BIG LEAP: A comparison of insulin degludec to continuous subcutaneous infusion of insulin aspart for basal insulin delivery in type 1 diabetes

Protocol Number: MDEC2018

INVESTIGATOR INITIATED STUDY PROPOSAL

Universal Trial Number: U1111-1199-8692

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BACKGROUND AND SIGNIFICANCE

Physiologic insulin replacement for the treatment of type 1 diabetes, or intensive insulin therapy, is administered either by multiple daily injections (MDI) of insulin or via continuous subcutaneous insulin infusion (CSII) via insulin pump. Since its inception in the 1970's, CSII has improved continuously in terms of both the devices and the rapid acting insulin analogues they deliver so that today's insulin pumps are considered the "gold standard" of intensive insulin therapy. However, CSII has only shown advantages over MDI regimens which used older basal insulin products including intermediate-acting insulin (NPH) and first generation insulin analogues (glargine and detemir) including reducing the incidence of hypoglycemia, improving overall glycemic control and improving glycemic variability (1,2). CSII also has advantages in terms of patient convenience and comfort by eliminating the need for multiple daily insulin injections, portability of insulin, and the use of computerized bolus calculators to assist with bolus calculations. However, patients treated with CSII continue to show significant glycemic variability owing to different absorption characteristics of insulin infused subcutaneously at different body sites and due to the inherent variability of absorption of rapid-acting insulin analogues even when infused continuously in sub-unit quantities for basal insulin delivery by modern insulin pumps.

Insulin degludec is a new ultralong-acting insulin analogue with a unique mechanism of protraction giving it a flat, peakless pharmacodynamic profile with a coefficient of variation of the glucose infusion rate of approximately 25% that of insulin glargine in glucose clamp studies

and a half-life of 25 hours (3). Insulin degludec has also been shown to have a reduced incidence of hypoglycemia compared to insulin glargine in a head-to head clinical trial in patients with type 1 diabetes. (4). Whether insulin degludec might provide equivalent basal insulin coverage with a flatter 24 hour glycemic profile compared to CSII using a rapid-acting insulin analogue is currently not known as these have not been compared in a clinical trial. Part of the reason for this is because patients using CSII use a pump for both the basal and bolus component of their insulin regimen; currently, no "bolus only" insulin delivery device exists. Also, there was no compelling reason until now to study a hybrid model for basal/bolus insulin regimens since there was no true 24 hour basal insulin product which had any therapeutic advantage over basal insulin delivered by CSII. Furthermore, it is now recognized that the use of insulin infusion sets of various design in CSII lead to increased glucose variability by virtue of local inflammation and micro-occlusions of the sets, which interfere with consistent insulin basal delivery (5). Insulin degludec, however, appears in clinical use to possibly have a flatter glycemic profile than CSII can provide, with equivalent or even lower glycemic variability and less hypoglycemia. If so, patients with type 1 diabetes may achieve better overall glycemic control with, and therefore prefer, a daily injection of insulin degludec for their basal insulin needs in combination with their pump (with its bolus calculator) for their bolus insulin needs.

The purpose of this investigator-initiated trial is to compare the effect of a daily injection of insulin degludec vs. basal insulin delivery via CSII, both in combination with bolus insulin delivery via the patient's usual insulin pump with insulin aspart, on glycemic variability, overall blood glucose control and incidence of hypoglycemia, all assessed by continuous glucose monitor (CGM), as well as patient satisfaction, in patients with type 1 diabetes currently using CSII.

SPECIFIC OBJECTIVES

The primary objective of this trial is to determine whether insulin degludec will provide an equally stable and consistent basal glycemic profile with lower glycemic variability as determined by CGM compared to insulin aspart delivered by CSII in patients with type 1 diabetes experienced in use of insulin pump therapy. Specifically, this study will determine if the percent time in the target glycemic range (70 to 180 mg/dl) by CGM is superior using insulin degludec than continuously infused insulin aspart, and if degludec is associated with lower GV as assessed by the standard deviation (SD) of the mean daily glucose by CGM. Particular attention will be given to the nocturnal glucose profile (from midnight to 6 am) which most closely reflects basal insulin action as it is typically the time of day least affected by bolus insulin, food intake or exercise. Quality of life questionnaires regarding treatment preference will be used to capture patient preference for method of basal insulin delivery.

