A Randomized Controlled Trial Comparing the Safety and Efficacy of Liraglutide versus Glargine insulin for the Management of Patients with Type 2 Diabetes After Hospital Discharge

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Protocol Title

Degludec -Glargine Hospital Trial: A Randomized Controlled Trial Comparing Insulin Degludec and Glargine U100 for the Inpatient Therapy and Post-Hospital Discharge Management of Medicine and Surgery Patients with Type 2 Diabetes

INVESTIGATOR-SPONSORED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN): U1111-1185-1178

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I. BACKGROUND AND SIGNIFICANCE:

The association between hyperglycemia and poor clinical outcomes in hospitalized patients with and without diabetes is well established [1-5]. Extensive data from observational and prospective randomized controlled trials (RCT) in hospitalized patients have reported a strong association between hyperglycemia and poor clinical outcome, such as increased mortality, morbidity, hospital length of stay (LOS), infections and overall complications [1,4,6-8]. Clinical trials in both critically ill and in non-ICU medicine and surgery patients have shown that improvement of glycemic control in patients with hyperglycemia reduces LOS, systemic infections [9-11] and short- and long-term mortality [6,11].

Randomized multi-center trials have shown that basal bolus treatment with glargine U100 improve glycemic control and reduce the rate of hospital complications compared to sliding scale regular insulin (SSI)[12-14]. In general surgery patients, the basal bolus approach results in significant reduction in a composite of hospital complications including postoperative wound infection, pneumonia, bacteremia, and acute renal and respiratory failure.[15] The hypoglycemia rate was reported in 3% in medicine [12] and 12% in surgery [13] patients treated with basal bolus regimen. Based on these results, clinical practice guidelines have recommended the use of basal bolus approach as the preferred insulin regimen for the management of non-ICU patients with diabetes [15-17].

The Food and Drug Administration and the European Commission recently approved insulin degludec for the treatment of patients with diabetes. Insulin degludec, a long-acting basal insulin analog with a half-life of >25 hours and activity of >40 hours [18,19], results in comparable glycemic control to glargine [19-21], but with lower rates of hypoglycemia [19,20,22]. The efficacy and safety of degludec is well documented in ambulatory patients; however, no studies have assessed the safety and efficacy of these new formulations in the hospital setting. Although we can anticipate a reduced number of hypoglycemic events with insulin degludec, certain features needs to be investigated in the hospital including 1) prolonged duration of action, which may limit the ability to make day-to-day adjustments in insulin dosage; 2) a steady-state insulin concentration achieved after second or third day of therapy [21,23]; and limited safety data in acutely ill patients with altered nutritional status. Accordingly, the present pilot randomized trial will compare the efficacy and safety of a basal bolus regimen with degludec U100 and glargine U100 in medicine and surgery patients with type 2 diabetes (T2D).

Significance and Innovation. Degludec is a new generation basal insulin analog with a longer duration of action compared to insulin glargine [18,19]. Several outpatient trials have reported that treatment with degludec results in comparable improvement in HbA1c levels and in lower rates of hypoglycemia compared to glargine U100 insulin. No previous studies; however, have compared the safety and efficacy of the long-acting basal insulin degludec in the inpatient management of patients with diabetes. It is expected that a large number of patients with diabetes will be started or transitioned to this new insulin formulation; so acquiring knowledge on their safety and efficacy is of great clinical interest. Accordingly, the proposed study will provide novel and clinically useful information on the efficacy (BG control) and safety (hypoglycemia) of degludec in the inpatient setting and after hospital discharge in general medicine and surgery patients with T2D.

II. SPECIFIC OBJECTIVES:

Objective 1. To determine differences in inpatient glycemic control, as measured by mean daily blood glucose concentration and the frequency of hypoglycemia in general medicine and surgery patients with T2D treated with basal bolus regimen with insulin degludec or glargine once daily plus aspart insulin before meals. We will analyze a total of 180 subjects with T2D treated prior to admission with diet, oral hypoglycemic agents, short-acting GLP1-RA (except long-acting exenatide, dulaglutide and albiglutide), or insulin therapy (except degludec and glargine U300) will be included in this prospective, randomized, open label trial to compare the safety and efficacy of a basal bolus regimen with degludec and glargine in patients with T2D admitted to general medicine and surgery services. Secondary end points include length of stay, hospital complications, and hospital readmissions.

Objective 2: To determine differences in glycemic control after hospital discharge between treatment with degludec and glargine in medicine and surgery patients T2D. Patients with poorly controlled diabetes (HbA1c ≥7.0%) enrolled in Aim 1 will be invited to participate in this open label prospective outpatient study. At hospital discharge, patients will be treated following an HbA1c based algorithm[24] for a total duration of the outpatient follow-up of 3 months (see hospital discharge algorithm, page 7).

III. RESEARCH DESIGN AND METHODS

III.A Study Hypothesis (hypotheses):

Hypothesis #1*:* Treatment with degludec and glargine will result in equivalent glycemic control in general medicine and surgery patients with T2D. Degludec will result in lower number of hypoglycemia compared to glargine.

Hypothesis: treatment with degludec and glargine will result in a similar improvement in HbA1c levels after hospital discharge. Degludec will result in lower number of hypoglycemia compared to glargine.

III.B Endpoints:

The primary endpoint of the trial is non-inferiority in mean differences between treatment groups in their mean blood glucose concentrations during the first 10 days of therapy (non-inferiority will be determined at a difference <18 mg/dl). All participants who receive ≥ 2 doses of study drug will be included in the analysis.

Secondary outcomes include differences between treatment groups in any of the following measures: Endpoints 1-4 (glycemic control) will be analyzed during the first 10 days of therapy and endpoints 5, 7, 8, and 9 (length of stay and complications) will be analyzed during hospital stay. Endpoint 6 (readmissions) will be evaluated up to 12 weeks after hospital discharge.

1. Proportion of BG readings between 70 mg/dl and 180 mg/dl before meals
2. Number of hypoglycemia (< 70 mg/dl and 54 mg/dl) and severe hypoglycemia (< 40 mg/dl) episodes during the first 10 days of therapy in the inpatient setting.

