Brief Title: Comparison of Glargine to Degludec Insulin Transition With or Without a Bridging Glargine Dose (GLIDING)

Official Title: A Randomized Comparison of Transitioning From Insulin GLargine to Insulin Degludec usING a Bridging Dose of Glargine Versus Direct Conversion, in Patients With Type 1 Diabetes Mellitus - a Pilot

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A randomized comparison of transitioning from insulin GLargine to Insulin Degludec usING a bridging dose of glargine versus direct conversion, in patients with type 1 diabetes mellitus – a pilot study

(GLIDING STUDY)

INVESTIGATOR-SPONSORED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN): U1111-1214-3257

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1. BACKGROUND AND SIGNIFICANCE:

Insulin degludec (IDeg), an ultra-long-acting basal insulin, is increasingly used to treat patients with type 1 diabetes (T1D). IDeg has a half-life of 25 hours and duration of action exceeding 42 hours in patients with T1D (1,2) and as a result does not require as stringent a dosing schedule as other basal insulins. It has been shown to have a 4-fold lower within-patient variability in its pharmacodynamic response compared to insulin glargine over the 24 hour dose interval (3). The rate of symptomatic and severe hypoglycemia in T1D patients has also been shown to be lower with IDeg than insulin glargine (4). A recently published systematic review and meta-analysis of 15 clinical trials comparing IDeg to insulin glargine showed lower fasting plasma glucose and less nocturnal hypoglycemia with IDeg (5). The total basal insulin dose invariably decreases with the transition to IDeg (6,7). The lower insulin use and lower rate of hypoglycemia may eventually translate into medical cost savings too (8). Moreover, patients have expressed more satisfaction with their regimen and quality of life with IDeg compared to other agents in one study that compared this objectively using questionnaires, before and after transition (9). All of these factors give IDeg an advantage over other basal insulins currently in the market. However, steady state concentration of IDeg is not reached until 2 to 3 doses are administered daily, and this may result in greater glycemic variability in the 24 to 72 hours following the initiation of therapy with IDeg (10). There is currently no evidence-based guidance on how to minimize glucose excursions when transitioning patients from their existing basal insulin to IDeg. The package insert for IDeg suggests a 1:1 dose conversion from other basal insulin regimens to IDeg for adult patients. However, this does not account for the time it takes IDeg to achieve steady state and can result in worsening of glycemic control in the 48-72 hours after the transition is made. Many practitioners at the University of Washington Diabetes Clinic have seen better glycemic control within the first 12 to 24 hours in T1D patients in whom we gave 50% of their usual dose of insulin glargine at bedtime along with the first dose of IDeg. This leads to our hypothesis that a bridging therapy involving the use of a reduced amount of patients' prior basal insulin at the time of initiating IDeg will lead to improved glycemic control in the first 24-72 hours on IDeg, minimizing the morbidities associated with hyperglycemia and the need for correctional insulin and also avoiding hypoglycemia resulting from over-correction due to use of additional rapid-acting insulin. Additionally, we will follow what has been done in prior clinical trials of conversion from other basal insulins to IDeg and hence, convert them from their insulin glargine total daily dose to 80% of that dose as IDeg (4). An improvement in the safety and ease of transitioning from the more commonly used glargine to IDeg may greatly encourage more providers and patients to adopt IDeg as the basal insulin of their choice. Another benefit would be knowing how to transition patients back to their outpatient IDeg therapy when they are being discharged home from an inpatient stay and were switched to insulin glargine during their hospitalization, as IDeg is not formulary in many hospitals. The purpose of this pilot study is to gain preliminary evidence of whether bridging with insulin glargine while transitioning to IDeg provides better glycemic results in the transition period compared to direct conversion.

2. ENDPOINTS AND OBJECTIVES:

Primary endpoint:

Change in percent time spent in target glycemic range (TIR, glucose 70-180 mg/dL, both values included) in the 48 hours before and the 48 hours after the 1st dose of IDeg

Primary objective:

To compare the mean change in percent time in range (as defined by the primary endpoint) between patients who transition directly to IDeg to the mean change in patients who use a bridging dose of insulin glargine along with 1st dose of IDeg.

Secondary end points:

These will include the following data obtained from their CGM download in the 48 hours following the first dose of IDeg as measured as a difference compared to the 48 hours preceding the dose:

1. Coefficient of variation of percent-time-in-range for each treatment within each group
2. Nocturnal time in range of 70-180 mg/dL (between mid-night and 0600 hours, both values included)
3. Percent time above 180 mg/dL (TAR-1), percent time above 250 mg/dL (TAR-2) for each treatment within each group
4. Percent time below 70 mg/dL (TBR-1), percent time below 54 mg/dL (TBR-2) for each treatment within each group
5. Number of correction boluses for each treatment within each group

Secondary objectives:

To compare each of the secondary endpoints between patients who use a bridging dose to patients who transition directly to IDeg.

3. RESEARCH DESIGN AND METHODS

3.1 Study Hypothesis:

Our hypothesis is that among patients who transition from insulin glargine to IDeg, those who use a bridging dose of insulin glargine will not have a significant change, on average, in time spent in target glycemic range during the transition period, whereas, those transitioning directly to IDeg will have a significant change in this parameter. We further hypothesize that those using the bridging dose of insulin glargine will have less hypoglycemia, less hyperglycemia and need fewer correction boluses than the direct-conversion patients during the transition period.

3.2 Study type:

This will be a double-blind, randomized, single-center, proof-of-concept study. Randomization will be stratified by use of insulin glargine once daily or twice daily at baseline. Randomization will be conducted using permuted-block design with a block size of 4, ensuring equal numbers of bridging and non-bridging patients in each of the 2

resultant strata after every 4th patient is randomized within a stratum. The 2 strata with blocked randomization within each stratum will result in 4 groups as follows:

1. **Bridging Groups:**
   - **i.** Patients transitioning from once daily insulin glargine to once daily IDeg with a bridging dose of insulin glargine.
   - **ii.** Patients transitioning from twice daily insulin glargine to once daily IDeg with a bridging dose of insulin glargine.
2. **Direct-Conversion Groups:**
   - **i.** Patients transitioning from once daily insulin glargine to once daily IDeg without a bridging dose of insulin glargine (but with a bridging dose of placebo solution to preserve blinding).
   - **ii.** Patients transitioning from twice daily insulin glargine to once daily IDeg without a bridging dose of insulin glargine (but with a bridging dose of placebo solution to preserve blinding).