RESEARCH DESIGN AND METHODS

Study hypothesis

It is anticipated, based on the low glycemic variability of insulin degludec shown in glucose clamp studies and seen in clinical practice, that insulin degludec will provide more stable 24 hour basal insulin action than insulin aspart by CSII in patients with type 1 diabetes.

OUTCOME MEASURES/SPECIFIC ENDPOINTS

Primary endpoint

Percent time in euglycemia (BG 70 to 180 mg/dl) by CGM during the final 14 days of each treatment period during steady state (with basal insulin delivery as either one daily injection of insulin degludec or as insulin aspart via CSII).

Key secondary endpoints

1. SD of interstitial fluid glucose by CGM for 2 week period during each basal insulin delivery method. (Note: because the Dexcom Platinum G5 CGM is currently only FDA approved for 7 days of use, two contiguous CGM periods using 2 sensors, each for 7 days, will be performed to capture 2 weeks of continuous CGM data.) Dexcom G6 is approved by FDA for 10 days of use so 2 sensors will be used during the CGM periods.
2. SD of blood glucose by CGM during the nocturnal period (midnight to 6 am) during each basal insulin delivery method

Other secondary endpoints

1. Percent time in hypoglycemia by CGM, captured at 2 levels of hypoglycemia: BG $\leq$ 54 mg/dl (level 2) and BG 55-69 mg/dl (level 1), for each basal insulin treatment.
2. Percent time in normoglycemia (BG 70 to 140 mg/dl) by CGM during each basal treatment period.
3. Time to recovery from level 2 hypoglycemia (BG >70 with resolution of symptoms) on each treatment. If a second event (BG $\leq$ 70 mg/dl) occurs within 60 minutes of a previous hypoglycemic event, this will be considered part of the same hypoglycemic episode.
4. Patient satisfaction by TRIM-D and TRIM-DD questionnaires with each basal insulin treatment.
5. HbA1c after 20 weeks of each basal insulin treatment.
6. Total daily insulin dose, total basal insulin dose, and total bolus insulin dose on each treatment.

See Table 1: Study Visit Table for study procedures at each visit and when specific endpoints will be measured.

STUDY TYPE

This will be a randomized, cross-over, open label, single-center study consisting of a 20 week period on each of two basal insulin delivery methods, both in combination with insulin aspart with boluses taken by insulin pump. Each 20 week period will consist of a 4 week insulin optimization period for titration of basal and bolus insulin doses, followed by a 16 week maintenance period. The final 2 weeks of the maintenance period during each treatment arm will be used for endpoint data collection. The treatment sequence will occur in random order. The study population will include patients with type 1 diabetes with good baseline glycemic control who are experienced in the use of both CSII and CGM; the cross-over design allows each subject to serve as his or her own control.

STUDY POPULATION

In order to confirm a 10% improvement in the time spent in euglycemia by CGM with 85% power, 47 subjects will be studied. Thus, between 55 and 60 subjects will be screened to allow for a 10% drop-out rate. (See "Statistical Analysis Plan" for sample size calculation.)

INCLUSION CRITERIA

1. Male and female patients > 18 years of age with type 1 diabetes using CSII with any pump for > 12 months.
2. Females must be using adequate contraception, defined as oral contraceptive pill, barrier method of contraception, or surgical method (tubal ligation or hysterectomy).
3. Good glycemic control (HbA1c $\leq$ 8.0%).
4. Patients are experienced in carbohydrate counting, evidenced by pump downloads showing frequent meal boluses with realistic carbohydrate entries, few over-rides of the pump bolus calculator, few to no omitted boluses (at least 3 boluses per day), and post-meal glucose levels generally below 200 mg/dl indicating accurate carbohydrate assessment.
5. Patients are regular ($\geq$85% of time) users of the Dexcom G5 or G6 CGM.
6. Pump download confirms correct use of insulin pump features, including appropriate use of bolus calculator with minimal overrides, entering carbohydrate content of meals, at least 3 boluses taken per day, appropriate use of correction boluses, and infusion set changes every 2 to 3 days.
7. No serious comorbidities including: retinopathy requiring active intervention, eGFR < 30, CV event within the previous 6 months, active malignancy with ongoing treatment, any condition requiring chronic use of systemic glucocorticoids, or any other condition which in the opinion of the investigator would interfere with the subject's ability to comply with the study protocol or acutely affect insulin requirements.
8. Able to comply with study protocol.
9. Ability to provide written informed consent prior to any study-related procedures.