3. Number of episodes of severe hyperglycemia (BG > 240 mg/dl) after the first day of treatment until the tenth day of therapy
4. Daily dose of basal insulin, daily dose of prandial insulin, and total daily dose
5. Length of hospital stay.
6. Number of readmissions (hospitalization) and Emergency room visits.
7. Cardiac complications are defined as myocardial infarction, cardiac arrhythmia requiring medical treatment, or cardiac arrest.
8. Acute kidney injury defined as an increment in serum creatinine ≥ 0.3 mg/dL from baseline or ≥1.5 times baseline creatinine (KDIGO) [25].
9. Hospital mortality.

III.C Study type:

This is a prospective, randomized, open label multicenter trial to compare the safety and efficacy of a basal bolus regimen with degludec and glargine in patients with T2D admitted to general medicine and surgery services.

This study will include male or female subjects > 18 years. Due to the design of this hospital study, there will be no run-in period. Upon arrival to the emergency department or medical or general surgical wards, subjects will be screened. A total of 180 subjects will be analyzed. A maximum of 108 (60%) surgical or medical patients will be randomized in the study to ensure a balanced proportion of each group is included. Patients with a known history of T2D treated with diet alone, any combination of OADs, short acting GLP-1 RA (liraglutide or exenatide) and insulin prior to admission will be considered potential candidates for this study. Patients treated with degludec, glargine U300 or with long-acting GLP1-RA (dulaglutide, albiglutide and weekly exenatide) prior to admission will be excluded. Patients admitted with acute or chronic medical illnesses, emergency or elective surgical procedures and trauma would be included in the study.

Insulin therapy will be aimed to maintain fasting and pre-meal blood glucose levels between 100 mg/dl and 180 mg/dL while avoiding hypoglycemia. Blood glucose levels between 70 and 100 mg/dL are still considered at goal, however BG values in this range will trigger insulin adjustment to minimize the risk of hypoglycemia as recommended by professional associations. Patients with T2D will be randomized to receive:

Group 1. Basal bolus with degludec once daily and aspart insulin before meals (n=90)

Group 2. Basal bolus with glargine U100 once daily and aspart insulin before meals (n=90)

Aim 1. Inpatient (Hospital) Arm: Patients will be treated with a basal bolus insulin regimen as previously reported.[12-14,16] In brief, subjects treated with insulin prior to admission will receive 80% of the total daily outpatient insulin dose given. Insulin naïve patients will discontinue oral agents and will receive a starting total daily dose (TDD) of 0.4 U/kg/day for BG between 140 mg/dl and 400 mg/dL. The starting TDD will be reduced to 0.3 U/kg/day in patients ≥ 70 years or with a GFR < 60 ml/min. Both groups will be treated with bolus regimen given half of TDD as basal (degludec or glargine) once daily and half as aspart divided in three equal doses before meals. Patients with poor oral intake or with medical instruction to withhold oral intake (NPO)

will receive the basal dose, but prandial dose will be held.[14] Insulin dose will be adjusted daily to maintain a fasting and pre-dinner BG between 100 mg/dl and 180 mg/dl.

Initiation and Dosing of Basal insulin

Patients treated with insulin prior to admission will receive 80% of their total home daily insulin dose. Half of the total daily dose will be given as basal degludec/glargine) and half as prandial (aspart) insulin. The basal insulin will be given at the same time every day. The prandial (aspart) insulin will be held in patients with poor oral intake or NPO, but they will receive the usual basal insulin dose.

Insulin naïve patients will receive a starting insulin dose of 0.4 U/kg/day. Half of the total daily dose will be given as basal degludec/glargine) and half as prandial (aspart) insulin. The basal insulin will be given at the same time every day. The prandial (aspart) insulin will be held in patients with poor oral intake or NPO, but they will receive the usual basal insulin dose.

Adjustment/Titration of daily insulin dose:

The basal insulin dose will be adjusted daily per fasting blood glucose concentration. The target BG concentration during insulin treatment is 100-180 mg/dl. The daily basal (degludec/glargine) dose will be increased by 10% if the fasting BG is between 180 and 240 mg/dl or by 20% if fasting BG concentration is >240 mg/dL The total daily insulin dose (basal and prandial insulin) will be increased by 20% in patients with mean BG > 240 mg/dl. In addition, the basal insulin dose will be reduced by 10% if any BG is between 70-100 mg/dl, and by 20% in patients with any BG < 70 mg/dl. The total daily dose will be reduced 30-40% in the event of severe hypoglycemia (BG < 40 mg/dl).

Several clamp studies in patients with type 1 and type 2 diabetes and observations from clinical practice showed that insulin degludec quickly reaches steady state after the 2nd or 3rd day of therapy, a similar period reported with other basal insulin analogs [26,27]. Based on its steady-state condition, clinical pharmacology studies show that insulin degludec has a flatter, less variable and more consistent glycemic effect.

Treatment randomization. Patients will be randomized using a computer-generated randomization table. Treatment randomization/assignment will be coordinated by the research pharmacy. A research pharmacist at each institution will follow a computer-generated block randomization table based on glucose levels (BG≤200 or BG>200) at randomization.

TREATMENT PROTOCOL - Basal Bolus Insulin Regimen with Degludec or Glargine Once Daily plus Aspart before Meals

Patients Treated with Insulin Prior to Admission

- Discontinue oral antidiabetic drugs on admission.

Subjects treated with insulin prior to admission will receive 80% or 100 % of the total daily dose (TDD) given as basal bolus regimen.

Starting Insulin Doses:

- **BG < 200 mg/dl give 80% of TDD***
- **BG ≥ 200 mg/dl give 100% of TDD***

- Half of TDD will be given as degludec or glargine and half as rapid-acting insulin.
- Degludec and glargine will be given once daily at the same time of the day
- Patients will receive the full-dose of degludec or glargine (even if NPO) the day of surgery or diagnostic procedure(s).
- Aspart insulin will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, aspart insulin dose will be held.

