemia, congestive heart failure, sleep apnea, etc.). The burden of disease management with multiple daily injections of insulin also serves as a barrier to A1C goal attainment as maintaining compliance with such complex regimens is often challenging in the real-world setting.

Once patients with T2D require multiple daily injections of insulin to obtain glycemic control, it is generally considered to be a permanent/life-long therapy. However, reports have demonstrated the safety and effectiveness of adding once-daily glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide to basal insulin therapy in order to obtain glycemic control (1, 2), and in clinical practice, the addition of liraglutide (or other FDA-approved GLP-1RAs) to basal insulin often negates or delays the need to initiate prandial insulin. Subsequently, a newer form of anti-diabetic therapy, a once-daily injectable combination of GLP-1RA and basal insulin, became available and demonstrated promise that perhaps glycemic control may even be obtained with less complex regimens (i.e., less daily injections). There are currently two GLP-1RA/basal insulin combination therapies that are FDA approved: iGlarLixi (Soliqua®), and iDegLira (Xultophy®) (3, 4). While these observations with iGlarLixi and iDegLira demonstrating an improvement in A1C while avoiding prandial insulin injections are very exciting, what remains unclear is if patients with reasonable glycemic control (A1C $\leq$ 7.5%) currently receiving MDI (basal/bolus, 3-4 injections per day) could potentially maintain or even improve glycemic control by switching to a once-daily injectable product like Xultophy® or Soliqua®. Currently, there are no studies available (or planned) that have answered this clinical question. One limitation of these combination products in the clinical setting is the inability to independently titrate the GLP-1RA and basal insulin components. If a patient begins to experience hypoglycemia, and/or their fasting BG values are currently within the goal range, the dose of these combination products cannot be further titrated, limiting one's ability to further improve glycemic control in patients with a residual A1C elevation.

What also remains unclear is if some of the newer formulations of GLP-1RA may also be able to reduce the burden of disease management and maintain glycemic control in patients who are currently well-controlled on a regimen of MDI. Recently, subcutaneous (sc) once-weekly semaglutide has been demonstrated to be capable of improving glycemic control in patients with T2D in combination with insulin therapy. In SUSTAIN-5 (5), at week 30, subcutaneous semaglutide 0.5 and 1.0 mg was demonstrated to reduce A1C by 1.4% and 1.8%, respectively, vs 0.1% with placebo [mean baseline A1C value, 8.4%] in a population of T2D patients receiving stable therapy with basal insulin with or without metformin. Moreover, mean body weight (kg) decreased with semaglutide 0.5 and 1.0 mg vs placebo from baseline to end of treatment: 3.7, 6.4, and 1.4 kg, respectively. Premature treatment discontinuation due to adverse events was higher for semaglutide 0.5 and 1.0 mg vs placebo

(4.5%, 6.1%, and 0.8%), mainly due to gastrointestinal disorders. Even if the transition from MDI to once-daily sc semaglutide in combination with basal insulin were successful in only a minority of patients, the clinical advantage and reduction in burden of disease management that would be associated with transitioning from 3-4 injections of insulin per day to a regimen of once- weekly sc semaglutide and a once-daily injection of basal insulin would be a rather dramatic and remarkable transformation for patients, and one that would likely improve patients' diabetes treatment satisfaction. It would also help to solidify the effectiveness and safety of semaglutide in yet another population of patients with T2D. What cannot be minimized is the tremendous impact that a successful transition to once-weekly semaglutide and once- daily basal insulin could have on patients in terms of reducing their insulin requirements, assisting with weight loss (or mitigating further weight gain), and reducing the frequency and burden of hypoglycemia. In my clinical experience, once patients are titrated to full dose GLP-1RA therapy and attain adequate glycemic control, insulin doses (particularly prandial insulin) can often be further reduced or eliminated without negatively impacting glycemic control. Continuing the insulin therapy at higher doses in these patients simply suppresses the glucose-dependent secretion of endogenous insulin being promoted by the GLP-1RA therapy. Often, only an abrupt cessation of prandial insulin, or a step-wise down- titration of insulin therapy in these patients, will reveal that insulin therapy is no longer required at higher doses to maintain glycemic control. When this does successfully occur, the impact on patients is transformational.

In a recent treat-to-target trial utilizing albiglutide (6), patients with T2D and A1C $\geq$ 7.0% to $\leq$ 9.5% receiving basal plus prandial insulin ($\leq$ 140 units total daily dose of insulin and $\leq$ 70 units of prandial insulin per day) were optimized over 4 weeks before participants were randomized (1:1) to albiglutide + optimized basal insulin glargine and lispro (dose reduced by 50% at randomization; subsequently, lispro injections were fully discontinued 4 weeks later) (n=402) or to continued optimized lispro plus optimized glargine (n=412). The mean ± SD A1C at baseline was 7.8% ± 0.6% in the albiglutide + glargine group and 7.7% ± 0.6% in the lispro + glargine group. The A1C was reduced at week 26 to 6.7% ± 0.8% and 6.6% ± 0.8%, respectively (least squares [LS] difference 0.06% [95% CI 20.05 to 0.17]; non-inferiority $P < 0.0001$). In the albiglutide + glargine group, 218 participants (54%) replaced all prandial insulin without reintroducing lispro up to week 26. Total daily prandial insulin dose was similar at baseline but was lower by 62 units/day (95% CI -65.9 to -57.8; $P<0.0001$) at week 26 in the albiglutide + glargine group, and the total number of weekly injections was also reduced from 29 to 13 per week. Less severe/documented symptomatic hypoglycemia (57.2% vs. 75.0%) occurred in the albiglutide + glargine group with meaningful weight differences (LS ± mean SE -2.0 ± 0.2 vs. + 2.4 ± 0.2 kg; $P <$ 0.0001) vs. lispro + glargine. Gastrointestinal adverse events were higher with albiglutide + glargine (26% vs. 13%).