EXCLUSION CRITERIA

1. Subjects with type 2 diabetes.
2. Subjects with HbA1c > 8.0%

3. Subjects not using CSII and CGM (ie, on MDI)
4. Subjects inexperienced in the use of CSII, or whose pump download shows poor utilization of bolus calculator features, ie fewer than 2 boluses per day, lack of correction boluses, frequent overrides of the recommended boluses, unrealistic carbohydrate entries (suggestive of under-bolusing), not changing infusion set at least every 3 days, or other evidence of poor insulin pump usage.
5. Subjects inexperienced in or not regular users (>85% of time) of Dexcom G5 or G6 CGM
6. Subjects who are using a Medtronic pump with low blood glucose suspend who are unwilling to use the Dexcom CGM or to disengage the low blood glucose suspend feature of the pump.
7. Use of any other CGM than Dexcom G5 or G6.
8. Serious concomitant illness.
9. Females unwilling to use adequate contraception, intending to become pregnant, or breastfeeding.
10. Known or suspected allergy to study products, their excipients or related products.
11. Previous participation in this trial. Note: subjects who screen fail because of A1c may rescreen once if, in the opinion of the investigator, the HbA1c was explainable (ie, recent steroid injection or illness, etc) and atypical for the subject.
12. Hypoglycemic unawareness.
13. Episode of severe hypoglycemia (requiring assistance for treatment) within the previous 90 days.

WITHDRAWAL CRITERIA

Subjects may withdraw at will for any reason.
Females who become pregnant will be discontinued from the study.
Subjects who do not comply with CGM use or switch from use of CSII to MDI will be discontinued.

Subjects who are discontinued from the study will not be replaced.

RATIONALE FOR THE STUDY POPULATION

A population of well controlled patients with type 1 diabetes who are experienced in the use of both CSII and CGM was chosen in order to assess the effect of the change in glycemic profile using two different methods of basal insulin delivery. Studying a population with expertise in diabetes self-management with these devices will minimize the effect of incorrect device use and allow assessment of the effect of the change of insulin regimen itself. Allowing the subjects to use their insulin pumps for bolus insulin delivery, as they are accustomed, will minimize the chances of skipping meal boluses and correction doses.

Replacing basal insulin delivery by CSII with a single daily injection of degludec will add minimal, if any, treatment burden which will be offset by potential therapeutic benefits. These benefits include the potential for reduced glycemic variability and the elimination of the risk of

hyperglycemia and DKA with basal insulin interruption which can occur with infusion set occlusion or dislodgement inherent to CSII. Subjects may also enjoy the freedom afforded by a basal insulin injection which will allow them to disconnect from their pumps safely without sacrificing glycemic control for prolonged periods of time (which is not an option using CSII for basal insulin delivery).

VISIT PROCEDURES

Please see pages 16-18 for "Visit Procedures", which describes a detailed list of procedures and assessments at each visit, and page 19 for the "Study Flow Sheet", which summarizes study-related procedures at each visit in spreadsheet format.

ASSESSMENTS OF EFFICACY

Primary endpoint

Percent time spent in euglycemia by CGM: data will be downloaded from the Dexcom G5 or G6 (either by download of receiver or from Dexcom Clarity cloud-based application); this will yield the percent time in euglycemia, hyperglycemia, hypoglycemia and SD for endpoint analyses.

Other endpoints

1. HbA1c: This will be measured by central laboratory (LabCorp, Burlington, NC). 2. GlycoMark (1,5 anhydroglucitol) will be measured by commercial assay (LabCorp, Burlington, NC). All laboratory specimens will be drawn and processed by site staff and shipped under required conditions to LabCorp by courier with pick-up daily. GlycoMark is a marker of glycemic variability which essentially reflects postprandial glucose control. It will be captured as a safety measure to ensure that change of method of basal insulin delivery does not impact postprandial glucose control in any way, since patients using CSII may on occasion have increased postmeal basal insulin infusion rates (to compensate for inadequate mealtime insulin dosing) which cannot be reproduced in the degludec treatment arm.