*** If patient was on basal only therapy consider adding prandial dose as calculated above.**

Insulin Naïve Patients Treated with Oral Agents or GLP1-RAs

- Discontinue oral antidiabetic drugs on admission.
- Starting total daily insulin dose:
  - 0.4 U/Kg/day when randomization BG between 140-400 mg/dL
  - Reduce TDD to 0.3 units per kg in patients ≥ 70 years of age and/or with an eGFR < 60 ml/min.
- Half of TDD will be given as glargine or degludec and half as aspart.
- Degludec or glargine will be given once daily, at the same time of the day.
- Patients will receive the full-dose of degludec or glargine insulin (even if NPO) the day of surgery or diagnostic procedure(s).
- Aspart insulin will be given in three equally divided doses before meals. To prevent hypoglycemia, if a subject is not able to eat, the dose of aspart insulin will be held.

Supplemental insulin. Aspart insulin will be administered following the "supplemental or correction insulin scale" protocol (Appendix 1, page 21). Supplemental doses will be given for BG > 140 mg/dl before meals. At bedtime, supplemental insulin will be reserved for patients with BG > 250 mg/dl.

- If a patient is able and expected to eat most of his/her meals, supplemental insulin will be administered before meals and at bedtime following the "usual" dose of the insulin scale protocol.
- If a patient is not able to eat, supplemental insulin will be administered every 6 hours (Appendix 1) following the "sensitive" dose of the supplemental insulin scale protocol.

Basal Insulin adjustment.

- Daily basal insulin dose will be adjusted as follow:
  - If the fasting and/or pre-dinner BG is between 100 - 140 mg/dl in the absence of hypoglycemia the previous day: no change
  - If the fasting and/or pre-dinner BG is between 141 - 180 mg/dl in the absence of hypoglycemia: increase basal insulin by 10% every day*
  - If the fasting and/or pre-dinner BG is 181 – 299 mg/dl in the absence of hypoglycemia the previous day: increase basal insulin (degludec or glargine) dose by 20% every day*
  - If the fasting and/or pre-dinner BG is ≥ 300 mg/dl in the absence of hypoglycemia the previous day: increase basal insulin (glargine) dose by 30% every day*
  - If the fasting and pre-dinner BG is between 70 - 99 mg/dl in the absence of hypoglycemia: decrease TDD (basal and prandial) insulin dose by 10% every day

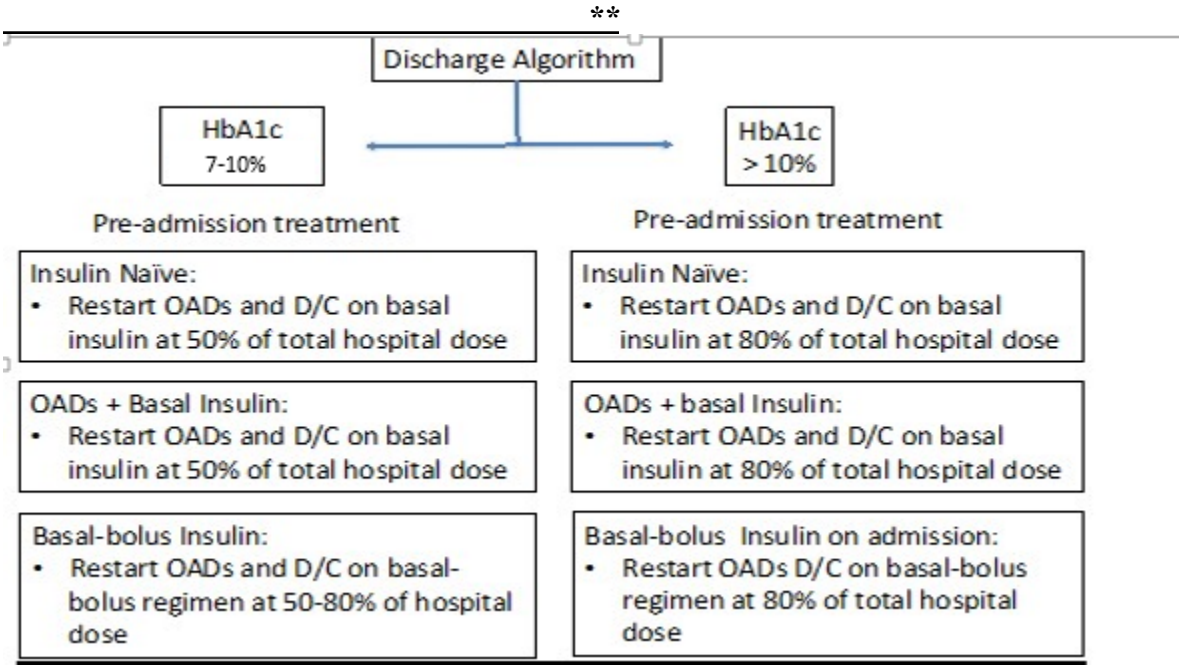
- If a patient develops hypoglycemia (BG <70 mg/dL), the insulin TDD (basal and prandial) should be decreased by 20%.
- If a patient develops severe hypoglycemia (BG <40 mg/dL), the insulin TDD (basal and prandial) should be decreased by 30-40%.

*Consider adjusting prandial dose according to medical discretion

Aim 2: Outpatient (Post-Discharge) Arm: To determine differences in glycemic control after hospital discharge between treatment with degludec and glargine in medicine and surgery patients T2D. We will compare the efficacy and safety of degludec and glargine after hospital discharge. Several outpatient insulin trials have shown that treatment with degludec results in similar improvement in glycemic control [19,20,28], but in significant reduction in hypoglycemia. We expect that degludec treatment will be a safer alternative to current use of glargine U100 formulation.