All patients will be instructed to use their own prescription insulin medications till before the 1st dose of IDeg. On the night they have to transition to IDeg, they will start using study drugs for their basal insulin (see section 3.10.4). Starting with the 1st dose of IDeg, their basal insulin will be from study drug only, till visit #3 (see section 3.10.6), at which time, they will resume their original insulin prescriptions. They will remain on their own prescription short-acting insulin throughout the study. On the night of the transition, all patients will be instructed to take their 1st dose of IDeg and along with this, they will take a second injection from a pre-filled syringe of a pre-specified dose of insulin glargine or matched placebo (normal saline), that participants will collect from Investigational Drug Services Pharmacy (IDS) on the same day. The dose will be calculated ahead of time by study staff on visit 2 (see under section 3.10.2.1). Neither the patients, nor the research staff will be aware of their randomization, which will be done by IDS. Patients will act as their own controls, as we will collect glycemic data from 48 hours prior to the first dose of IDeg, which will be compared to the data seen in the 48 hours after the first dose of IDeg. During this observation period of the 48 hours before and after the first dose of IDeg, no adjustments will be made to the calculated and recommended doses of insulin glargine or IDeg. Patients will be followed for up to 1 week after the first dose of IDeg.

3.3 Rationale for study Design

Though IDeg is being increasingly used in clinical practice, there are no guidelines on what is the best way to transition patients from other long-acting insulins, such as glargine, to IDeg. The package insert recommends 1:1 dose conversion from other basal insulins to IDeg, but this does not account for the time taken by IDeg to achieve steady state (typically 48-72 hours). There is no guidance on what to do in those 48-72 hours. Given the time taken for IDeg to achieve steady state, the period of transition from one insulin to another, can result in significant glycemic variation in the 24-72 hours after the first dose. We want to study how best to avoid or minimize this and the option of using a small dose of their original long-acting insulin has anecdotal evidence of success in our practice.

3.4 Study population:

We aim to recruit patients with type 1 diabetes mellitus only. We will screen 50 patients with the plan to randomize approximately 40 patients to start IDeg. The IDS at the University of Washington will randomize patients (1:1) to either receive or not receive a bridging insulin glargine dose along with the 1st dose of IDeg, within the stratified groups of once- or twice-daily insulin-glargine regimens.

3.5 Inclusion Criteria

Patients must meet ALL inclusion criteria to be included in the study.

1. Patient age is 18-75 years.
2. Diagnosis of T1D of at least 1-year duration.
3. Has the ability to provide informed consent before any trial-related activities.
4. Treated with insulin glargine as their basal insulin in the 3 months preceding screening visit.
5. Stable insulin regimen (defined as change of <20% in the total daily dose of insulin and no change to the basal insulin agent) over the 3 months preceding the screening visit.
6. Patient willing to dose their basal insulin at bedtime.
7. Hemoglobin A1c < 9% in the 3 months preceding screening visit.
8. Able to self-administer their insulin doses.
9. Able to do self-monitoring of blood glucose using a glucose meter and willing to do this at least 2 times daily for patients using a CGM that requires calibration prior to the study and 4 times daily for patients who were not using a CGM prior to the study.
10. Agreeable to the use of a continuous glucose monitor (CGM) for the duration required in the study. If already using a CGM prior to the study, then agreeable to wearing the blinded study CGM concurrently during the study period.
11. Will be reachable by phone and/or email to comply with study procedures.
12. Will be able to comply with study procedures, per investigator's opinion.
13. Patient agrees to not use correctional insulin unless BG ≥250 for the 48 hours before and after 1st dose of IDeg.

3.6 Exclusion Criteria

Patient must not have ANY of the exclusion criteria to be included in the study.

1. Patients with eGFR <30 on at least 2 measurements within 1-year of the screening visit.
2. History of myocardial infarction within 6 months preceding the screening visit.
3. Patients taking non-insulin medications for the glycemic management of T1D (including metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, pramlintide)
4. Known or suspected allergy to IDeg or one of its excipients.
5. Pregnant, planning to become pregnant in the next 3 months or breastfeeding.
6. Participation in a clinical trial with investigational drug within 1 month of the screening visit or at present.

7. Skin condition that prevents the insertion of the CGM.
8. Previously randomized and received drug in this study.
9. Presence of decompensated or poorly controlled psychiatric conditions.
10. Current known or suspected illicit substance use.
11. Any anticipated surgery or procedure in the next 14 days.
12. Patients using U-300 glargine as their basal insulin.
13. Patients using insulin afrezza as their short-acting insulin.
14. Use of glucocorticoid burst/pulse therapy within 14 days prior to screening visit (chronic stable glucocorticoid doses are acceptable).

3.7 Withdrawal Criteria

Patients have the right to withdraw from the study at any stage and for any reason.

Patients **may be** discontinued prematurely, by the investigator for any of the following reasons:

- Emergence of a severe condition(s) such that, in the judgement of the investigator, continuation in the trial would negatively impact the health of the patient.
- Lack of compliance with study medication or visits as judged by the Investigator.
- Patient lost to follow-up.
- Major protocol violation.
- Inter-current illness that, in the judgment of the investigator, should result in premature discontinuation.
- Use of prohibited medications (see the Inclusion/Exclusion criteria)
- Onset of glucocorticoid burst/pulse therapy during the study period.
- Knowledge of new risks necessitating new benefit/risk evaluation.
- Patient voices intention to become pregnant in the immediate future.

Patients **must be** discontinued for any of the following reasons:

- If Novo Nordisk determines that the study must be stopped, all patients will be required to end participation at that time.
- Trial closed-out.
- Patient becomes pregnant.

A patient will not be discontinued early from the study solely because of missing the scheduled transition from insulin glargine to IDeg. The research staff will discuss the matter with the patient and determine whether they feel he/she can continue moving forward in the study following all study procedures, including dosing. If after this discussion, the patient and the research team are in agreement about continuing in the study, the investigator will decide if he/she may remain in the study.