ASSESSMENTS OF SAFETY:

Hypoglycemia will be captured by fingerstick BG and by CGM. All episodes of severe hypoglycemia (requiring assistance) will be documented and reported as AE's in diaries. Categories of hypoglycemia that will be captured include: percent time in two categories of hypoglycemia (BG < 54 mg dl and 55-69 mg/dl) by CGM, episodes of symptomatic BG-confirmed hypoglycemia (<54 mg/dl), nocturnal hypoglycemia and severe hypoglycemia. In the event where the SMBG and the CGM readings are discordant, the SMBG will be considered the primary source.

Time to recovery from hypoglycemia, defined as BG $\geq$ 70 with resolution of symptoms, during each treatment will also be captured.

OTHER ASSESSMENTS

Patient satisfaction with each study treatment will be assessed by TRIM-D and TRIM-DD questionnaires.

ASSESSMENT OF SUBJECT COMPLIANCE

Compliance of study subjects with use of CSII and CGM will be assessed by review of device downloads which capture percent time devices are used, set changes, boluses and carbohydrate intake. Since subjects will be using their insulin pumps to bolus, all bolus insulin doses and carbohydrate intake will be captured in both treatment arms by review of insulin pump downloads at each study visit.

Compliance with administration of basal insulin during the degludec treatment arm will be assessed by documentation of insulin doses and times in subject diaries. Number of missed injections will be captured during the degludec treatment arm; number of infusion set changes, set occlusions, and missed boluses will be captured during both treatment arms.

STATISTICAL CONSIDERATIONS

Sample Size Determination

The subjects in a recent study (4) should closely reflect the population we are going to study. Using the statistics from that source as an estimate of population parameters, power analyses were done for: (1) percent time in euglycemia (BG 70 to 180 mg/dl), desired effect size 0.4, (2) SD of BG by CGM, desired effect size 0.44, and (3) HbA1c, desired effect size 0.44. The repeated independent variable is degludec vs CSII. These a priori analyses – using G*Power, version 3.1.9.2 http://www.gpower.hhu.de/en.html – assumed a Type I error of .05 and a power of .85 (Type II error of .15).

The sample size estimate required for percent time in euglycemia was the largest at n = 47. Allowing for a 10% dropout rate a final sample size of 53 will be sought – more if possible.

Statistical Methods

Ho: For Type 1 DM subjects using degludec vs CSII, there is no difference between mean percent time in euglycemia, mean SD of BG by CGM, or mean HbA1c.

Ha: For Type 1 DM patients using degludec vs CSII, there will be mean differences between percent time in euglycemia, SD of BG by CGM, and HbA1c. (No one tailed tests are planned.)

Dependent Variable

One group of patients will first use degludec for 20 weeks then switch to CSII for 20 weeks. As all eligible patients who sign the IRB consent form are identified, a random number will be

generated to determine the treatment with which they begin first. The other group of patients will start with CSII and after 20 weeks switch to Tresiba for 20 weeks. Randomization sequence will be determined by computerized randomization program. All patients will receive both treatments unless they drop out. Dropouts are unlikely since the participants are all regular continuing patients of the site's clinical practice.

Since each patient will be measured twice - insulin degludec vs CSII by pump – this repeated measure will be the dependent variable.

Since study participants are all ongoing patients of the three physicians at the site, there should be no missing data, per-protocol, or intention-to-treat issues. Only patients who complete the entire 46-week study will be used in the final analysis.

No continuous or ratio variables will be categorized.

No interim analysis will be performed.

Control/covariate variables

These will be recorded at the beginning of the study to help reduce error variance in the dependent measures:
1) Time elapsed since diagnosis of Type 1 DM (ratio variable)
2) Age (ratio variable)
3) Physician attending each patient – there are 3 physicians (nominal).
4) Whether each patient started with CSII by pump or insulin degludec (nominal)
5) Race of patient (if there is any variability; unlikely) (nominal).

Statistical Analysis

Statistical analyses will be performed using STATA version 15.0, revision 25, released September 2017. (www.stata.com)

Since all the dependent variables are interval and the independent and control/covariate variables are a mixture of ratio and nominal, a General Linear Model for Repeated Measures analysis can be used. Depending on the final sample sizes a hierarchical stepwise analysis could be performed to identify the more useful control/covariate variables.