The results obtained with the transition of uncontrolled patients with T2D receiving MDI with albiglutide are encouraging, but would likely have been more robust had a modern and more effective long-acting GLP-1RA been utilized. Unfortunately, 46% of the patients randomized to receive albiglutide had to resume prandial insulin prior to week 26 because of inadequate glycemic control. The number of patients that would have been able to fully discontinue prandial insulin would have likely been much higher had the patient's level of glycemic control been at target for a longer period of time prior to the transition of the

patient's prandial insulin to GLP-1RA (i.e., resolution of glucose toxicity), and if a more potent and efficacious GLP-1RA, such as once-weekly sc semaglutide, were utilized.

The purpose of this study is to investigate the ability of once-weekly sc semaglutide (in combination with once-daily basal insulin) to maintain or improve glycemic control in patients currently receiving MDI, while providing the patients with a significant reduction in the burden of disease management. In addition, this approach may also furnish a positive effect on weight management, a reduction in hypoglycemic episodes, and improvement in diabetes treatment satisfaction, when substituted for basal/bolus therapy in patients with T2D who currently have adequate glycemic control (A1C $\leq$ 7.5%) with a regimen of MDI (requiring a total of $\leq$ 80 units of insulin per day). The A1C cut-point of $\leq$ 7.5% was chosen because many patients on complex treatment regimens (MDI) with reasonable control, i.e., 7-7.5%, would be expected to have a realistic chance of success by switching from MDI to sc semaglutide and basal insulin combination therapy. Also, many patients taking complex insulin regimens (MDI) fall in the close to A1C goal range of 7-7.5%, so using this cut-point, vs. < 7%, would make recruitment easier. Lastly, patients receiving MDI who are older and/or with heart disease also have higher individual A1C goal/targets around 7.5%. This study will also assess the impact that a successful substitution may have on the patients' diabetes treatment satisfaction, an important, yet under-appreciated aspect of diabetes management.

2. SPECIFIC OBJECTIVES:

2.1 The primary overall objectives and specific aims of this project include:

To determine the ability of once-weekly sc semaglutide in combination with once-daily insulin degludec to replace/negate the need for MDI (basal-bolus regimen) in patients with T2D under adequate glycemic control (A1C ≤ 7.5%) with MDI, while simultaneously providing the patients with a significant reduction in the burden of disease management.

2.2 Secondary objectives and specific aims of this project include:

1) To determine the effect on weight in patients with T2D on MDI transitioned from MDI to once-weekly sc semaglutide in combination with once-daily insulin degludec.
2) Record the frequency and severity of hypoglycemia
3) Assess the impact that a successful substitution may have on a patients' diabetes treatment satisfaction.

3. RESEARCH DESIGN AND METHODS

Study Hypothesis (hypotheses):
Therapy with once-weekly sc semaglutide in combination with once-daily insulin degludec will be capable of maintaining (or improving) glycemic control, when substituted for MDI, in patients with T2D with adequate glycemic control (≤ 7.5%) on MDI-based regimens (≤ 80 units of insulin per day), vs. further titration of insulin therapy in those continuing MDI.

Transitioning MDI to once-weekly sc semaglutide in combination with once-daily insulin degludec will be associated with weight loss, less blood glucose confirmed hypoglycemic episodes, as well as a reduction the frequency of severe hypoglycemic events, and an improvement in diabetes-treatment satisfaction, when compared to continued therapy with MDI.

3. 1 Endpoints:

3.1.1 Primary endpoints

All variables will be assessed at baseline and at 26 weeks.

1) Glycemic control per the HbA1C at 26 weeks
    a. Percentage of subjects maintaining the treatment target of HbA1c ≤ 7.5% at week 26
        i. Calculated as the percentage of subjects achieving treatment target of HbA1c ≤ 7.5% at week 26

3.1.2 Secondary endpoints

1) Weight at 26 weeks
    a. Mean change from baseline in body weight at week 26
2) Hypoglycemic episodes [defined using the classification scheme outlined in the American Diabetes Association 2020 Standards of Care (6)]
    a. A plasma glucose < 70 mg/dL (3.9 mmol/L and ≥ 54 mg/dL (3 mmol/L)

b. A plasma glucose value <54 mg/dL (3.0 mmol/l), regardless of symptoms.

c. A severe event characterized by altered mental status/and or physical status requiring assistance for treatment of hypoglycemia

d. The timing of hypoglycemic episodes will be recorded for the overall study period, and will be stratified further into those which occurred during the titration (first 12 weeks) and maintenance (last 14 weeks) phases of the study.

3) Mean change from baseline in A1C at week 26
    i. Calculated as an estimate of the mean change from baseline in A1C at week 26
4) Change from baseline in diabetes treatment satisfaction at week 26
5) Daily insulin requirements (units/kg/day) at week 26
    a. Mean±SD
6) Daily prandial insulin requirements (units/kg/day) at week 26
    a. Mean±SD
7) Daily basal insulin requirements (units/kg/day) at week 26
    a. Mean±SD
8) Total daily insulin dose (units) required at week 26
    a. Mean±SD
9) Daily basal insulin dose (units) required at week 26
    a. Mean±SD
10) Daily prandial insulin dose (units) required at week 26
    a. Mean±SD
11) Number of patients that had to resume prandial insulin in the semaglutide arm prior to week 26

3.2 Study type:
Study Type: Interventional
Study Design: Allocation: Prospective, Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment, Active Comparator
Masking: Open Label
Primary Purpose: Treatment
Number of Treatment Arms: Two
Duration of Study Period: 26 week active comparator

3.3 Rationale for study Design
The proposed study design allows for evaluation of glycemic control rates within the once-weekly sc semaglutide in combination with once-daily insulin degludec arm, and allows for comparison against a control arm. The planned unbalanced randomization allows for more precise estimation of these control rates in the primary intervention group and also then allows for further evaluation of predictors of glycemic control within this group. Randomization provides improved balance on both observed and unobserved demographic and clinical factors, minimizing the need to control for covariates in the primary analysis.