A subject cannot be considered lost to follow-up until the research center performs and documents at least three (3) attempts to contact him by phone, email or letter.

3.8 Patient Replacement

Patients discontinuing from the study will not be replaced. IDS will continue to assign randomization of the next participant to a specific group, based on the original randomization plan, when the next participant has completed screening procedures and is ready for randomization. We will include data from all randomized participants in our data analysis.

3.9 Rationale for Study Population

The main objective of our study is to determine if the use of a bridging dose of insulin glargine is able to improve glucose control in first few days after the first dose of IDeg. As a result, we will recruit participants who are reasonably well controlled on their baseline insulin regimens. We will exclude participants on non-insulin glucose-lowering agents, as these can affect glycemic variability themselves and confound the results. We are not excluding patients with known severe hypoglycemia or hypoglycemia unawareness in this study, as these are the patients who stand to benefit the most from the transition from insulin glargine to IDeg. We are excluding patients with stage 4 or 5 CKD. We will be excluding patients with a myocardial infarction in the last 6 months. These patients will be excluded as they carry a higher risk that hypoglycemia or hyperglycemia may result in mortality.

3.10 Visit Procedures

Subjects will be screened for study eligibility and interest in participating in this study (Screening Visit/Visit 1). All subjects will have the study explained to them and sign the informed consent prior to beginning any study procedures. Subjects must meet the inclusion criteria and have no exclusions.

Randomization and treatment will be initiated only once eligibility is confirmed.

There will be 4 phases to the study:

- A ***screening phase*** to establish eligibility that spans from screening visit till insertion of study CGM (up to 2 weeks).
- A ***baseline observation*** phase to collect CGM data on their original insulin glargine regimen, starting from insertion of study CGM to first dose of IDeg administration (~3 days)
- A ***treatment phase*** starting from 1st to last dose of IDeg and consisting of at least 3 days of IDeg therapy (3-7 days).
- A ***follow-up phase*** from removal of study CGM to exiting from the study (till up to 7 days after the last dose of IDeg)

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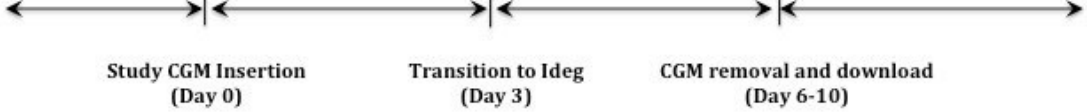

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*** Could be extended by 2 days if inadequate CGM data noted on day 3 (see section 3.11.4)**

3.10.1 Screening Visit (Visit 1):

Participants will be seen at the research wing of the Diabetes Care Center (DCC) at the University of Washington, Seattle, WA. Research staff will obtain informed consent after explaining study procedures. A detailed diabetes and medical history will be collected from the subjects. Their current medication regimen will be verified from them, particularly the actual number of units of the different insulins they are using. Subjects will undergo assessment of vital signs (pulse, blood pressure, weight, height, BMI) and a focused physical exam. If there is no available record of eGFR within the last year and/or hemoglobin A1c within the last 90 days, these will be obtained by phlebotomy at this visit. 2 tubes of blood (1x 3cc lavender and 1x 4 cc lime green) will be drawn and sent off to measure hemoglobin A1c (by HPLC method) and basic metabolic panel to the UWMC clinical laboratory, if required. Subjects will be instructed to not alter their diet, alcohol consumption or exercise regimen from the time of study CGM insertion till 48 hours after the first dose of IDeg.

If they are considered to be eligible for the study, then the research staff will contact IDS. IDS will then randomize the participant to one of the two arms within the two stratified groups. (Refer to sections 3.5 and 8.5 for details). Research staff will then contact the participant by phone or email to have them return for visit 2 for insertion of the study CGM.

Important considerations for keeping things as uniform as possible in the study are as below:

- We will ensure that all subjects on once daily insulin glargine are taking it at bedtime. Subjects who were taking it in the morning only at screening visit, will be switched to bedtime dosing at least 7 days prior to study CGM insertion.
- We will ensure that subjects on twice daily insulin glargine at screening visit are taking their 2nd dose of the day at bedtime.

* Could be extended by 2 days if inadequate CGM data not

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3.10.2 CGM insertion visit (Visit 2):

Participant will return to the DCC, within 2 weeks of visit 1, to meet with a research coordinator who will assist with the insertion of the CGM (Dexcom G6). At this visit, study staff will also perform any teaching and training that may be required for the participant to know how to use the CGM device. This visit needs to be conducted before 1200 hours. They will be given CGM supplies to last up to 1 week. They will be instructed to keep the study CGM on at all times for this duration. If they have their own CGM, then they will be allowed to keep that on in addition to the study CGM, should they desire to do so. They will be instructed to replace the sensor, if needed. The study CGM insertion day will be considered day 0. The next day will be day 1. Transition to IDeg will be done on Day 3 as below. Subjects will be dispensed a log book in which they will need to document carbohydrates consumed, exercise duration and time, timing and doses of basal and bolus insulin (broken down as prandial and correction), self-monitored blood glucose values, hypoglycemia symptoms and intervention for each day they are in the study (from CGM insertion to removal) (See Appendix A and B). We will inquire about any change to concomitant medications and document insulin doses being administered.

3.10.2.1 Insulin Dosing:

At visit 2, subjects will also be given written instructions on how to do the transition from insulin glargine to IDeg.

Calculation of IDeg dose

The dose of IDeg that subjects will be switched to will equal 80% of the total daily dose of insulin glargine they reported using at visit 1. This reduction is what was done in the clinical trials of conversion from any basal insulin to IDeg with lower risk of hypoglycemia (4). For example, if a subject was on 25 units of glargine at screening visit, then they will need to switch to 20 units of IDeg (0.8 X 25 = 20). Number of units will be rounded up to the next whole number if decimal points are ≥ 0.5 and rounded down if <0.5.

Timing of IDeg dose

To keep things consistent across participants, we will instruct all patients to start their first dose of IDeg 3 days after the study CGM is inserted. The rationale for this is that the first 24 hours of data on the CGM is not very accurate and after that we want 48 hours of baseline glucose data on insulin glargine, prior to transitioning to IDeg. This will be used later as their baseline to compare with the values seen on IDeg. Subjects will be instructed to administer their first dose of IDeg at 2100 hours on the 3rd day after insertion of study CGM. They will then administer the same dose of IDeg every night for 5 ± 2 consecutive doses.