DATA HANDLING AND RECORD KEEPING

The study data (CGM data and laboratory endpoints including HbA1c and GlycoMark) will be uploaded and stored in the cloud in HIPAA-compliant electronic files. Pertinent data for endpoint safety and efficacy analyses will be entered into and electronically filed in password-protected Excel spreadsheets. Hypoglycemia diaries will be on paper and stored as source documents along with paper CRF's capturing study-related procedures (history, physical exam,

vital signs, con meds, AE's) at each visit. Patients will complete TRIM-D and TRIM-DD questionnaires, and responses will be tabulated into Excel spreadsheets for statistical analysis.

All paper source documents and CRFs will be stored on site. All electronic data will be stored in the cloud in HIPAA-compliant electronic files.

ETHICAL CONSIDERATIONS

The sponsor (Mountain Diabetes and Endocrine Center), its investigators and site staff will comply with all applicable regulatory and legal requirements, ICH GCP guidelines and the Declaration of Helsinki in obtaining and documenting the informed consent**.**

Informed consent will be obtained by a medically qualified site member (MD or RN) after each subject has had time to review the informed consent document and have any questions about the study answered. This is performed in a conference room at the study site in a private and unhurried fashion. The subjects may bring family members with them to witness the informed consent process. The informed consent documents will be paper documents that will be retained at the site, signed by the subject and investigator, and a copy will be provided to each subject.

Upon approval of the study protocol, the study will be submitted for approval to IntegReview IRB in Austin, Texas for review and approval. The informed consent document will include information about the IRB and contact information for the IRB, the site, and the study principal investigator.

The study will be conducted in accordance with ICH GCP guidelines and the Declaration of Helsinki.

STUDY SCHEDULE

Planned recruitment period: 6 to 9 months

Expected milestones: Start of study: immediately upon IRB approval (March 2018)

First patient first visit (FPFV): within 1 week of IRB approval (site is ready to begin recruitment with subjects available to start upon protocol and IRB approval and obtaining study insulin)

Last patient first visit (LPFV): within 6 to 9 months of FPFV

Last patient last visit: 46 weeks after LPFV

Estimated study duration (FPFV to LPLV): 14 months (March 2018 to May 2019)

Completion of final study report: within 6 weeks of study completion

Time to submission of study for publication: within 12 weeks of study completion

STUDY DRUGS AND MATERIALS

Study medication: insulin degludec (Tresiba) U100 or insulin degludec (Tresiba) U200 (Novo Nordisk) with insulin aspart (administered as bolus insulin via insulin pump) (Novolog, Novo Nordisk) for one treatment arm; insulin aspart (Novolog) administered by CSII for both basal and bolus insulin in second treatment arm.

Study Devices: subjects' own insulin pumps will include Medtronic (530, 730 models; no low blood glucose suspend models or closed loop pumps will be used), Animas Ping, Animas Vibe, Tandem T-slim and Insulet Omnipod.

The study CGM will be Dexcom G5 or G6.

PACKAGING AND LABELLING OF STUDY MEDICATION AND DEVICES

Study insulins (insulin degludec and aspart) will be distributed at study visits to each subject from the site. Insulin degludec will be supplied in injection pens (5 per box for U100 and 3 per box for U200). Insulin aspart will be supplied in vials (as bolus insulin will be administered via insulin pump.) Subjects will use their own insulin pumps and pump supplies during the study. Dexcom sensors will be supplied for a two week period (using one sensor weekly) at baseline and for the final two weeks of each treatment period. These will be distributed and placed at CGM dispensing/insertion site visits (see study visit flow sheet).

STORAGE AND DRUG ACCOUNTABILITY OF STUDY MEDICATION

Study insulins will be received in temperature-controlled containers and the temperature of the medication upon receipt will be recorded. Study insulins will be stored at the study site in refrigerators maintained between 2 and 8 degrees Celsius; the temperature will be monitored and recorded daily. No trial medication will be dispensed to any individual not enrolled in the study. All medication used in the study will be recorded in the CRF at each study dispensing visit. Subjects will be provided with sufficient study insulin for study completion.

Subjects will be instructed not to refrigerate opened insulin degludec (Tresiba U100 & U200) and to store the product at room temperature. Properly stored opened insulin degludec can be used for up to 8 weeks (7). Subjects may choose to refrigerate or not refrigerate an opened vial of insulin aspart (Novolog), maintaining the vial at a temperature of less than 86°F (30°C) for up to 4 weeks (8).

AUXILIARY SUPPLY

Study subjects will use their own insulin pumps and insulin pump supplies.