3.4 Study population:

This is a single-center study with a planned enrollment of 60 subjects with T2D. The subjects will be randomized in a 2:1 fashion into one of two arms. Forty subjects will be randomized into the once-weekly sc semaglutide in combination with once-daily insulin degludec arm and twenty subjects will be randomized into the MDI arm requiring multiple daily injections of insulin.

3.5 Inclusion Criteria

1. Gender: men and women
2. Ethnicity: all ethnic groups
3. Language: English
4. Age: ≥ 18 to 75 years
5. Type II diabetes
   - -Currently treated with MDI (basal/bolus regimen) for at least 6 months
   - -MDI must consist of three or more injections of insulin per day, with at least 2 injections being prandial/rapid-acting insulin
   - -Prandial insulin restricted to insulin aspart, glulisine, and lispro
   - -Basal insulin restricted to long acting once-daily analogues (insulin detemir U-100, insulin glargine U- 100, insulin degludec (U-100 or U-200), or insulin glargine U-300)
   - -A1C within 30 days of randomization must be ≤ 7.5% on the present therapy
   - -Less than or equal to 120 units of total insulin therapy per day
   - -Total daily Prandial insulin dose ≤ 0.5 units/kg/day

6. Ability to provide informed consent before any trial-related activities. Trial-related activities are any procedure that would not have been performed during normal management of the subject.

3.6 Exclusion Criteria

1. GAD-65 antibody positive
2. ESRD Current glucocorticoid therapy greater than 5 mg of daily prednisone (or equivalent dose of other glucocorticoid)
3. Known or suspected allergy to trial medication(s), excipients, or related products, i.e., GLP-1RA therapy or insulin aspart or insulin degludec.
4. The receipt of any investigational drug within 90 days prior to this trial.
5. Previous participation in this trial (Randomized)
6. Mental incapacity or language barrier (non-English speaking)
7. Use of incretin-based therapies <3 months before inclusion in the study
   - -DPP-4 inhibitors sitagliptin, saxagliptin, linagliptin, alogliptin
   - -GLP-1RA (exenatide, liraglutide, exenatide LAR, dulaglutide, albiglutide, lixisenatide, semaglutide)
   - -GLP-1RA/Basal Insulin combination (IGlarLixi, IDegLira)
8. Present use of oral anti-diabetic agents other than metformin and/or a SGLT-2 inhibitor. The dose of metformin and/or SGLT-2i dose must be unchanged and stable for the immediate 3 months prior to baseline.
9. Pregnant, breast-feeding or the intention of becoming pregnant or not using adequate contraceptive measures
10. Personal or family history of medullary thyroid carcinoma
11. Personal or family history of Multiple Endocrine Neoplasia syndrome type 2

12. History of acute or chronic pancreatitis, severe liver disease or LFT's ≥ 2.5X ULN, or severe disease of digestive tract
13. History of bariatric surgery/procedure (gastric banding, gastric sleeve, or Roux-en-Y)
14. Known elevation of serum calcitonin ≥ 50 ng/L

3.7 Withdrawal Criteria

The subject may withdraw at will at any time. If a subject has withdrawn their consent, the investigator will attempt to bring in the subject for a final study visit to help ensure a safe exit from the study. If a subject is difficult to reach for their study visits, three attempts will be made to contact the subject (i.e. two phone calls and one written contact). If the attempts to contact the subject are unsuccessful, the subject will be withdrawn from the study and noted as "lost to follow up".

Female subjects will be instructed to notify the investigator immediately if they become pregnant while participating in the study. Subjects randomized to the once-weekly sc semaglutide in combination with once-daily insulin degludec arm that become pregnant must discontinue treatment. Following discontinuation of study treatment, subjects will be requested to maintain adherence to the study visits.

3.8 Subject Replacement

Subjects who have withdrawn their consent to participate will not be replaced. The investigator will attempt to bring subjects in for a final study visit.

3.9 Rationale for Study Population

The rationale used for the selection of the study population was to identify a group of patients that would have a reasonable chance of being switched from MDI to once-daily sc semaglutide in combination with once-daily insulin degludec without a dramatic deterioration in glycemic control. Thus, a population of patients on MDI, with good glycemic control on their current regimen was chosen. Good glycemic control is defined here as ≤7.5% at baseline (screening). The rationale for selecting ≤ 120 units/day of total insulin requirements as an eligibility criterion at baseline was as follows:

- At week 26 in the study by Rosenstock et al (6), the patients randomized to receive albiglutide + insulin glargine vs. insulin lispro + glargine were receiving 9.8 ± 17.3 units of prandial insulin vs 71.9 ± 40.1 units, respectively, in addition to their basal insulin doses of 59.3 ± 24.1 and 58.6 ± 25.9 units, respectively.
- The basal and bolus components yielded total daily insulin doses in the albiglutide + insulin glargine group of 69.0 ± 33.2 units and 130.4 ± 61.1 units in the insulin lispro + insulin glargine group.
- The prandial insulin dose at week 26 was lower by 62 units/day in the albiglutide + insulin glargine group.
- Thus, one would expect a group of well-controlled patients receiving MDI, ≤ 120 units of insulin per day, could be controlled on a basal insulin dose on the order of 0.5 units/kg (a physiologic approach), and prandial dose ≤ 0.5 unit/kg/day, plus a highly effective GLP-1RA that could substitute/replace 62 or more units of prandial insulin while maintaining glycemic control.
- Allowing higher doses of insulin, up to 140 units/day, and up to 70 units of

prandial insulin per day, as was allowed by Rosenstock et al, may result in a failure rate on the order of 50%, as noted in their study where ~50% of patients in the albiglutide arm had to resume some prandial insulin prior to week 26.