Insulin Discharge algorithm:

Patients with poorly controlled diabetes (HbA1c ≥7.0 %) enrolled in Aim 1 will be invited to participate in this open label prospective outpatient study. The total duration of the study is 3 months. Patients with an HbA1c between 7.0% and 10% will be discharged on preadmission oral antidiabetic agents plus degludec or glargine once daily. Patients with an admission A1C ≥ 10% will be discharged on basal bolus regimen with degludec or glargine and aspart insulin before meals. Participants will be trained in using each devices including how to differentiate these from each other (rapid acting from long acting insulin).



**If previous basal bolus only therapy and/or contraindications to previous oral therapy, discharge on basal bolus at 100% of daily hospital dose.

Follow-up Care:

- Provide degludec or glargine 1 or 2months supply at each clinic visit.

- A member of the diabetes research team will contact patients via telephone call every 2 weeks for a total of 3 months.
- Patients will be asked to attend outpatient visits at 4 and 12 weeks after hospital discharge.
- Recommendation on insulin adjustment to be provided after each telephone contact and/or clinic visit by research staff under supervision of research licensed healthcare professional.
- Research staff will follow the algorithm for outpatient insulin dose adjustment according to fasting blood glucose levels (FBG) and/or random blood glucose levels (RBG) described below (algorithm for primary care physician).

During follow up we will collect the following information:

1. Glycemic control:
    a. Mean daily fasting and premeal blood glucose levels
    b. HBA1C at 1 and 3 months after hospital discharge
    c. Hypoglycemic events
        i. A glucose alert value of <70mg/dl.
        ii. Clinically important hypoglycemia (BG < 54 mg/dl)
        iii. Severe hypoglycemia, as defined by the ADA, which denotes severe cognitive impairment requiring external assistance for recovery
    d. Hyperglycemic events (BG > 240 mg/dl)

2. Diabetes treatment:
    a. Number of patients receiving insulin
    b. Insulin dosage (unit/day)
    c. Use of oral agents
    d. Protocol adherence
3. Clinical Outcome:
    a. Hospital readmissions
    b. Emergency room visits
    c. Postoperative complications

4. Management after end of study
    a. Post treatment telephone call (telephone contact 2 weeks after last clinic visit) to confirm appropriate number of refills and follow up with primary care physician
    b. Collect information on adverse events post treatment

Primary care physicians will be provided with the following algorithm for outpatient insulin dose adjustment according to fasting blood glucose levels (FBG) or random blood glucose levels (RBG)

Basal Insulin (degludec and glargine)	
If mean **FBG > 180 mg/dL** for the last 3 consecutive days and no hypoglycemia or no random BG (RBG) <70 mg/dL	**Increase daily dose by 4 IU**
If mean **FBG > 140 mg/dL** for the last 3 consecutive days and no hypoglycemia < or	**Increase daily dose by 2 IU**

no RBG <70 mg/dL	
If mean **FBG between 100 – 140 mg/dL** and no hypoglycemia or no RBG <70 mg/dL	**No Change**
If any FBG between 70 – 99 mg/dl	**Decrease by 4 IU or 10% of total daily dose**
If any FBG or RBG 40- 69 mg/dl	**Decrease by 8 IU or 20% of total daily dose**
If any FBG or RBG < 40 mg/dl	**Decrease total daily dose by 30 – 40%**

For patients discharged on basal bolus, prandial insulin will be adjusted according to postprandial blood glucose levels (PPG) measured 2 hours after the start of the meal.

Prandial Insulin (rapid acting insulin)	
PPG < 180	**No change**
PPG 180-240 mg/dl	**Increase dose by 2 IU**
PPG >240 mg/dl	**Increase dose by 4 IU**

Rationale for study Design

Aim 1, Hospital: Several studies have shown improved clinical outcome with improved glycemic control in hospitalized patients with T2D [4,5,9,11,29-31]. RCTs in medicine and surgical patients with T2D have shown that basal bolus regimen with glargine results in a lower mean daily BG concentration compared to the sole use of SSI and in lower rate of hospital complications (see preliminary results section). Insulin degludec results in similar improvement but in lower rate of hypoglycemia than treatment with glargine [19,20,28]. No previous studies; however, have compared the efficacy and safety of degludec and glargine in the management of hyperglycemia and diabetes in hospital setting. Determining the safety and efficacy of new insulin formulations in the hospital, an environment associated with reduced insulin sensitivity and altered nutritional intake, is an exceedingly important clinical question.

Aim 2, Outpatient (post-discharge): Few studies have addressed the efficacy of insulin alone or in combination with oral agents after hospital discharge. In a recent study (see preliminary results section), patients were discharged on a combination of OADs and glargine U100 insulin or on a basal bolus regimen according to HbA1c levels and achieved a marked reduction in HbA1c from 8.75% on admission to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge. However, the use of glargine U100 alone or in combination to oral agents or as basal bolus insulin resulted in 30% and close to 40% incidence of hypoglycemia, respectively. In this study, we will compare the efficacy and safety of degludec and glargine after hospital discharge. Several outpatient insulin trials have shown that treatment with degludec results in similar improvement in glycemic control [19,20,28], but in significant reduction in hypoglycemia. Thus we expect that degludec treatment will be a safer alternative to current use of glargine U100 formulation.

IV. Study population:

Number of subjects to be studied: 180
Planned number of subjects to be screened/consented: 220-250
Planned number of subjects to be treated in run-in period: No run-in period as patient will be admitted to the hospital with an acute medical/surgical illness.
Planned number of subjects to be randomized/started on study medication(s): 180

Anticipated number of trial sites: 3 sites (Emory University Hospitals/Grady Hospital in Atlanta, GA; additional Sites: Mount Sinai, NY-PI: Dr. David Lam and Providence Medical Research Centre PI: Dr. Radica Alicic)
Anticipated number of subjects to be randomised/started on trial medication(s) at each trial site: 60.
Country planned to participate: United States.