Dexcom glucose sensors (6 per subject) will be purchased by the site and supplied to subjects for two weeks at 3 times (baseline and for the final two weeks of each treatment period). Subjects will use their own CGM receiver devices which will be downloaded at appropriate study visits. Site will have back up receivers to supply to subjects in case of loss or malfunction of subject's own device (not likely). Subjects will use their own sensors for each treatment period except for the 3 two week periods of CGM data capture as described above.

RANDOMIZATION AND BLINDING

This is an unblinded study as the two basal insulin delivery methods (degludec via injection vs. aspart via CSII) cannot be blinded. For a description of the randomization and treatment allocation, please refer to the Statistical Methods section above.

CONCOMITANT ILLNESSES AND MEDICATIONS

Definitions:
Concomitant illness: any illness that is present at the start of the trial (at the first study 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 will be recorded at trial entry (at the first study visit). Any changes in concomitant medication will be recorded at each visit.
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.

ADVERSE EVENTS

Adverse events will be captured at each study visit and recorded on CRF's. Special AE and SAE reporting forms have been created to capture these events. SAE's will be reported within 24 hours of discovery to appropriate local and federal authorities as well as to the IRB when appropriate. The study site will comply with all local legal, regulatory, and IntegReview IRB requirements.

Mountain Diabetes and Endocrine Center, its investigators, and site staff will be responsible for reporting of all adverse events including serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs) and serious adverse drug reactions (SADRs) to the competent authority and independent ethics committee/institutional review board based upon federal regulations and local/IRB policies.

Mountain Diabetes and Endocrine Center, its investigators, and site staff will 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 site becoming aware of such adverse events, whichever comes first.

Mountain Diabetes and Endocrine Center, its investigators, and site staff will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification

3. Event (with appropriate diagnosis)
4. Drug
5. Reporter identification

Also 6) Causality, and 7) Outcome might be reported, if appropriate.

DEFINITIONS

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. This will also include any events related to the malfunction of a medical device (i.e. an insulin pump or Dexcom CGM). The following will 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 event that results in any of the following:

- Death
- A life-threatening* experience
- In-patient hospitalization 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 must always be considered an SAE.

*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.

Suspected Unexpected Serious Adverse Event (SUSAR):

Mountain Diabetes and Endocrine Center will inform the appropriate regulatory authorities, the IRB, and Novo Nordisk of trial product-related SUSARs in accordance with reporting requirements and GCP guidelines.

Serious Adverse Drug Reaction (SADR):
An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study drug and the occurrence of the event is suspected. The ADR will be classified as **serious** if it meets one or more of the seriousness criteria.

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 fulfill the definition of an SAE.

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

Relationship to study medication Assessment Definitions:

- Probable: Good reason and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial product

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 will be rated as an SAE
- Not recovered
- Fatal
- Unknown

Collection, Recording, Evaluating, and Reporting of Adverse Events

All events meeting the definition of an adverse event will be collected, reported, and evaluated from the first trial-related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol. All adverse events

resulting from incorrect storage or usage of study product as per product labelling, if applicable, will be reported to the appropriate institutions (7,8). The investigator will copy Novo Nordisk when expediting SAE information to health authorities and will report all SAEs related to Novo Nordisk products to the local Novo Nordisk affiliate safety department. SAE submission to Novo Nordisk will be within 15 days from the investigator's first awareness of the event.

Follow-up of Adverse Events

During and following a subject's participation in this clinical trial, Mountain Diabetes and Endocrine Center, its investigators and site staff, 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 will 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 will 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.

Pregnancy

Study subjects will be instructed to notify the site and study physician immediately if they become pregnant.

Mountain Diabetes and Endocrine Center, its investigators and site staff, will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by the site will occur within the same timelines described above for reporting of Adverse Events.

Pregnancy complications will 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.

Precautions/ Insulin Over-dosage

Study subjects will be prescribed glucagon kits and treatment of hypoglycemia will be reviewed with subjects upon enrolment into the study.

LIABILITY AND SUBJECT INSURANCE:

During and following a subject's participation in trial, Mountain Diabetes and Endocrine Center and the study physicians 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.

Mountain Diabetes and Endocrine Center and its 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 sponsor-investigator's obligations or representations; or (b) sponsor-investigator's 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.