Dosing of Insulin Glargine

Dosing of insulin glargine will depend on the group a subject is randomized to:

If randomized to bridging dose:

For subjects on once-daily glargine, up to day 2 after study CGM insertion they will administer their usual insulin glargine dose at bedtime. On day 3, they will administer **50% of their usual glargine dose** (using study drug) at 2100 hours **along with** only their **FIRST IDeg** dose, as calculated. Thereafter, they will not administer insulin glargine till after the 5 (± 2) days of IDeg are completed.

For subjects on twice-daily glargine, on day 3 after study CGM insertion they will administer their AM glargine dose as usual (i.e. 100%). On the same night, they will administer **50% of their bedtime glargine dose** (using study drug) at 2100 hours **along with** only their **FIRST IDeg** dose as calculated above. Thereafter, they will not administer insulin glargine till after the 5 (± 2) days of IDeg are completed.

If randomized to direct conversion:

For subjects on once-daily glargine, up to day 2 after study CGM insertion they will administer their usual insulin glargine dose at bedtime. On day 3, they will administer the **first dose of IDeg**, as calculated above, at 2100 hours **and a placebo solution** in a dose equivalent to 50% of their usual glargine dose. They will **NOT administer any insulin glargine** from that night till after 5 (± 2) days of IDeg are completed.

For subjects on twice-daily glargine, on day 3 after study CGM insertion they will administer their AM glargine dose as usual (i.e. 100%). On the same night, they will administer the **first dose of IDeg**, as calculated above, at 2100 hours **and a placebo solution** in a dose equivalent to 50% of their bedtime glargine dose. They will **NOT administer any insulin glargine** from that night till after 5 (± 2) days of IDeg are completed.

Use of short-acting insulin

At the CGM insertion visit (visit 2), subjects will be instructed to use their prandial insulin to carbohydrate ratios or pre-specified doses of prandial insulin the way they would have otherwise, during the study. *For the 48 hours before and after the first dose of IDeg, however, all subjects will be instructed not to use any correctional insulin unless their blood glucose is >250, both around meals and otherwise.* While we understand that subjects might be reluctant to allow their blood glucose to run in the 180-250 range without correction, we feel this is a necessary part of our study protocol. The main reason for this is that our primary study end point is time in range (TIR). If the change from insulin glargine to IDeg results in more time in the 180-250 range in patients not receiving the bridging dose of glargine, patients are likely to correct this aggressively with the use of correctional insulin. This would dilute any measurable differences in our primary end point (TIR). It would only potentially show differences in the secondary end points of dose and number of correctional insulin used. However, by telling them to avoid bolusing till glucose rises above 250, we will be able to discern any differences in TIR that might arise from the change of basal insulin, while at the same time, not being unsafe for the patients over a 96 hour period of time.

3.10.3 Telephone Encounters #1:

This will be on day 1 (i.e. the day after the study CGM is inserted). We will ensure that the study CGM is working and the subject does not have any questions or concerns. Study staff will also assist the subject with any troubleshooting, if necessary. Subjects will be instructed to upload their CGM data on day 3, for research staff to review it. Subjects will be instructed not to alter their insulin glargine dose for the following 48 hours, till the night of day 3, when they transition to IDeg. We will inquire about any adverse events and change to concomitant medications and document doses of insulin being administered by patient.

3.10.4 Telephone Encounter #2:

Research staff will review patient's CGM data upload on day 3. We will inquire about adverse events, any change to concomitant medications and also document doses of insulin being administered.

If there is ≥ 38 hours of usable CGM data, then they will be instructed to proceed with their first dose of IDeg that night, as scheduled. In order to obtain the bridging dose of insulin glargine or matched placebo, subjects will be instructed to proceed to IDS at the University of Washington to collect their study drug the same day.

If there is < 38 hours of usable CGM data, then subjects will be instructed to wear their CGM, per study protocol, while remaining on their original insulin regimen, and to again upload CGM data on day 5. Research staff will review this data on day 5.

If there is ≥ 38 hours of usable CGM data from day 3-5, they will be instructed to proceed with their first dose of IDeg that night, as scheduled. Subjects with < 38 hours of usable CGM data will be discontinued from the study.

3.10.5 Telephone Encounter #3:

This will be on day 4, i.e. the day after the first bedtime dose of IDeg (or on day 6 for subjects who needed to repeat baseline CGM data collection). We will inquire about adverse events and any change to concomitant medications. The doses of insulin administered will be obtained and documented. The main purpose of this call is to ensure that the subject implemented the transition from insulin glargine to IDeg, correctly. If it is discovered that the subject forgot to transition, then they will be given repeat instructions to dose on night of day 4. If it is discovered that the subject executed the transition incorrectly, then they will need to undergo a 3-day "wash out period", during which they will resume their original insulin glargine regimen (with alterations as deemed necessary by study physician on day 4), and then they will be instructed to execute the transition again on night of day 7. If a subject performs the transition erroneously a second time, he/she will be discontinued from the study and replaced by a new subject as the study supplies allow. Subjects will be instructed not to alter their dose of IDeg for at least the first 3 doses (i.e. 48 hours after 1st dose).

3.10.6 CGM Removal and Download Visit (Visit 3):

Subjects will come in approximately 8 ± 2 days after their CGM insertion. At this visit, their study CGM will be removed and downloaded. We will inquire about adverse events and any change to concomitant medications. We will collect and review their study logbook. They will also be given instructions on how to transition back to insulin glargine.

Once-daily glargine users: Approximately 24 hours after their last dose of IDeg, subjects will be instructed to administer 50% of their original total daily dose of glargine at bedtime. At 48 hours after their last dose of IDeg, they will return to their original bedtime insulin glargine dose.

Twice-daily glargine users: Approximately 24 hours after their last dose of IDeg, they will administer 50% of their original bedtime insulin glargine dose. Approximately 36 hours after their last dose of IDeg they will again administer 50% of their original morning insulin glargine dose. Approximately 48 hours after their last dose of IDeg, they will resume their original insulin glargine dosing regimen (i.e. 50% of total dose twice daily).