- As the primary objective of this study is to demonstrate the ability to maintain good glycemic control via switch to sc semaglutide and insulin degludec vs. continuing a regimen of MDI, while reducing the patient's burden of diabetes management, a more conservative approach is necessary to avoid the need to resume prandial insulin in many of the study subjects prior to week 26.

3.10 Visit Procedures

The duration of the study visits is anticipated to last 18 months. All visits include a window of +/- 7 days.

3.10.1 Screening Visit

Potential subjects will be screened against the inclusion and exclusion criteria. Potentially eligible subjects will be contacted by the study team to introduce the study. The screening encounter may occur during a routine visit with their provider or subjects may be contacted by telephone. If subjects agree to voluntarily participate, signed informed consent will be obtained.

Physical examination will be performed by the study investigator. Gender, age, ethnicity, blood pressure, pulse, height, weight, BMI, total daily insulin dose (total, basal and bolus components, both in daily units, and as units/kg/day for each component), metformin therapy status, SGLT-2 inhibitor therapy status, and the subject's self-reported duration of Type II diabetes will be recorded.

Blood samples will be collected to obtain the following laboratory values: HbA1C, GAD-65, serum creatinine and AST/ALT. GAD-65 positive subjects will be excluded from continuing in the study.

Subjects can withdraw from the study at any time by notifying their study doctor to ensure a safe transition to standard of care therapy.

3.10.2 Randomization Visit

The randomization visit will occur within 3 weeks of the screening visit.

Weight, BMI, blood pressure, pulse, and total daily insulin dose (basal and bolus) will be collected. The study investigator will review screening labs and confirm eligibility of each subject before randomization.

To assess the impact that a successful substitution may have on a subject's diabetes treatment satisfaction, the subject will complete the Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs).

Eligible subjects will be randomized 2:1 to either switch to once-weekly sc semaglutide in combination with once-daily insulin degludec or continue MDI. Block randomization will occur to ensure equal distribution of patients between arms that are receiving <80 units of insulin per day and between 80-120 units of insulin per day.

Study medications will be dispensed through the Cleveland Clinic Investigational Pharmacy.

Patients randomized to continue with MDI will be transitioned from their existing regimen to the rapid-acting insulin product insulin aspart and their basal insulin switched to once-daily insulin degludec (both provided by the study). This will allow for treatment uniformity, and to avoid gaps in treatment that often occur in the real-world setting (secondary to insurance copays, deductibles, donut-hold coverage gaps in Medicare patients, etc.). Patients randomized to MDI will be allowed to continue correction rapid-acting insulin, in addition to their prandial doses of rapid-acting insulin, throughout the duration of the study.

In patients randomized to MDI, basal insulin will be adjusted to 0.5 units/kg/day (if their pre-trial daily dose of basal insulin is >0.5 units/kg/day, otherwise, if it is ≤ 0.5 units/kg/day, their current dose will be continued), and the dose of basal insulin will continue to be titrated to obtain fasting glucose levels of 70-90 mg/dL as outlined in the table below.

Basal Insulin Algorithm

Point of Care Fasting Glucose Value (mg/dL)	< 70	70-90*	>90
Basal insulin degludec dose adjustment	Decrease by 2 units	Continue Current Dose	Increase by 2 units

*Fasting Blood Glucose Goal: 70-90 mg/dL

Their existing doses of prandial insulin, and number of injections, will be continued. Pre-meal glucose values of < 130 mg/dL will be targeted, in accordance with the recommendations outlined in the ADA Standards of Medical Care in Diabetes-2020 Position Statement (7). Prandial insulin doses will be increased by 2 unit increments every three days (using lowest pre-meal glucose value over the preceding three day period) until goal attainment is reached. For example, if the pre-lunch glucose values are consistently above range (> 130 mg/dL), the breakfast dose of prandial/rapid-acting insulin will be increased by 2 units. The lower limit for pre-prandial blood glucose will be 70 mg/dL. If a patient's lowest pre-meal glucose value over the preceding three days is < 70 mg/dL, the prandial insulin dose will be lowered by 2 units. For example, if the pre-lunch glucose value is < 70 mg/dL, the breakfast dose of prandial/rapid-acting insulin will be decreased by 2 units. See below table.

Prandial Insulin Algorithm

Point of Care Pre-prandial Glucose Value (mg/dL)	< 70	70-130*	>130
Prandial insulin aspart dose adjustment	Decrease by 2 units	Continue Current Dose	Increase by 2 units

*Prandial Blood Glucose Goal: 70-130mg/dL

Patients will be asked to check their blood sugar four times daily via point-of-care (POC) measures at meals (AC: pre-breakfast, pre-lunch, pre-dinner) and bedtime (HS). These values will be used to adjust their insulin regimen, guide dosing of corrective insulin aspart and monitor the degree of glycemic control between physician encounters and lab assessments.

Correction Insulin Algorithm

Point-of-care BG Value (mg/dL)	< 150	151-200	201-250	251-300	301-350	351-400	> 400
Dose of Correction Insulin to be Administered (units)	0	2	4	6	8	10	10*

Goal Blood Glucose (BG) Ranges: Pre-prandial/Bedtime BG: < 130 mg/dL, Fasting BG 70-90 mg/dL
*Patient instructed to also notify study team

If hypoglycemia is noted to occur the daily basal insulin degludec dose and total daily insulin aspart dose will both be reduced by 10% by the investigator.