Inclusion Criteria

1. Males or females between > 18 years admitted to a general medicine or surgical service.
2. A known history of T2D treated either with oral monotherapy, any combination of oral antidiabetic agents, short-acting GLP1-RA (exenatide, liraglutide) or insulin therapy except for degludec and glargine U300.
3. Subjects with diet alone and HbA1c>7.0%
4. Medical and surgical patients expected to be admitted (LOS) longer than 2 days
5. Subjects must have a randomization BG > 140 mg and < 400 mg/dL without laboratory evidence of diabetic ketoacidosis (bicarbonate < 18 mEq/L, pH < 7.30, or positive serum or urinary ketones).
6. Signed, informed consent and HIPAA documentation prior to any study procedures

Exclusion Criteria

1. Subjects with increased BG concentration, but without a known history of diabetes (stress hyperglycemia).
2. Subjects treated with diet alone (no antidiabetic agents) and admission HbA1c <7%.
3. Admission or pre-randomization BG≥400 mg/dl
4. Subjects with a history of diabetic ketoacidosis and hyperosmolar hyperglycemic state, or ketonuria [32].
5. Patients treated with degludec or glargine U300, or with long-acting weekly GLP1-RA (weekly exenatide, dulaglutide or albiglutide).
6. Patients with acute critical or surgical illness admitted to the ICU, except for observation (<24 hours and did not require vasopressors and/or mechanical ventilation).
7. Patients with history of clinically relevant hepatic disease (diagnosed liver cirrhosis and portal hypertension), ongoing corticosteroid therapy (equal to a prednisone dose ≥5 mg/day), or impaired renal function (eGFR< 30 ml/min), or congestive heart failure (NYHA- IV).
8. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
9. Female subjects who are pregnant or breast-feeding at time of enrollment into the study.
10. Known or suspected allergy to trial medication(s), excipients, or related products.
11. Previous participation in this trial.

Withdrawal Criteria

1. The subject may withdraw at will at any time.
2. The subject may be withdrawn from the trial at the discretion of the investigator due to a safety concern or if judged non-compliant with trial procedures or included in contravention to the inclusion and/or exclusion criteria.

3. Subject admitted to the ICU who required continuous intravenous insulin infusion to maintain glycemic control.
4. Pregnancy or intention to become pregnant.
5. Treatment with oral or injectable corticosteroid (equivalent or higher than prednisone 5mg/day), parenteral nutrition and immunosuppressive treatment after randomization.

Treatment Failure Criteria

Subjects with persistent hyperglycemia (≥ 2 glucose readings ≥ 400 mg/dL, ≥ 3 consecutive glucose readings > 280 mg/dL, or with a mean daily blood glucose concentration ≥ 280 mg/dL) and no treatable intercurrent cause for the hyperglycemia has been identified, will be considered as treatment failure and discontinued from the study. Subjects will be started on continuous insulin infusion if needed.

Subject Replacement

There will be no replacement of subjects in this trial.

V. Visit Procedures

Upon arrival to the emergency department or medical or general surgical wards, subjects will be screened. Patients with a known history of T2D treated with diet alone, any combination of OADs, and insulin prior to admission will be considered potential candidates for this study. Patients admitted with acute or chronic medical illnesses, emergency or elective surgical procedures and trauma would be included in the study.

Patients will be treated with a basal bolus insulin regimen as previously reported. In brief, subjects treated with insulin prior to admission will receive 80% of the total daily outpatient insulin dose given. Insulin naïve patients will discontinue oral agents and will receive a starting total daily dose (TDD) of 0.4 U/kg/day for BG between 140 mg/dl and 400 mg/dL. The starting TDD will be reduced to 0.3 U/kg/day in patients ≥ 70 years or with a GFR < 60 ml/min. Both groups will be treated with bolus regimen given half of TDD as basal (degludec or glargine) once daily and half as aspart divided in three equal doses before meals. Patients with poor oral intake or to be kept NPO will receive the basal dose, but prandial dose will be held.[14] Insulin dose will be adjusted daily to maintain a fasting and pre-dinner BG between 80 mg/dl and 180 mg/dl.

Aim 1. Inpatient Arm – Flow Chart

Visit Type	Hosp-Day 1	Hosp-Day 2	Hosp-Day 3	Hosp-Day 4	Hosp-Day 5	Hosp-Day 6	Hosp-Day 7	Hosp-Day 8	Hosp-Day 9	Hosp-Day 10
Visit #	1	2	3	4	5	6	7	8	9	10
Time-days	1	2	3	4	5	6	7	8	9	10
Inf. consent	x									
Inclusion/excl criteria	x									
Randomization	x									
Withdrawal criteria	x	x	x	x	x	x	x	x	x	x
Dose adjustment		x	x	x	x	x	x	x	x	x
Efficacy										
Vital signs	x									x
Phys Exam	x									x
Body weight	x									x

BMI	x									
HbA1c[1]	x									
Fasting BG		x	x	x	x	x	x	x	x	x
Pre-meal BG	x	x	x	x	x	x	x	x	x	x
Safety										
Adv events	x	x	x	x	x	x	x	x	x	x
Hypoglycemia	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x									
Trial material										
Drug dispense[2]	x									

[1] From medical records if < 3months, order it otherwise after subject has provided consent for study participation.

[2] As needed

Aim 2. Outpatient Arm – Flow Chart

Visit Type	Discharge Day 1	TC	Clinic visit	TC	TC	TC	Clinic visit	post treatment follow-up
Visit #	1	2	3	4	5	6	7	8
Time-wks[1]	0	2	4	6	8	10	12	14
Inf. consent	x							
Incl/excl criteria	x							
Random	x							
Withdrawal criteria		x	x	x	x	x	x	
Drug Compliance		x	x	x	x	x	x	
Dose adjustment		x	x	x	x	x	x	
Efficacy								
Vital signs	x		x				x	
Phys Exam	x		x				x	
Body wgt	x		x				x	
BMI	x		x				x	
HbA1c			x				x	
Fasting BG	x		x				x	
Safety								
Adv events	x	x	x	x	x	x	x	x
Hypoglycemia	x	x	x	x	x	x	x	x
Urine pregnancy test			x					
Chem, GFR	x		x				x	
Trial material								
Drug dispense	x		x					
Drug account	x		x				x	

[1]Telephone calls (TC) and outpatient visits can be completed ±7 days

Assessments for Efficacy

Laboratory measurements will be conducted per standard hospital practices. Samples will be collected and labelled at the clinical research center at each individual institution. Samples will not be stored. Clinical research coordinators and research nurses will obtain data and blood samples to be sent to the central lab at each institution for standard measurements (HbA1c, chemistry)

Assessments for Safety

Potential Risks to the Subject:

Protection against risks:

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor capillary BG at the bedside using a hand-held glucose meter, b) only experienced nurses/or phlebotomist will draw blood samples, and c) women of reproductive age who are sexually active will undergo a urine pregnancy tests prior to participation in the study. To prevent significant clinical events, no patients with history of significant liver (diagnosed liver cirrhosis and portal hypertension), renal impairment (eGFR<30ml/min/1.73m^2) or severe cardiac failure will be recruited in this study.