Subjects will receive a gift card for $50 for participation in the study.

3.10.7 Exit Visit/Telephone encounter #4 (Visit 4):

This visit will be approximately 7 days after the study CGM removal (+/- 2 days). Subjects will be called to see if they have any concerns or questions. They will be instructed to follow up with their original endocrinologist for any further insulin adjustments.

3.11 Assessments for Efficacy

On the screening visit (visit 1), if there is no available record of eGFR within the last year and/or hemoglobin A1c within the last 3 months, these will be obtained by venipuncture at this visit. The research team nurse or physician will perform this. 2 tubes of blood (1x 3cc lavender and 1x 4 cc lime green) will be drawn and sent off to measure hemoglobin A1c (by HPLC method) and basic metabolic panel to the UWMC clinical laboratory. No extra blood will be collected from the subjects. There will be no other instances of blood collection during the study. These will help ensure that appropriate subjects are enrolled in the study.

At the various telephone encounters, study staff will verify that the subjects are following study instructions correctly. Specifically, on Telephone Encounter #2, only if adequate usable CGM data is available on the data uploaded by the patient will they be allowed to proceed with the transition (see section 3.11.4).

By measuring the time a patient spends in range (TIR = 70-180 mg/dL), we are assessing the efficacy of the use of IDeg as a basal insulin.

3.12 Assessments for Safety

The primary safety concern in this study is the risk of hypoglycemia. Hypoglycemia management will be revised at screening visit to ensure appropriate education and all medications and supplies needed to manage hypoglycemia will be prescribed at screening. Subjects will be instructed that if they see BG <70 mg/dL on their personal CGM that persists longer than 15 minutes or notice symptoms of hypoglycemia regardless of glucose reading, they need to perform a capillary blood glucose (CBG) measurement to confirm if the meter shows a reading <70 mg/dL. If it does, they need to complete a hypoglycemia episode form (Appendix B). Upon onset of a hypoglycemic episode, subject is recommended to check CBG every 15 minutes until the value is ≥ 70 mg/dL and/or symptoms have resolved. Repeated CBG measurements and/or symptoms, occurring within a period of 60 minutes after onset on a hypoglycemic episode, will by default be considered as one hypoglycemic episode until a succeeding CBG value is ≥ 70 mg/dL and/or symptoms have been resolved and should be reported as one hypoglycemic episode. CBG measurements < 70 mg/dL or hypoglycemic symptoms after the 60 minutes period shall trigger the reporting of a new hypoglycemia episode and prompt the subject to fill out a new hypoglycemic episode form until a succeeding measurement is ≥ 70 mg/dL and/or symptoms have been resolved. In case of several low CBG values within the 60 minutes interval, the lowest value is the one that will be reported as the CBG value for the hypoglycemic episode but the start time of the episode will remain as the time for the first CBG value and/or symptom. Whenever a subject completes a hypoglycemia episode form, they should notify study staff within 24 hours. When they notify study staff, details of the events around the low blood glucose (activity, food intake, insulin administration) will be collected from them and then recommendations will be made, as deemed necessary, by the study physician.

Hyperglycemia is the other risk of this study. Subjects will be instructed at screening to notify study staff within 24 hours of a blood glucose >250. Study staff will try to ascertain from the subject if any investigations are needed and make management recommendations, as deemed necessary, by the study physician.

By measuring the time a patient spends above or below range (>180 mg/dL or <70 mg/dL) and assessing the frequency of use of correctional doses of short-acting insulin, we are assessing how safe their glycemic management regimen is.

3.13 Patient Compliance

Patient compliance to study procedures will be assessed during the telephone encounters. Compliance will be defined by the following (all 3 need to be met to be considered compliant), assessed during the 48 hours prior to and after the first dose of IDeg:

- No missed doses of basal insulin
- No missed doses of nutritional insulin with meals
- Wearing the study CGM for >19 hours a day

4. STATISTICAL CONSIDERATIONS:

The primary objective of this pilot study is to calculate the change in percent time that BG is "in range" (TIR defined as 70-180 mg/dL) in the 48 hours before the first IDeg dose vs. the 48 hours after the first dose, and to compare the mean of this change between patients who are randomized to receive bridging glargine and those who are randomized to not receive bridging glargine. Randomization will be stratified by glargine use (once vs. twice daily). For each patient, the TIR in the 48 hours before first IDeg use will be calculated, as will the TIR in the 48 hours after first IDeg use. The difference of these values will then be calculated, and the mean of the differences compared between the randomized arms. Our primary hypothesis will assume that the "bridging effect" is similar between patients who take glargine once daily and twice daily. However, we plan an exploratory look at this assumption as a secondary objective.

If we assume the true change in TIR (before first dose of IDeg minus after first dose of IDeg) to be 0% for the bridging group and 15% for the non-bridging group, and if we assume a common standard deviation of 15% (meaning the distributions of change in TIR are separated by 1 standard-deviation unit), then 20 patients in each group will provide 87% power to observe a statistically significant (at the two-sided level of .05) difference in mean change of TIR.

As noted above, we'll assess the magnitude of this difference as a function of once- vs. twice-daily glargine use. With only 40 patients, it's highly unlikely that a statistically significant interaction will be observed, but if the directions of the difference in mean changes are the same in the once-daily vs. twice-daily groups we shall consider the results to be consistent with each other.

Secondary endpoints to be assessed in a descriptive manner include the following:

1. Coefficient of variation of TIR for each treatment within each group
2. Nocturnal time in range of 70-180 mg/dL (nTIR; both values included) (between mid-night and 0600 hours)
3. Percent time above 180 mg/dL (TAR-1), percent time above 250 mg/dL (TAR-2) for each treatment within each group
4. Percent time below 70 mg/dL (TBR-1), percent time below 54 mg/dL (TBR-2) for each treatment within each group
5. Number of correction boluses for each treatment within each group

The overarching goal of this pilot study is to collect data in a controlled setting on a variety of long-acting insulin regimens and gain an idea if there is a signal. The data generated in this pilot study will be used to assist in the design of a future and larger study where a more definitive comparison of efficacy will be conducted.