EVALUABILITY OF SUBJECTS

Only the principal investigator has the authority to exclude any subjects or data observations after the initiation of the study, initial selection of subjects, and beginning of data collection. Possible reasons for such actions might be (1) questionable validity or reliability of data collection or measurement techniques for a particular subject, (2) misrepresentation of initial selection criteria by a subject, or (3) changes in the health conditions of subjects that might affect the reliability or validity of measurements or accuracy of data collection procedures. The reasons for any such action will be carefully documented by the principal investigator and kept on file for the actionable subject.

PREMATURE TERMINATION OF STUDY

The study will only be discontinued prematurely in the unlikely event of an unforeseen safety concern arising from the study protocol.

PUBLICATION PLAN

Upon approval, the study will be registered with www.clinicaltrials.gov.

Upon study completion, the study results will be submitted in a manuscript to a peer-reviewed journal. It is anticipated that the study results will be of sufficient interest and importance to be presented at one or more national meetings, notably ADA, AACE and AADE.

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APPENDIX: METHOD OF CONVERSION OF BASAL INSULIN BY CSII TO DEGLUDEC

Upon randomization to insulin degludec, or upon crossover from CSII to insulin degludec, the first dose of insulin degludec will be administered on day one and a 50% temporary basal reduction of the insulin pump for 24 hours will be activated. After 24 hours, the insulin pump basal rate will be lowered to the lowest hourly infusion rate (0.025 units per hour or 0.05 units per hour for a total daily basal insulin dose of either 0.6 or 1.2 units per day) for the duration of the insulin degludec treatment arm, with the remainder of the basal insulin dose administered as a single daily Tresiba injection.

The 24 hour basal insulin dose by CSII will be converted to degludec on a unit-for-unit basis. This is because both degludec and CSII are roughly equivalent methods with high efficiency (bioavailability) for delivery of a basal insulin dose. Although there are no head-to-head studies comparing basal insulin dose by CSII to degludec, clinical studies (and the experience of the investigator) suggest that the lowest basal insulin requirement for any given subject will be with either CSII or degludec compared to glargine, NPH or detemir.

A comparison of insulin degludec to continuous subcutaneous infusion of insulin aspart for basal insulin delivery in type 1 diabetes:

Visit Procedures

Note: Assessment of hypoglycemia and capturing of AE's (including technical complaints and device site reactions) will be performed at each study visit, as well as diabetes education.

Visit 1 (Screening Visit): Obtain written informed consent; review inclusion/exclusion criteria; demography (including child bearing potential and tobacco use); medical history; record concomitant medications; vital signs (incl. height); complete physical examination; review download of Dexcom and pump; HbA1c, GlycoMark, CBC, comprehensive metabolic profile (CMP), lipid panel, urine microalbumin/creatinine ratio (LabCorp); pregnancy test (urine); review treatment of hypoglycemia; insert Dexcom sensor; provide a hypoglycemia/basal dose diary

Phone Visit 2: Remind subject to insert new Dexcom sensor; assessment of infusion site reactions and occlusions; hypoglycemia assessment (insulin titration if required)

Visit 3 (Randomization): Review of inclusion/exclusion criteria; vital signs; CGM and insulin pump downloads; HbA1c (POC - Afinion); insulin optimization/titration; dispensing of hypoglycemia/basal dose diary; Tresiba pen teaching (degludec arm only); dispense trial product; treatment questionnaires

Visit 4: Vital signs; pump and CGM downloads; insulin optimization/titration; assessment of infusion site reactions and occlusions; dispensing of hypoglycemia/basal dose diary

Visit 5: Vital signs; pump and CGM downloads; insulin optimization/titration; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability and diabetes education.

Phone Visit 6: Ensure subject is changing insulin pump sites and CGM per protocol, assessment of infusion site reactions and occlusions; review of hypoglycemia (insulin titration if required)

Visit 7: Vital signs; pump and CGM downloads; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability

Phone Visit 8: Ensure subject is changing insulin pump sites and CGM per protocol, assessment of infusion site reactions and occlusions; review of hypoglycemia (insulin titration if required)

Visit 9: Vital signs; pump and CGM downloads; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability

Visit 10: Vital signs; pump and CGM downloads; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability

Visit 11: Dexcom sensor insertion; assessment of infusion site reactions and occlusions, review of hypoglycemia/basal dose diary