Hypoglycemia: It is possible that following the proposed protocol, patients receiving insulin degludec or glargine may develop hypoglycemia. The risk of hypoglycemia (BG < 70 mg/dl) in non-ICU patients treated with subcutaneous insulin is between 5–30% [13,33-35]. The number of hypoglycemia (< 70, < 54 and < 40 mg/dl) will be analyzed statistically. For the purpose of this analysis, hypoglycemia is defined as follows: 1) BG < 70mg/dL is a glucose alert value, 2) BG < 54 mg/dL will be considered as clinically important hypoglycemia, and 3) Severe hypoglycemia, will be defined as a BG < 40 mg/dl.[16,36] We expect that approximately 10% in the inpatient setting and ~20% in the outpatient (post-discharge) arm will experience one or more episodes of hypoglycemia. To minimize the risk of hypoglycemia, the starting dose will be reduced in the basal bolus insulin regimen (TDD: 0.4 units per kg of body weight), in addition, in patients ≥ 70 years of age and/or eGFR < 60 ml/min the TTD will be further reduce to 0.3 units/kg. To avoid hypoglycemia, the total daily dose of insulin will be decreased by 10% for BG between 70-99 mg/dl and by 20% after each episode of hypoglycemia (BG < 70 mg/dl). In addition, in patients treated with insulin at home, the TDD of insulin will be reduced by 20% on admission and the attending physician may further reduce insulin dose in the presence of severe hypoglycemia.

Hypoglycemia will be treated with dextrose infusion. Dextrose 50% solution will be given for glucose values < 70 mg/dl. If the patient is awake, 25 ml (1/2 amp) will be given IV or oral juice/snack (crackers) as per protocol. If the patient is not awake: 50ml (1 amp) will be given STAT. Blood glucose levels will be repeated in 15 minutes and dextrose administration will be repeated as needed for values < 70 mg/dl.

Subject Compliance

Aim 1. Inpatient (hospital) trial. We will use electronic medical records and nursing records to document day and time of insulin administration of study drug (degludec and glargine) given once daily and prandial- rapid-acting insulin (aspart) given before meals. We will also record dose and number of units given as supplement (correction) to correct hyperglycemia.

Aim 2. Patients will be contacted every 2 weeks after discharge by a study coordinator to assess insulin administration, glycemic control, hypoglycemia and medication adherence. Patients are to bring all used and unused insulin pens (study drug). Patients will keep daily record of time and dose of insulin administered every day during the study period.

VI. STATISTICAL CONSIDERATIONS:

VI.A Aim 1. To determine differences in inpatient glycemic control in patients treated with degludec or glargine in patients with T2D.

Sample Size and Power Calculations:

The primary endpoint in this study is glycemic control measured by mean daily BG concentration. To show the non-inferiority of degludec and glargine in terms of glycemic control, we set the equivalence margin as 18 mg/dl (1 mosm/l), from a view that a difference <18 mg/dl is usually not considered as clinically significant [12-14,37]. Based on the results of the Rabbit medicine and surgery trials, it is reasonable to assume the standard deviation of mean daily BG is bounded above by 45 mg/dl. Assuming the true BG difference between the treatment groups is zero, and using one-sided, two-sample t-tests, we require 78 subjects for each treatment group to achieve 80% power with alpha=0.05. Accounting for 10-14% attrition rate, we would need 90 patients per treatment group, which means 180 subjects in total, to achieve >80% power in Aim 1.

Analysis of Primary Endpoint:

The primary endpoint for Aim 1 is non-inferiority in mean differences between treatment groups in their mean blood glucose concentrations during the first 10 days of therapy (non-inferiority will be determined at a difference <18 mg/dl). Blood glucose will be measured before each meal and at bedtime. Average mean daily BG between the two study groups will also be compared based on the nonparametric Wilcoxon tests. We will also perform cross-sectional analysis of mean daily BG recorded on different days based on Wilcoxon tests or linear regression that accounts for potential confounders. In addition, we will conduct repeated measures ANOVA or repeated measures linear regression to estimate and test the difference in mean daily BG between the two treatment groups while simultaneously examining mean daily BG across multiple days during treatment. Transformations will be applied if normality violation is detected. Stepwise, backward, or forward model selection strategy will be adopted to determine the variables to be included in the final model. Standard diagnostic and model checking procedures will be applied to examine the fit of the developed models.

Analysis of Secondary Endpoints:

Secondary endpoints for Aim 1 in this study include incidence of hypoglycemia, number of hypoglycemic events, number of severe hyperglycemia, mean daily fasting BG, daily insulin dose, length of hospital stay, acute renal failure and hospital mortality. Blood glucose will be measured before each meal and at bedtime. For discrete outcomes (such as hypoglycemia outcomes), we will first conduct nonparametric comparisons based on a two-sided Chi-square test (or Fisher's exact test), followed by the Cochran-Mantel-Haenszel test, which adjusts for the potential center effect. We will further conduct logistic regression (for binary outcomes) and Poisson or Negative Binomial regression (for count outcomes) to assess and estimate the treatment effect while adjusting for potential confounders. We will analyze continuous secondary outcomes by following the plan proposed for the primary outcome.