5. DATA HANDLING AND RECORD KEEPING:

Study information will be collected for each participant by research staff using standardized Case xReport Forms (CRFs). CRFs will not report information about

658 treatment assignment in order to maintain blinding of treatment allocation. Forms will be 659 stored at a secure location at the clinical site. We expect that the majority of data will be 660 collected via CRFs; however, other data sources, such as CGM download and laboratory 661 data, may be used. All study data will be entered into the Research Electronic Data 662 Capture (REDCap), a web-based data entry and management system that is HIPPA 663 compliant and powered by the Institute of Translational Health Sciences, by research 664 staff. The clinical data management procedures will be consistent with the International 665 Conference on Harmonisation (ICH E6) standards for Good Clinical Practice (GCPs)[1].
666
667

668 6. ETHICS:

669 Ethical considerations related to the trial include ensuring that all patients receive an 670 amount of insulin deemed appropriate by the clinicians for treatment of their diabetes 671 mellitus both during the study period and following the conclusion of the study. Patients 672 should have prompt treatment for both hypoglycaemia and hyperglycemia with blood 673 glucose level of > 250mg/dl, as well as other possible complications related to treatment 674 with insulin, according to the standard of care following the guidance of their clinicians. 675 Potential participants will be sought from among the patients attending the study center, 676 University of Washington's Diabetes Care Center in Seattle, WA. An application will be 677 submitted for approval by University of Washington's IRB prior to conducting the 678 research study. Potential candidates will be identified and contacted according to the 679 procedures established by University of Washington's IRB in compliance with local laws 680 protecting patient confidentiality and in accordance with the Declaration of Helsinki and 681 the ICH GCP guidelines[1]. Patients meeting the inclusion and exclusion criteria of the 682 study will be identified by clinicians at the study center and offered the opportunity to 683 participate in the study. An informed consent form will be given to all patients meeting 684 the inclusion and exclusion criteria. This informed consent form will clearly offer the 685 possibility to opt out of any further contacts with the study. Written consent will be 686 obtained from all subjects invited to participate in the study after explaining again the 687 purpose and procedures of the study. In the initial contact and at the time of the 688 screening visit, study subjects will be encouraged to ask questions and they will be 689 reassured that they may withdraw from the study at any time. Clinician investigators and 690 Novo Nordisk, will comply with all applicable regulatory and legal requirements, ICH 691 GCP guidelines and the Declaration of Helsinki in obtaining and documenting the 692 informed consent[1].
693
694

695 7. STUDY SCHEDULE:

696 The study will begin recruitment of patients immediately following the approval of 697 University of Washington's IRB. We plan to recruit patients over a 12-month period. 698 Following the completion of patient recruitment and data collection, we plan to perform 699 data analysis and complete the integrated final study report over a 4-month period.
700

7.1 Study Schedule

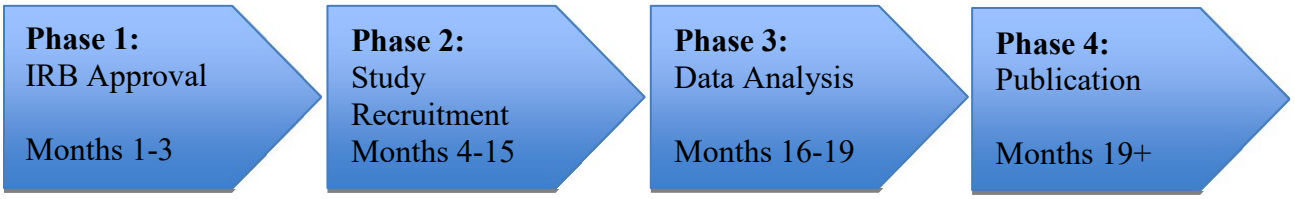
Event	Screening Visit	Observation on Glargine		Treatment with IDeg			Follow-Up
	Up to 2 weeks	Day 0	Day 1	Day 3	Day 4[a]	Day 7 ± 2[a]	Day 14 ± 2[a]
Informed consent/ HIPPA	x						
History/focused exam	x						
Weight and vital signs	x						
Documentation of insulin doses	x	x	x	x	x	x	
Documentation of concurrent medications	x	x	x	x	x	x	
Inquiry of adverse events		x	x	x	x	x	x
Download of data from home glucose meter and/or CGM[b]	x						
Labs	x						
Eligibility	x						
Randomization	x[c]						
Study Drug Dispensation				x			
Placement of study CGM		x					
Daily Insulin logbook and hypoglycemia episode form dispensation		x					
Telephone Encounter			x	x	x		x
Collection of data from study CGM Upload				x			
Study Drug Administration				x	x	x	
Study Logbook/Hypoglycemia form Collection						x	
Download data from study CGM						x[d]	

a. Day 4, 7, and 14 may be extended by 2 days if patients do not have ≥ 38 hours of usable study CGM data. See Section 3.11.4.

b. Download of data from patients' CGM will be performed if patients wear their own CGM prior to participating in the study.

c. Randomization will be performed at the end of the screening visit after patients complete informed consent and have been deemed eligible to participate in the study.
d. Downloaded data include all endpoints listed under Section 3.2.

7.2 Study Milestones



8. STUDY DRUGS AND MATERIALS:

8.1 Study medication(s) / devices(s)

- Insulin glargine, 100 units per mL injected subcutaneously daily, dosage as determined by the clinician and study protocol. Manufacturer: Sanofi or Lilly
- IDeg, 100 units per mL injected subcutaneously daily, dosage as determined by the clinician and study protocol. Manufacturer: Novo Nordisk.
- Placebo, 9g/L sodium chloride (normal saline) injected subcutaneously daily, dosage as determined by the clinician and study protocol.
- Pen needles for injecting insulins.
- Dexcom G6 Mobile CGM System, inserted subcutaneously and worn for 3-10 days. Manufacturer: Dexcom, Inc.
- Glucose meter and 100 test strips, to perform self-monitoring of blood glucose, one box dispensed per patient. Source: Diabetes Care Center. Manufacturer: Accucheck Aviva Plus

8.2 Packaging and Labelling of Study Medication(s)

- IDS will package the glargine and placebo as pre-filled syringed from vials identically. IDS will then label the syringes with dose, dosing instructions, and 2 patient identifiers based on study drug request order entered by research staff, after being notified about treatment assignment by IDS.
- IDeg will be dispensed in the original manufacturer's packaging, and IDS will label IDeg with dose, dosing instructions, and 2 patient identifiers.
- Dexcom G6 Mobile CGM System will be distributed to patients in its original manufacturer packaging.