The patients randomized to once-weekly sc semaglutide in combination with once-daily insulin degludec will start at 0.25 mg of sc semaglutide and adjustment of their dose of basal insulin to 0.5 units/kg/day of basal insulin degludec (if their pre-trial daily dose of basal insulin is >0.5 units/kg/day, otherwise, if it is ≤ 0.5 units/kg/day, their current dose will be continued). Their doses of prandial insulin therapy will be stopped. The dose of insulin degludec will be administered once-daily at bedtime, and the dose of once-weekly sc semaglutide will be administered on a weekly day of choice determined by the patient. Participants assigned to 0.25 mg once-weekly sc semaglutide will undergo dose escalation to 0.5 mg at 4 weeks and to the maintenance dose of 1 mg at 8 weeks. The insulin degludec dose will remain stable until the patients reach their maximum tolerated dose of sc semaglutide. If hypoglycemia is noted to occur during this period, the daily basal insulin degludec dose will be reduced by 10% by the investigator. Subsequently, after week 8-12 (depending on when the patients reach their maximum tolerated dose of once weekly sc semaglutide), the lowest fasting blood glucose value over the preceding three day period will be used for insulin degludec titration purposes. The target fasting plasma glucose will be 70-90 mg/dL. Patients will be instructed on how to self-titrate the insulin degludec and will follow the same basal insulin titration algorithm described above.

3.10.3 Semaglutide Dose Titration in Setting of Intolerability/Side Effects

If a subject does not tolerate (and is unwilling to continue) the 0.25 mg weekly dose of sc semaglutide initiated at the randomization visit, it will be stopped until their next study visit. If the patient is willing, it will be reinitiated at that the week 4 study visit. If they once again report intolerance that precludes them from continuing, at that time, the sc semaglutide will be stopped, and the subject monitored to determine the need for rescue therapy, per protocol.

If a subject does not tolerate the sc semaglutide dose increase from 0.25 mg weekly to 0.5 mg weekly at week 4 study visit, they will resume the 0.25 mg weekly dose until their week 8 study visit. If the subject is tolerating the 0.25 mg weekly dose at the time of the week 8 study visit, their dose will be increased to 0.5 mg weekly. If they are tolerating the 0.5 mg weekly dose at week 12 study visit, the patient would then continue that dose of sc semaglutide and initiate insulin degludec titration. Further dose escalation of the sc semaglutide to 1.0 mg at the week 12 study visit will not be attempted.

If the patient reports not tolerating the 0.5 mg dose (at any point in time after the reattempt to increase the dose at the week 8 visit) the subject will be instructed to resume 0.25 mg weekly and commence titrating the insulin degludec at that point in time. They will then continue 0.25 mg weekly through the remainder of the study period.

If a subject does not tolerate the sc semaglutide dose increase from 0.5 to 1.0 mg, initiated

at the week 8 study visit, they will be placed back on 0.5 mg weekly and the titration of insulin degludec will commence at that point in time (rather than waiting until week 12 study visit).

At the 12 week follow-up appointment/assessment, the number of daily POC blood glucose assessments will be reduced to 1-2 daily measures, per the discretion of the investigator. Additional POC assessments may be requested if the investigator feels they are warranted.

The group of patients randomized to sc semaglutide in combination with once-daily basal insulin will be allowed to continue correction rapid-acting insulin as described in the table above up until the time of their 12 week follow-up appointment/assessment, or until achieving their maximum tolerated dose of sc semaglutide, whichever comes first, to help address uncontrolled post-prandial hyperglycemia until the dose of sc semaglutide can be adequately titrated and maintained.

A failure of once-weekly sc semaglutide in combination with once-daily insulin degludec will be defined as a mean daily glucose level consistently > 180 mg/dL despite the maximum tolerated dose of sc semaglutide in combination with once-daily insulin degludec at a dose greater than 1 unit/kg/day or per the discretion of the investigator. At this point, the patients will continue semaglutide but resume prandial insulin for the remaining duration of study and titrate according to protocol.

3.10.4 4-week Assessment Visit

Physical examination will be performed by the study investigator. Weight, BMI, blood pressure, pulse, and total daily insulin dose (basal and bolus) will be recorded.

Study medication will be continued/titrated according to the subject's assigned study arm described in the baseline visit procedures.

Frequency and severity of hypoglycaemia will be assessed through subject self-reporting and a review of the subject's glucose monitor.

3.10.5 8-week Assessment Visit

Physical examination will be performed by the study investigator. Weight, BMI, blood pressure, pulse, and total daily insulin dose (basal and bolus) will be recorded.

Study medication will be continued/titrated according to the subject's assigned study arm described in the baseline visit procedures.

Frequency and severity of hypoglycaemia will be assessed through subject self-reporting and a review of the subject's glucose monitor.

3.10.6 12-week Assessment Visit

Physical examination will be performed by the study investigator. Weight, BMI, blood pressure, pulse, and total daily insulin dose (basal and bolus) will be recorded.

Blood samples will be collected to obtain the following laboratory values: HbA1C, serum creatinine and AST/ALT.

Study medication will be continued/titrated according to the subject's assigned study arm described in the baseline visit procedures.

Frequency and severity of hypoglycaemia will be assessed through subject self-reporting and a review of the subject's glucose monitoring log.

Study medications will be dispensed through the Cleveland Clinic Investigational Pharmacy.

3.10.7 26-week Assessment Visit (Final)

Physical examination will be performed by the study investigator. Weight, BMI, blood pressure, pulse, and total daily insulin dose (basal and bolus) will be recorded.

Blood samples will be collected to obtain the following laboratory values: HbA1C, serum creatinine and AST/ALT.

Frequency and severity of hypoglycaemia will be assessed through subject self-reporting and a review of the subject's glucose monitoring log.

To assess the impact that a successful substitution may have on a subject's diabetes treatment satisfaction, the subject will complete both the Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs) and the Diabetes Treatment Satisfaction Questionnaire Change Version (DTSQc).