Visit 12 (Cross-over Visit): Vital signs; complete physical examination; pump and CGM downloads; insulin optimization/titration; treatment crossover; Tresiba pen training (degludec arm only); HbA1c, GlycoMark, CBC, comprehensive metabolic profile (CMP), urine microalbumin/creatinine ratio (LabCorp); pregnancy test (urine); dispense trial product; treatment questionnaires; dispensing of hypoglycemia/basal dose diary; assessment of infusion site reactions and occlusions; drug accountability

Visit 13: Vital signs; pump and CGM downloads; insulin optimization/titration; assessment of infusion site reactions and occlusions; dispensing of hypoglycemia/basal dose diary

Visit 14: Vital signs; pump and CGM downloads; insulin optimization/titration; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability

Phone Visit 15: Ensure subject is changing insulin pump sites and CGM per protocol, assessment of infusion site reactions and occlusions; review of hypoglycemia (insulin titration if required)

Visit 16: Vital signs; pump and CGM downloads; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability

Phone Visit 17: Ensure subject is changing insulin pump sites and CGM per protocol, assessment of infusion site reactions and occlusions; review of hypoglycemia (insulin titration if required)

Visit 18: Vital signs; pump and CGM downloads; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability

Visit 19: Vital signs; pump and CGM downloads; assessment of infusion site reactions and occlusions; dispense trial product; dispensing of hypoglycemia/basal dose diary; drug accountability

Visit 20: Dexcom sensor insertion; assessment of infusion site reactions and occlusions, review of hypoglycemia/basal dose diary

Visit 21 (End of study visit): Vital signs; complete physical examination; review download of Dexcom and pump; HbA1c, GlycoMark, CBC, comprehensive metabolic profile (CMP), lipid panel, urine microalbumin/creatinine ratio (LabCorp); pregnancy test (urine); review treatment of hypoglycemia; insulin optimization for post-trial treatment; assessment of infusion site reactions and occlusions; drug accountability; treatment questionnaires

Phone Visit 22 (Follow-up phone visit): Capture AE's; review of hypoglycemia

Trial Procedures	Screen-ing		Random-ization	Treatment Period 1 (First treatment group)									Treatment Period 2 (Second treatment group)								EOT	F/U
Visit (V), Phone (P)	V1	P2	V3	V4	V5	P6	V7	P8	V9	V10	V11	V12	V13	V14	P15	V16	P17	V18	V19	V20	V21	P22
Timing of Visit (Weeks)	-2	-1	0	2	4	6	8	10	12	16	18	20	22	24	26	28	30	32	36	38	40	44
Visit Window (Days)		± 2	± 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 2	± 3	+ 3
Informed Consent	X																					
In/Exclusion Criteria	X		X																			
Demography & Tobacco Use	X																					
Physical Examination	X											X									X	
Concomitant Illness /Medical History	X	X	X																			
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Child Bearing Potential	X																					
Pregnancy Test, Urine	X											X									X	
Height	X																					
Body Weight	X		X	X	X		X		X	X	X	X	X	X		X		X	X	X	X	
Vital Signs	X		X	X	X		X		X	X	X	X	X	X		X		X	X	X	X	
Dexcom Sensor Insertion	X	X									X									X		
CGM Download	X		X	X	X		X		X	X	X	X	X	X		X		X	X	X	X	
Insulin Pump Download	X		X	X	X		X		X	X	X	X	X	X		X		X	X	X	X	
Insulin Optimization			X	X	X							X	X	X								
Blood Sampling	X		X									X									X	
Point-of-Care HbA_{1C}			X																			
HbA_{1C} (central laboratory)	X											X									X	
GlycoMark	X											X									X	
CBC	X											X									X	
CMP	X											X									X	
Lipids	X																				X	
Urine MA	X											X									X	
Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemia Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical Complaints				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Infusion Site Reactions				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Infusion Site Occlusions				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization			X																			
Dispensing of Trial Product			X		X		X		X	X		X		X		X		X	X			
Drug Accountability					X		X		X	X		X		X		X		X	X		X	
Treatment Crossover												X										
Questionnaires/Surveys			X									X									X	
Diabetes Education	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																						
Attend Visit Fasting	X											X									X	

Degludec Pen Instruction			X*									X*									
Hand out Hypo/Basal Dose Diary	X		X	X	X		X		X	X	X	X	X	X		X		X	X	X		

* Dependent upon to which treatment group the subject is assigned.