Labelling of all medications and device will be in accordance with local law and study requirements.

8.3 Storage and Drug Accountability of Study Medication(s)

All investigational and/or trial products received will be accounted for by the IDS. Accountability logs are maintained for each product and dispensing is logged out as individual line items. Other than syringes and needles, subjects will return used, partly used, and unused products, and these will be documented on the accountability logs and may be retained for reconciliation.

All products will be stored at the designated temperature (e.g. refrigerated or room temperature) with temperature monitoring by the institutional system, TempTrak. This is a continuous monitoring system with temperature time points taken every 15 minutes. Temperature graphs are accessible via a web-based system. TempTrak sensors are calibrated on a yearly basis. A second overlay is the use of Min/Max thermometers with manual recording of temperature daily on Mon - Fri. All Min/Max thermometers have a calibration certificate and are replaced prior to the expiration date.

Destruction of trial products are by incineration at an EPA approved site as contracted by the University of Washington Medical Center, currently by Clean Harbors Environmental Services. If preferred, trial products can be shipped back to the Novo Nordisk. Destruction of returns can be performed on an on-going basis. At study closure, all trial products are accounted for and any unused remaining inventory can be destroyed or shipped back to Novo Nordisk.

At the time of study drug prescription and dispensing, research staff will provide patients with instructions to store the study drug at room temperature (below 86ºF), keeping the study drug away from direct heat and light. Research staff will verify the conditions for storage with patients on day 7±2 of study intervention period. However, research staff will not specifically require patients to measure or record the storage temperature of the study drug because of the short duration of the study intervention period, making it extremely unlikely for the study drug to be compromised as long as patients properly follow the storage instructions. There will be no trial medication(s) dispensed to any person not enrolled in the study. IDS will store unused study drug separately from used study drugs in the refrigerator at 36°F to 46°F (2°C to 8°C) until the drug's expiration date. Patients will be instructed to return used/unused study drug, and University of Washington's IDS will destroy the returned study drug per its standard protocol outlined above.

8.4 Auxiliary Supply

There is no additional item or equipment needed other than the ones listed under the section of Study medication(s) / devices(s). Patients may continue to use the following medications and devices during the study period:

- A rapid-acting insulin analogue that patients normally take following the instructions of their clinicians, administered using either insulin pens or vials and syringes
- Glucagon emergency kit, inject 1 mg/mL subcutaneously or intramuscularly as needed for treatment of severe hypoglycemia

- Home glucose meters
- Home continuous glucose monitors

8.5 Randomization and Blinding

We will perform a randomized, placebo-controlled intervention study to minimise bias. Study participants will be randomized in a 1:1 ratio to one of two arms within 2 stratified groups groups (see Section 3.3). After a participant has been randomized, a study drug request will be sent to IDS to dispense the study drug. In keeping with the blinded procedure, the patient and research staff will not be aware of treatment assignment. The study drug request sent to IDS will reflect only the dose of bridging insulin they should receive. IDS with then dispense a prefilled syringe of either insulin glargine or matched placebo to reflect this dose, directly to the research participant on the day it needs to be administered. Participants will then administer the study drug at home according to the instructions provided to them by their clinician investigators and/or research staff according to their randomized assignment and the dosing described under Section 3.11.2.1.

8.6 Breaking of Blinded Codes

Breaking of the blinded code will not be applicable, as medical emergencies that may possibly associated with treatment with insulin will be no different between the control and the study groups. However, breaking the blinded code may be done if demanded by the patient. Whenever a code is broken, the person breaking the code must record the time, date and reason, as well as his/her initials in the source documents. All codes must be kept throughout the study period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure.

9. CONCOMITANT ILLNESSES AND MEDICATIONS:

9.1 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 and run-in periods.

Details of all concomitant illnesses and medication must be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication must be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, Novo Nordisk must be informed.

The information collected for each concomitant medication includes, at a minimum, start date, stop date or continuing, and indication.

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

10. ADVERSE EVENTS:

10.1 Definitions

The FDA approved version of the Prescribing Information or update thereof will be used for assessment of expectedness.

10.1.1 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

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).

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 hospitalisation 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.

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.

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.

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

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

10.2 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

10.3 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

10.4 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

10.5 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an adverse event will be collected and reported from the first study-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.

We intend to comply with all local legal, regulatory, and IRB requirements.

All AEs will be reported on the Adverse Events form that will be completed by the study staff, who are masked as to study treatment assignment, at each regular follow-up visits.

This will ensure that AEs are ascertained in an unbiased manner using the same standardized methodology for patients in both treatment arms. Forms will include standardized questions relating to specific events of import in diabetic patients on either of the study treatment arms, as well as any significantly abnormal physical findings identified on examination and any significantly abnormal laboratory results obtained on the patient between visits or at the time of the visit. AEs reported or ascertained between clinic visits will be captured and reported at the time of the next scheduled visit. Pre-existing conditions (that is, any condition that was known to be present prior to the signing of informed consent or was identified during the screening procedures) will not be considered or recorded as AEs unless the condition worsens in intensity or frequency after the initiation of study intervention. Likewise, continuing AEs will not be reported as AEs at subsequent visits unless they increase in severity or frequency between visits, they result in criteria for a SAE, and/or they resolve between visits. The investigators will report all adverse events including SAEs, SUSARs, serious adverse drug reactions (SADRs) to the competent authority and independent ethics committee/IRB based upon federal regulations and local/IRB policies. The investigators will also report all SAEs, SUSARs, and SADRs to Novo Nordisk at the same time such events are reported to regulatory authorities or within 15 days from the investigators becoming aware of such adverse events, whichever comes first.

The investigators will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification (e.g. initials, sex, age)
3. Event (preferably a diagnosis)
4. Drug
5. Reporter identification (e.g. Name, or initials)

Also 6) Causality, and 7) Outcome

10.6 Follow-up of Adverse Events

During and following a subject's participation in a clinical trial, the investigators 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. This 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.