4. Flow Chart and Table of Study Time Points

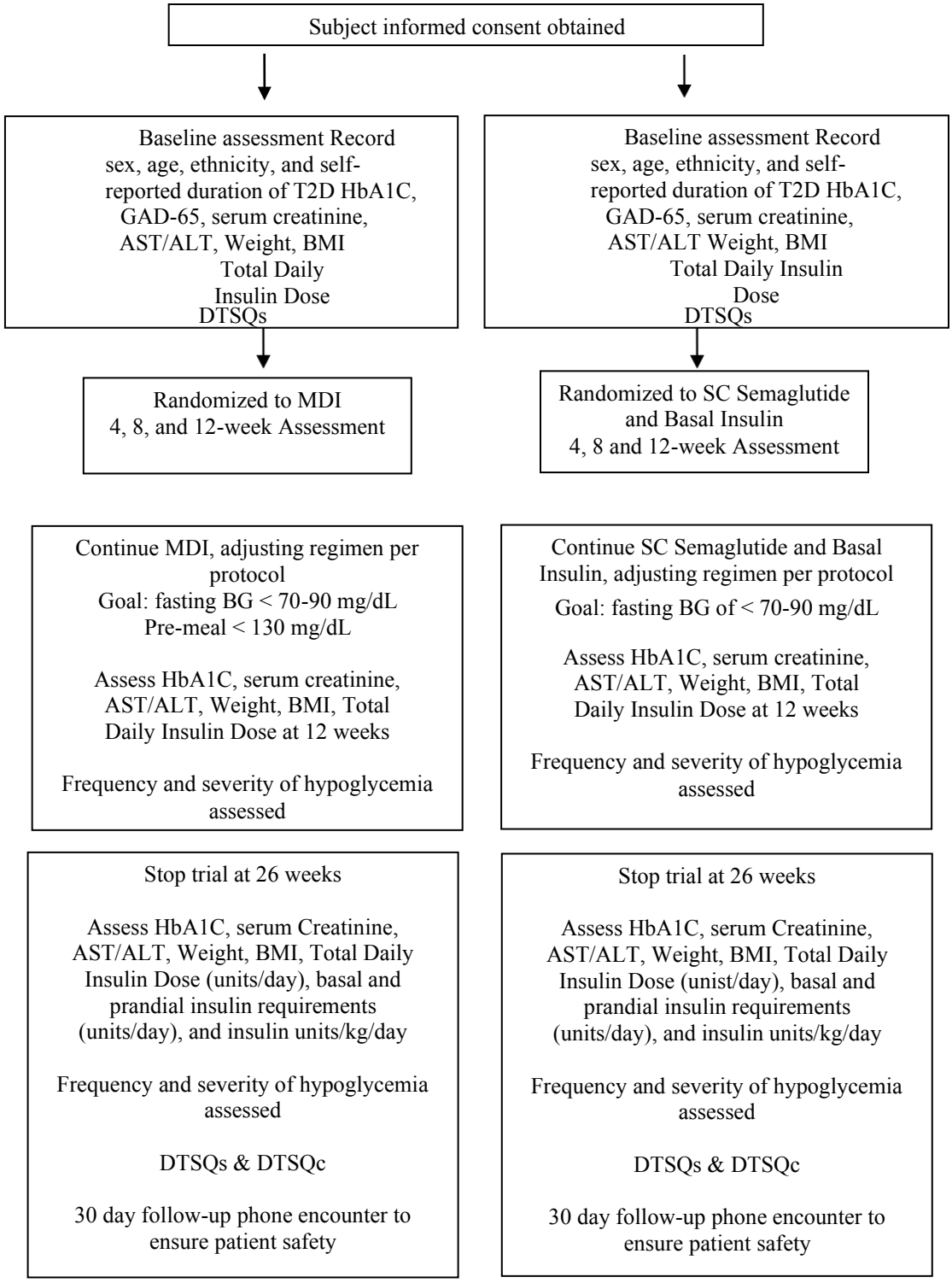

Table 1 Study Time Points Relative To Randomization
Measurement per protocol

Baseline Assessment	Randomized	4-Weeks	8-Weeks	12-Weeks	26-Weeks
Physician Encounter Demographics Lab Assessment Weight/BMI DTSQs[a]	MDI[c] or SC Semaglutide and Basal Insulin	Physician Encounter	Physician Encounter	Physician Encounter Lab Assessment Weight/BMI	Physician Encounter Lab Assessment Weight/BMI DTSQs DTSQc[b]

a Diabetes Treatment Satisfaction Questionnaire Status Version
b Diabetes Treatment Satisfaction Questionnaire Change Version
c Multiple daily injections

5 ASSESSMENTS:

5.1 Assessments for Efficacy

Laboratory testing for the protocol indicated HbA1C, GAD-65, serum creatinine and AST/ALT will be performed through Cleveland Clinic laboratories. The laboratory values will be assessed by the investigator and/or designated study team members. All laboratory values will be recorded in the subject's electronic medical record. All blood samples will be collected by the designated study team members and transported to the Cleveland Clinic laboratory consistent with clinical procurement and processing methods.

5.2 Assessments for Safety

All protocol indicated laboratory values will be assessed for clinical significance by the investigator and/or designated study team members.

Subject safety and adverse event assessment will occur during each study visit. Following randomization, the frequency and severity of hypoglycemia will be assessed at each visit. All severe hypoglycemia episodes self-reported by the subject will be documented and reported to the Cleveland Clinic Institutional Review Board (IRB) consistent with IRB policies and procedures.

A severe hypoglycemic episode is defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon or other corrective action.

In order to ensure participant safety upon completion of the clinical trial, a telephone encounter will be conducted on all study subjects, 30 days after study completion. This encounter will attempt to ensure patient safety and identify any issues regarding the patient's level of glycemic control post-trial. Any identifiable issues will be addressed by the study investigator, in collaboration with the patients other healthcare providers (primary care provider, diabetologist, or endocrinologist.

5.3 Other Assessments

Treatment Satisfaction will also be assessed using the Diabetes Treatment Satisfaction Questionnaire Status and Change Versions (8-10). The patients will complete a diabetes treatment satisfaction questionnaire DTSQ(s) survey at baseline, and a DTSQ(s) and DTSQ(c) at the 26 week visit.