VI.B Aim 2: Sample Size and Power Calculations: The primary endpoint in Aim 2 is difference in glycemic control (mean daily BG) after hospital discharge. Under the same assumptions for equivalence margin and BG variability as in Aim 1, we have the same sample size requirement (i.e. 78 subjects per group after 10% attrition). Accounting for 10-14% attrition rate, we would need 90 patients per treatment group, which means 180 subjects in total, to achieve >80% power.

Analysis of Primary Endpoint: The primary endpoint in this study is glycemic control measured by mean daily BG concentration after hospital discharge. Secondary outcomes include rate of hypoglycemia during follow-up, change in HbA1c, body weight, number of episodes of severe hyperglycemia, complications and emergency room visits or hospital readmissions at 12 weeks post-discharge. To analyze these outcomes, we will follow the same analytic strategy proposed for the secondary endpoints of Aim 1. We will first compare the primary outcome using two-sample t-tests (or Wilcoxon tests) or one-way ANOVA, followed by multivariate linear regression to estimate and test the difference between the two treatment groups while simultaneously accounting for other potential confounders. Transformations will be applied if normality violation is detected. Stepwise, backward, or forward model selection strategy will be adopted to determine the variables to be included in the final model. Standard diagnostic and model checking procedures will be applied to examine the fit of the developed models.

VII. DATA HANDLING AND RECORD KEEPING:

Data collection records with personal identifiers will be stored in locked file cabinets. Blood samples drawn in conjunction with this study will not be labeled with information that could directly identify study subjects. Blood samples will be not be stored. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, research coordinators, and the IRB at Emory University.

VIII. ETHICS:

Informed Consent.

After identification of eligible patients these individuals will be provided basic information regarding the study and, if interested, a member of the research staff using inclusion/exclusion criteria delineated elsewhere in the protocol will then screen patients. Informed consent will be obtained before any trial related procedures including screening procedures. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have questions, and a member of the research staff will answer questions. The principal investigator (PI) will also be available at all times to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed only by trained research personnel familiar with the study protocol procedures, informed consent process, who have undergone CITI training in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office.

The study will be conducted in accordance with the Declaration of Helsinki and will be conducted in accordance with the ICH GCP guidelines. The sponsor-investigator will comply with all applicable regulatory and legal requirements, ICH GCP guidelines and the Declaration of Helsinki in obtaining and documenting the informed consent.

Recruitment Procedure.

We screen all patients with hyperglycemia admitted to the hospital every day. Patients with diabetes and hyperglycemia will be identified electronically following inclusion/exclusion criteria. Once a potential candidate is identified, we will approach the primary team as well as

the patient and family for consent. We estimate that we will screen approximately 220-250 patients to analyze a total of 180 subjects, and expect to recruit about 2-4 patients per week"

IX. STUDY SCHEDULE:

FIRST PATIENT IN	DEC 2017
SCREENING	~220-250
ANALYZED	180
LAST PATIENT RECRUITED	MARCH 2020
LAST PATIENT IN	JUNE 2020
DATA ANALYSIS	AIM 1: 09/2020 ; AIM: 2: 12/2020
SUBMISSION TO CONGRESS OR JOURNAL	1/ 2021 (ADA); 4/2021: EASD

X. STUDY DRUGS AND MATERIALS:

Study medication(s) / devices(s)

Degludec insulin (U-100): 100 units/mL (U-100): 10 mL multiple-dose vial (1 vial per subject during hospital admission): Inpatient arm: 90 patients. Total number of vials: 90
Degludec insulin 100 Units/mL, provided in 3 mL pen cartridges (outpatient arm).
Outpatient arm: 90 patients, average insulin dose: 30-45 U/day. Total number of cartridges: 100

Glargine insulin (U-100): 100 units/mL (U-100): 10 mL multiple-dose vial (1 vial per subject during hospital admission): Inpatient arm: 90 patients. Total number of vials: 90
Glargine (U-100) insulin 100 Units/mL, provided in 3 mL pen cartridges.
Outpatient arm: 90 patients, average insulin dose: 30-45 U/day. Total number of cartridges: 100

Aspart insulin (U-100): 100 units/mL (U-100): 10 mL multiple-dose vial (1 vial per subject during hospital admission): Inpatient arm: 180 patients. Total number of vials: 180
Aspart (U-100) insulin 100 Units/mL, provided in 3 mL pen cartridges
Outpatient arm: 180 patients, average insulin dose: 20-30 U/day. Total number of cartridges: 180
BG-Meters are considered standard of care and will not be provided.

Packaging and Labelling of Study Medication(s)

Degludec, aspart, and glargine will be stored and dispensed by the research pharmacy at each institution. During the hospital stay (Aim 1) insulin will be kept at nursing stations and dosing will be administered by nursing staff as per hospital protocol. Once dispensed and in use (after first opening), insulin glargine can be stored for one month at room temperature (+15°C to +30°C)/(59°F to 86°F) or in a refrigerator (+2°C to +8°C)/(+36°F to +46°F).
During the outpatient trial, all insulin prefilled pens \ will be stored in a refrigerator at a temperature between +2°C and +8°C (+36°F and +46°F). Once dispensed and in use (after first opening), insulin glargine can be stored for one month at room temperature (+15°C to +30°C)/(59°F to 86°F) or in a refrigerator (+2°C to +8°C)/(+36°F to +46°F

Drug accountability: The trial product will be dispensed to each subject as required according to treatment group. The research/clinical staff will perform drug accountability by asking patients to return all unused, partly used and unused cartridges and vials of degludec and glargine insulin at each visit.

Randomization and Blinding

This is an open label randomized multicenter controlled trial. Patients will be randomized consecutively using a computer-generated randomization table provided by Dr. Limin Peng at the Emory School of Public Health. The randomization table will be mailed to the research pharmacist at each institution who will be in charge of the randomization and group assignment.

XI. CONCOMITANT ILLNESSES AND MEDICATIONS:

Definitions:

During the hospital arm (Aim 1), all oral agents and insulin formulations will be discontinued at randomization and patients will be treated as per study protocol with degludec/glargine as basal bolus regimen with aspart as prandial insulin.