10.7 Pregnancy

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

The investigators will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by investigators 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.

10.8 Precautions/Over-dosage

All patients enrolled in the study will have access to and be instructed to wear a CGM from day 0 until the completion of study intervention. Patients may continue to wear the CGM as part of the standard of care for their diabetes beyond the study period. Use of a CGM has been shown to be effective in preventing hypoglycemia, which is a possible complication related to overdose of insulin, as well as morbidities and mortality related to hypoglycaemia (11). Clinician investigators and/or research staff will also provide patients with instructions on prompt recognition and proper treatment of hypoglycemia and prescribe patients with glucagon kit to be used for treatment of hypoglycemia as needed. Patients will have access to medical providers at the DCC by phone or e-care communication if additional guidance is needed in the event of overdose by the study drug during the study.

11. LIABILITY AND SUBJECT INSURANCE:

During and following a subject's participation in the clinical trial, the investigators and their 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. This medical care for study subjects will be provided regardless of their insurance status.

The investigators will be responsible for the conduct of the study and agree to defend, indemnify, and hold harmless Novo Nordisk, any of its parent companies, affiliates, or subsidiaries, and their respective officers, directors, employees, agents, representatives, distributors, salespersons, customers, licensees, and end-users from and against any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from or related to: (a) any breach of Novo Nordisk-investigators' obligations or representations; or (b) Novo Nordisk-investigators' negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived therefrom. This

indemnification shall not apply in the event and to the extent that a court of competent jurisdiction or a duly appointed arbiter determines that such losses or liability arose as a result of Novo Nordisk's gross negligence, intentional misconduct, or material breach of its responsibilities.

12. EVALUABILITY OF SUBJECTS:

For all analyses, patients not meeting the compliance criteria of the study listed under Section 3.13 will not be included in the analyses. Clinician investigators will determine patients' compliance with study drug based on patient's recorded log and patients' time spent wearing CGM after CGM data has been downloaded at the follow-up visit. We will include data from all randomized participants in our data analysis. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by the clinician investigators or staff prior to database release. The documentation will be stored together with the remaining trial documentation.

PK and/or PD Modelling

PK and PD modelling is not planned for this study.

13. PREMATURE TERMINATION OF STUDY:

All patients participating in the study will have already been taking insulin glargine prior to their enrolment in the study. Therefore, we do not anticipate patients developing any unforeseen adverse effect associated with the administration of insulin glargine. Similarly, we do not anticipate patients developing any unforeseen adverse effect associated with the administration of the placebo (normal saline).

IDeg will be discontinued if a patient:

- Experiences an SAE related to IDeg (with the exception of hypo- or hyperglycemia) or an intolerable AE, such as a persistent allergy or rash.
- Becomes pregnant or breastfeeding
- Withdraws consent for participation in the study

Date and reason for drug discontinuation will be recorded on the relevant Case Report Form. Refer to Section 3.7 for Withdrawal Criteria. All study discontinuations decided by the clinician investigators will be reviewed by University of Washington's IRB. Patients discontinued from the study will be placed back on their original home insulin regimen and asked to follow up with their outpatient endocrinologists within 2-12 weeks, or at an interval deemed appropriate by their outpatient endocrinologists. Major attempts will be made to schedule an end-of-study follow-up phone call for all patients who are lost to follow-up during the course of the study.

Patients who discontinue study drug or withdraw consent from the study prior to completion of data collection will not be replaced.

14. PUBLICATION PLAN:

Data and results generated from the study will be published or publicly presented at national and/or regional meetings in the form of abstracts, posters, and/or oral presentations. Clinician investigators will make good faith effort to publish data and results of this study in a peer reviewed scientific journal. The clinician investigators intend to register the study with clinicaltrials.gov.

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APPENDIX A: Sample Subject Daily Insulin Logbook, version-1.0

Trial ID: U1111-1214-3257
Subject No. XX Subject Initials: ABC Subject DOB: MMDDYY

Date: MMDDYY Study Day: #

Time point	Time (hh:mm)	BG value (mg/dL)	Carbohydrates consumed (grams)	Bolus insulin dose NUTRITIONAL (units)	Bolus insulin dose CORRECTION (units)	Basal insulin dose (units)
Before breakfast						
Before lunch						
Before dinner						
At bedtime						
*Extra time point #1						
*Extra time point #2						
*Extra time point #3						

* To be used only if needed. NOTE: please use these fields to enter any snacks consumed as well.

Did you exercise today? [ ] yes or [ ] no
If yes, then please specify when and how long: from_____to_____(hh:mm)

APPENDIX B: Sample Subject Hypoglycemia Episode Form, version 1.0
(see Section 3.12 for details on directions to fill out this form)

Trial ID: U1111-1214-3257
Subject No. XX Subject Initials: ABC Subject DOB: MMDDYY

Date: MMDDYY Study Day: #

1. When did the low BG start?_____(hh:mm)
2. What was the lowest BG value during the episode?_____(mg/dL)
3. Did you experience any of the following symptoms with this low BG?
   [ ] No or [ ] Yes (check all that apply)
   - [ ] Sweating
   - [ ]Trembling
   - [ ] Feeling hungry
   - [ ] Rapid or irregular heartbeat
   - [ ]Feeling confused
   - [ ]Feeling drowsy
   - [ ]Speech difficulty
   - [ ]Visual disturbances
   - [ ]Odd behavior
   - [ ]Impaired balance
   - [ ]Reduced coordination of movements
   - [ ]Headache
   - [ ]Feeling discomfort or unease
   - [ ]Seizure
   - [ ]Loss of consciousness
   - [ ]Other
4. Were you able to manage it by yourself? [ ] yes or [ ] no. If no, please fill out Q9-12 as well. If yes, please skip Q9-12.
5. How did you treat the low BG? _____
6. When did the low BG resolve?_____(hh:mm)
7. Did this episode happen in relation to physical activity? [ ]Yes or [ ]No
   If yes, then what were you doing? _____
8. Were you asleep when the low blood glucose happened? [ ]Yes or [ ]No
9. Who assisted in treatment of the episode? _____
10. Where was the treatment administered? _____
11. What treatment was provided to treat the episode? _____
12. Were your symptoms alleviated by this treatment? [ ]Yes or [ ] No