5.4 Subject Compliance

Treatment compliance will be assessed by monitoring study medication utilization. Subjects will be asked to bring along all used, partially used and unused study

medication including empty packaging at each visit. The study team member will assess the amounts of study medication used compared to expected usage since the last dispensing visit and, in case of discrepancies, question the subject. If a subject is found to be non-compliant, the study team member will remind the subject of the importance of following the instructions given including taking the study medications as prescribed.

6 STATISTICAL CONSIDERATIONS:

6.1 Sample Size Calculation

We plan to randomize patients 2:1 to sc semaglutide in combination with basal insulin degludec or MDI, and anticipate a total sample size of 60 patients. Sample size calculations were performed based on the precision with which differences in control rates between groups could be estimated, as well as the within group control rate precision. Since the exact glycemic control rate is unknown, calculations were performed based on data from Rosenstock et al (2020) where 60% of patients achieved HbA1c levels below 7.0% and an estimated 85% achieved levels below 7.5% (under the assumption that HbA1c levels were normally distributed). Based on these assumptions and use of a two-sided 95% confidence interval, with 60 patients randomized 2:1, the difference in control rates will be able to be estimated to within ± 19% (for pooled control rate of 85%) to 26% (with pooled control rate of 60%). With this sample size, the control rate with sc semaglutide in combination with basal insulin can be estimated to within ±11% to ±15% under the same assumptions for glycemic control rate as above. We feel that the gains in precision seen with extra enrollment (>60) do not justify the extra resources required to obtain these numbers.

Power Calculations. Confidence interval half-widths for efficacy rate and differences in efficacy

Total Sample Size	**100**	**90**	**75**	**60**	**45**
Group Ratio Semaglutide:MDI	**66:34**	**60:30**	**50:25**	**40:20**	**30:15**
Semaglutide Only					
85% control rate	0.09	0.09	0.10	0.11	0.13
60% control rate	0.12	0.12	0.14	0.15	0.18
Difference in Control Rates					
85% control rate	0.15	0.16	0.17	0.19	0.22
60% control rate	0.20	0.21	0.24	0.26	0.30

Although identification of risk factors for control with sc semaglutide and once-daily basal insulin is an exploratory aim, with this sample size, univariable analyses can be performed that will allow for identification of patient characteristics that are associated with HbA1c control with sc semaglutide and basal insulin and may warrant future study.

6.2 Statistical Methods

The primary analysis will be performed using the intent-to-treat cohort. Given the early stage of this research, per-protocol analyses among those continuing therapy will also be performed to assess efficacy among those who tolerate the therapy. This will help to

measure efficacy, in an optimal setting and also perhaps identify subjects where the regimen might be most useful in future research. Categorical factors will be described using frequencies and percentages, while continuous measures will be summarized using means, standard deviations, and percentiles of interest. For the primary outcome, control rates will be calculated as proportions, and the difference in control rates with 95% confidence limits will be estimated. Categorical variables, including the frequency and severity of hypoglycemia, will be compared between groups using Poisson regression models, chi-square tests or Fisher exact tests, as appropriate. Relative rates and odds ratios with 95% confidence limits will be presented as appropriate. Changes in continuous measures between initial and follow-up assessments will be compared using analysis of covariance models that include baseline levels of these variables as a covariate. Results will be presented as mean levels with 95% confidence limits. If necessary, transformations of continuous measures will be performed prior to analysis to meet assumptions of the models. The primary endpoint, and all secondary endpoints will be tested assuming an overall 0.05 significance level. If missing data exists, patterns of missing data will be explored, and if appropriate, alternate methods including the use of maximum likelihood estimation in mixed effect models or multiple imputation will be explored. Missing data is not expected among the primary endpoint, as patients that withdraw from active treatment and do not present at the last visit will be classified as failure to control, however assessment of missing data patterns will be performed regardless. Frequency tables will be provided to identify the reason for control failure (e.g. side effect, lack of efficacy, etc.). Exploratory analyses will also be performed to measure the association between patient characteristics and glycemic control overall, within assigned groups, and within per protocol groups using Pearson chi-square and t-tests to better understand efficacy within the population.

6.3 Interim Analysis

No interim analysis is planned, as complete enrolment will be necessary for evaluation of exploratory goals of the study.

6.4. Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

Not planned for this study.

7 DATA HANDLING AND RECORD KEEPING:

A file database will be created for data collection accessible only by authorized study personnel. Information will be entered into the database as it is collected and patients finish the study. Each patient will be assigned a study number consecutively as they are enrolled. Only the study number will be used to identify all study-related documents such as case report forms. A master list of study numbers linked to patient identifiers will be maintained by the study coordinator in a secured location. Study data will be collected and managed using REDCap (Research Electronic Data Capture); this will include patient identification number, medical record number, age, gender, and ethnicity.

If a subject withdraws from the trial or is lost to follow-up, then the subject's data which has already been collected will be retained by the investigator, entered into the database and used for the study reporting.

8 ETHICS:

The study will be conducted in compliance with ICH GCP and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.

Voluntary signed informed consent will be obtained from each study subject prior to initiating any research interventions. Informed consent will be documented in the subject's medical record.

This study is subject to the review and approval of the Cleveland Clinic Institutional Review Board prior to initiating any study activities.

9 STUDY SCHEDULE:

The duration of the study is anticipated to last 18 months with a planned 12 month recruitment period and a 26-week follow-up period. The study will begin following the receipt of an executed study agreement and approval from the Cleveland Clinic Institutional Review Board.

The planned completion of the final study report is 6 months from the completion of the last patient last visit or month 24.

10 STUDY DRUGS AND MATERIALS:

10.1 Study medication(s)

All study medications are FDA approved. Subcutaneous semaglutide (Ozempic®) will be provided by the manufacturer Novo Nordisk, as will NovoLog® FlexPen (insulin aspart) and Tresiba® FlexPen (insulin degludec injection 100 units/mL).