After discharge, patients will be treated with glargine or degludec insulin alone or in combination with oral agents according to HbA1c levels.

XII. ADVERSE EVENTS:

Definition: An adverse event (AE) is any untoward medical occurrence in a subject administered a product, and which does not necessarily have a causal relationship with this treatment. An AE is an unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period (telephone contact 2 weeks after last study visit).

AEs include a clinically significant worsening of a concomitant illness and clinical laboratory adverse event (CLAE). An AE is either a serious AE (SAE) or a non-serious AE.

The following AEs will be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- Suspicion of transmission of infectious agents via the trial product
- Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law)
-Death
-A life-threatening event in which the subject was at risk of death at the time of the event
-Inpatient hospitalization and prolongation of existing hospitalization
-Persistent or significant disability or incapacity
-Important medical events that may not result in death, or a life threatening event but may require hospitalization
-Episodes of severe hypoglycemia will be captured as serious AEs.
- A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be 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 Trial Product 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 aetiology other than the trial product

Adverse events will be actively collected from the signing of the informed consent and in all following contacts throughout the project. This includes events from all trial related activity after the subject has signed the informed consent, and until the post treatment follow-up period, as defined in the protocol.

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

Reporting of adverse events: All events meeting the definition of an AE must be collected and reported. The events must be recorded in the AE form in a timely manner. During each contact with the trial site staff (site visits and telephone contacts), the subject will be asked about AEs. After the ICF is signed, all adverse events related to protocol procedures are to be reported. 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. Serious adverse reaction (SAR): An Adverse event that fulfils both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.An SAE report should be completed for any event where doubt exists regarding its seriousness.
If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form. SAEs, whether related or not related to study drug, and pregnancies must be reported to Emory IRB and Novo Nordisk by fax or email. SAEs must be recorded on an SAE Report Form or similar form (e.g. CIOMS, MedWatch).
Within 15 days of becoming aware, the PI/sponsor will notify the FDA and all participating investigators via IND safety reports of events that are unexpected, caused by the study drug, *and* meet the FDA definition of "serious."

Reporting of pregnancies: Female subjects who are pregnant or breast-feeding will not be recruited in the study. Female subjects will be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy to the Emory IRB and Novo Nordisk. The pregnant subject will be asked to provide information about her pregnancy, delivery and the health of her infant until age one month. If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

Adverse events with additional data collection: Adverse events with additional data collection are those events thought to be [potentially] associated with the investigational compound or disease under study. The investigators will collect information on medical events of special interest including hypoglycemia, hyperglycemia (BG > 240 mg/dl), cardiovascular events (heart failure, acute myocardial infarction, and atrial fibrillation), and medication errors (e.g., incorrect dose of insulin).

XIII. LIABILITY AND SUBJECT INSURANCE:

Financial Obligation.
No additional cost to patients or to the institution will be incurred for research purposes. Patients will not be billed for the laboratory work or any test that is being done only for study purposes. Novo Nordisk will provide the study drugs (degludec, glargine and aspart insulin) at no cost to participants. Patients will be responsible for the cost of their usual ongoing medical care, including procedures and/or non-study medications that their doctor requires as part of their usual medical care.

Payment for Participation.
Participation in this study is voluntary. Patients will receive one hundred dollars ($100.00) during the hospital stay and seventy- five dollars ($75.00) after each clinic visit at 1 and 3 months after discharge. Total compensation will be two hundred and fifty dollars ($250.00).

Research Injuries.
If a patient is injured because of taking part in this study, Dr. Umpierrez and investigators at each institution, along with the medical facilities will make medical care available. Emory University, however, has not set aside any money to pay participants or to pay for their medical treatment. The only exception is if it is proved that the injury or illness is directly caused by the negligence of an Emory/Grady employee. “Negligence” is the failure to follow a standard duty of care. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

XIV. Publication Plan:

We anticipate completion of Aim 1 in September or October 2020 and Aim 2 in November 2020. Data will be analyzed in December 2020 (aim 1) and in March 2021(aim 2). One abstract will be submitted to the 2021 American Diabetes Association meeting and one to EASD 2021. Two manuscripts will be submitted during the first six months of 2021.

XV. References

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Appendix **1. Supplemental "sliding insulin scale" protocol**

BEFORE MEAL, Supplemental Sliding Scale Insulin (number of units) - Add to scheduled insulin dose.

****Check appropriate column and cross out other columns**

BG (mg/dL) ☐ **Insulin Sensitive** ☐ **Usual** ☐ **Insulin Resistant**

< 141	No sliding scale (supplemental)insulin		
141 – 180	2	3	4
181 – 220	3	4	6
221 – 260	4	5	8
261 – 300	5	6	10
301 – 350	6	8	12
351 – 400	7	10	14
> 400	8	12	16

BEDTIME sliding scale: **Supplemental Sliding Scale Insulin dose at bedtime starting at BG > 220 mg/dL**

BG (mg/dL) ☐ **Insulin Sensitive** ☐ **Usual** ☐ **Insulin Resistant**

< 220	No sliding scale (supplemental) insulin		
221 – 260	1	2	4
261 – 300	2	3	5
301 – 350	3	4	6
351 – 400	4	5	7
> 400	5	6	8

** Check appropriate column below and cross out other columns

The numbers in each column indicate the number of units of aspart insulin *per dose.*
Supplemental" dose is to be added to the scheduled dose of aspart insulin. If a patient is able and expected to eat all or most of his/her meals, supplemental insulin will be administered before each meal following the "usual" column dose.
Supplemental insulin at bedtime will be given ONLY for BG > 220 mg/dl = half of premeal insulin dose[38]. Example, a patient with blood glucose of 280 mg/dl will receive 5 U before a meal or 2 U at bedtime of supplemental insulin.
If a patient is not able to eat (NPO), supplemental insulin will be administered every 6 hours (6-12-6-12) following the "sensitive" column dose. Example, a patient kept NPO with blood glucose of 181 mg/dl will receive 3 U of supplemental insulin.