10.2 Packaging and Labelling of Study Medication(s)

Each study medication will be dispensed to the study subject in its respective FDA approved drug manufacturer's packaging. Labelling will be in accordance with local law and study requirements.

10.3 Storage and Drug Accountability of Study Medication(s)

Study medications will be stored and monitored in the Cleveland Clinic Investigational Pharmacy. Storage conditions for all study medications will be consistent with the approved product labelling. Temperature is monitored daily by the Pharmacy team.

Drug accountability will be reviewed with the subject during each study visit. Used/unused study medications returned to the study investigator will be discarded consistent with the Cleveland Clinic Investigational Pharmacy policies and procedures.

No study medications will be dispensed to any person not enrolled in the study.

10.4 Auxiliary Supply

Study medications (insulin pens), needles, blood glucose monitors and testing strips will be provided to the study subjects.

10.5 Randomization and Blinding

This is an open label study. Subjects will be randomized to the treatment groups in a 2:1

fashion (subcutaneous semaglutide in combination with once-daily basal insulin degludec: MDI).

11. CONCOMITANT ILLNESSES AND MEDICATIONS:

Definitions:

Concomitant illness: any illness that is present at the start of the trial *(i.e. at the first visit)*.
Concomitant medication: any medication other than the trial product(s) that is taken during the trial, including the screening period will be recorded. Details of all concomitant illnesses and medication will be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication will be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the Sponsor will be informed.

The information collected for each concomitant medication will include start date, stop date or continuing, and indication. For each concomitant illness, date of onset, date of resolution or continuing, will be recorded

12. ADVERSE EVENTS:

The investigator will be responsible for reporting of all adverse events including serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs), serious adverse drug reactions (SADRs) to the Cleveland Clinic institutional review board based upon federal regulations and local/IRB policies and procedures. The sponsor-investigator will also report to Novo Nordisk all SAEs, SUSARs, and SADRs at the same time such events are reported to regulatory authorities or within 15 days from the sponsor-investigator becoming aware of such adverse events, whichever comes first.

12.1 Definitions

12.1.1 Adverse Event (AE):

An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events reported from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures

12.1.2 Clinical Laboratory Adverse Event:

A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

12.1.3 Serious Adverse Event (SAE):

A serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening* experience
- In-patient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Suspicion of transmission of infectious agents

*The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

12.1.4 Serious Adverse Drug Reaction (SADR):

An adverse drug reaction (ADR) is an adverse event (AE) for which a causal relationship to the trial product is at least possible i.e. causal relationship is conceivable and cannot be dismissed. Serious adverse reaction (SAR): Adverse event which fulfils both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.

12.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR):
An SAE which is unexpected and regarded as possibly or probably related to the trial/study product by the investigator. The current approved summary of product characteristics (package insert) for Ozempic® will be used for assessment of expectedness.

12.1.6 Medical Events of Special Interest (MESI): A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

12.1.7 Non-Serious Adverse Event:
A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.8 Severity Assessment Definitions:
- Mild: 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

12.1.9 Relationship to study medication Assessment Definitions:
- Probable: Good reasons 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 an etiology other than the trial product

12.1.10 Outcome Categories and Definitions:
- Recovered: 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: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown

12.1.11 Collection, Recording and Reporting of Adverse Events
All events meeting the definition of an adverse event must be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the posttreatment follow-up period as stated in the protocol. At a minimum, the following information will be collected: study name, subject study ID number, age, sex, event (diagnosis), trial drug, causality, outcome, and reporter.

12.1.12 Follow-up of Adverse Events

During and following a subject's participation in a clinical trial, the sponsor-investigator and institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. Medical care for study subjects will be provided regardless of their insurance status.

All adverse events classified as serious or severe or possibly/probably related to the trial product must be followed until the subject has 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.

12.1.13 Pregnancy

Female subjects of childbearing potential must use adequate contraceptive methods until 4 weeks after the last dosage of Ozempic®.

Study subjects will be instructed to notify the investigator immediately if they become pregnant.

The investigator will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by the investigator will occur within the same timelines described above for reporting of Adverse Events.

Pregnancy complications should be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

12.1.14 Precautions/Over-dosage

Include information concerning precautions and procedures to be observed in the event of overdose by any trial product provided during the study.

13. LIABILITY AND SUBJECT INSURANCE:

During and following a subject's participation in trial, the sponsor-investigator and his/her institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. Medical care for study subjects will be provided regardless of their insurance status.

The Cleveland Clinic will indemnify, defend and hold harmless Novo Nordisk, including its affiliates or subsidiaries, and their respective officers, directors and employees for any claims, suits, actions, proceedings and related costs and expenses, and all damages, costs,

penalties, and expenses, including reasonable attorneys' fees directly related to The Cleveland Clinic's negligence, willful misconduct or illegal activity in the conduct of the study, except to the extent that such covered claims are due to the negligence or willful misconduct of Novo Nordisk or its agents in performing Novo Nordisk's obligations under this study and/or claims arising from a personal injury to a study subject to the extent directly caused by a manufacturing defect of Novo Nordisk's study products.

14. PREMATURE TERMINATION OF STUDY:

Novo Nordisk, the sponsor-investigator, the Cleveland Clinic IRB or a regulatory authority may decide to stop the trial or part of the trial, but an agreement from all parties on the procedures to be followed will first be obtained.

If the trial is suspended or prematurely terminated, the sponsor-investigator will inform the study subjects to ensure a safe withdrawal. The sponsor-investigator will promptly inform Novo Nordisk, the Cleveland Clinic IRB and regulatory authorities.

15. PUBLICATION PLAN:

Upon study completion, the data generated will be submitted in abstract form to the next eligible session of the annual American Diabetes Association National Meeting, and subsequently submitted to Diabetes Care for publication consideration.

The sponsor-investigator will plan to register the study with clinicaltrials.gov.

16. REFERENCES:

Literature references should be stated in accordance with the international accepted standards of "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".

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