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

NCT# NCT01919489

Date: October 28, 2019

Protocol Title:

Liraglutide Hospital Discharge Trial: 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

INVESTIGATOR-INITIATED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN)
U1111-1139-2991

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BACKGROUND and SIGNIFICANCE:

The association between hyperglycemia and poor clinical outcomes in patients with and without diabetes is well established (2-6). Extensive data from observational and prospective randomized controlled trials in hospitalized patients have reported a strong association between hyperglycemia and poor clinical outcome, such as mortality, morbidity, length of stay (LOS), infections and overall complications (2, 5, 7-9). Most clinical trials in critically ill and general medicine and surgery patients have reported that improvement of glycemic control reduces LOS, risk of multiorgan failure and systemic infections (10-12), as well as short- and long-term mortality (7, 12) in patients with hyperglycemia and diabetes.

Clinical guidelines from professional organizations (13-15) recommend the use of subcutaneous (SQ) insulin as the preferred therapy for glycemic control in general medical and surgical patients with T2D. The two most common SQ insulin regimens for inpatient glycemic management are sliding scale regular insulin (SSRI) and basal bolus insulin therapy in combination with correction insulin scale (16, 17). The use of basal bolus regimen results in better glycemic control and lower rate of hospital complications compared to sliding scale regular insulin (SSRI) (17-20). The basal bolus regimen, however, requires multiple insulin daily injections and is associated with a significant risk of hypoglycemia, which has been reported in up to 32% of non-ICU patients with T2D (17, 19, 20).

Increasing evidence indicates that incretin-based agents are safe and effective for the hospital management of patients with T2D. We recently completed a randomized open label trial comparing differences in glycemic control between treatment with sitagliptin (Januvia®) alone or in combination with glargine compared to a standard basal bolus regimen in general medicine and surgery patients with T2D (see preliminary result section). We found no differences in mean daily BG, frequency of hypoglycemia, length of hospital stay and complications. Similarly, the use of GLP-1 and its analogues have also been shown to improve glycemic control and to have a beneficial cardiovascular profile improving functional status and endothelial function (21), increasing left ventricular function in patients with heart failure (22) and in surgery patients undergoing CABG (22, 23), and to reducing infarct size and preserving left ventricular myocardial performance in ischemic models (24).

Liraglutide is a once-daily human GLP-1 analogue approved for the treatment of T2D. Liraglutide has been shown to lower blood glucose, stimulate endogenous insulin secretion, decrease plasma glucagon levels, inhibit gastric emptying, reduce food intake and body weight and improve ß-cell function when administered subcutaneously (25). Liraglutide increases insulin secretion in a glucose-dependent manner (i.e., only when plasma glucose levels are elevated), resulting in low-risk of hypoglycemia when used as monotherapy. When compared to insulin glargine therapy, the use of GLP1 has resulted in comparable reduction in HbA1c level,

lower rates of hypoglycemia and less weight gain (26). No prospective studies; however, have compared the efficacy and safety of liraglutide in the hospital setting or after hospital discharge.

SPECIFIC OBJECTIVES:

Primary objective is to compare the safety and efficacy of liraglutide (Victoza®) versus glargine insulin on glycemic control after 26 weeks of treatment in medicine and surgical patients with T2D after hospital discharge.

RESEARCH DESIGN AND METHODS

Study Hypothesis (hypotheses):

We hypothesize that treatment with liraglutide (Victoza®) will result in a similar improvement in HbA1c levels and in lower rate of hypoglycemic events compared to treatment with glargine (Lantus®) in patients with T2D after hospital discharge.

Specific Aim 1: To determine whether treatment with liraglutide (Victoza®) will result in similar glycemic control (HbA1c at 26 weeks) and a lower rate of hypoglycemic events compared to treatment with glargine (Lantus®) in patients with T2D after hospital discharge. Patients with poorly controlled (HbA1c ≥7%-10%) T2D treated with diet or oral antidiabetic agents, or on low-dose insulin therapy (TDD ≤0.4 unit/kg/day) will be randomized to liraglutide or glargine with or without oral agents at hospital discharge.

Endpoints:

Study Outcomes:

The primary outcome of the study is to determine differences in HbA1c concentration at 26 weeks from discharge between liraglutide and glargine insulin therapy.

The secondary outcome is to compare differences between treatment groups in any of the following measures during the 26 weeks following hospital discharge in patients with T2D:

- Self-measured blood glucose (SMBG) 7-point profiles
- Fasting and postprandial BG concentration
- Incidence rate and number of hypoglycemic events (<70 mg/dl) and severe hypoglycemic events (<40 mg/dl).
- Percent of patients with 26 week HbA1c <7.0% and no hypoglycemia
- Percent of patients with 26 week HbA1c <7.0% and no weight gain
- Percent of patients with 12 week HbA1c <7.0% and no hypoglycemia
- Change in body weight and BMI

- Cardiovascular risk factors including changes in blood pressure, heart rate, and lipid profile.
- Total daily dose of insulin
- Number of emergency room visits and hospital readmissions
- Acute renal failure during the 26-week follow-up defined as a clinical diagnosis of acute renal failure with documented new-onset abnormal renal function (increment in creatinine ≥ 0.5 mg/dL from baseline)

Study type:

The trial is a 26-week, randomized, open label-controlled two-armed, multi-center, multi-national trial investigating the efficacy and safety of liraglutide versus glargine insulin in medicine and surgical patients with T2D after hospital discharge.

We will recruit a total of 330 poorly controlled (HbA1c ≥7%-10%) patients with T2D treated with diet or oral antidiabetic agents (OAD) or on low-dose insulin therapy (TDD ≤0.4 unit/kg/day) prior to admission. Patients will be treated with a standard basal bolus insulin regimen during the hospital stay. Prior to hospital discharge, patients will be randomized to liraglutide or glargine with or without oral antidiabetic drugs. After discharge, a member of the diabetes research team will contact patients via telephone call every 2 weeks to assess response to therapy. In addition, patients will be asked to attend an outpatient clinic visit at 2 (optional), 4, 12 and 26 weeks after hospital discharge. Recommendation on insulin dose adjustment will be provided to patients at each telephone contact and clinic visits.

Recommendation for liraglutide dose escalation will be done every one or two weeks until the maintenance dose of 1.8 mg is reached. Dose escalation can be extended over 2 weeks at the discretion of the investigator in case of gastrointestinal adverse events. Liraglutide and insulin will be add-on to the subject's pre-admission OAD regimen. Dose of OAD should remain unchanged throughout the trial, however dose reduction of insulin and sulfonylurea is allowed due to hypoglycemia.

Study Groups:

We plan to analyze a total of 280 patients (who receive study medication) with T2D at the time of hospital discharge.

- Group 1. Liraglutide once daily in combination to OADs (n=140).

- Group 2. Glargine once daily in combination to OADs (n=140).

Study population:

This will analyze 380 general medicine and surgical patients with a known history of T2D, age 18-80, treated with diet alone and/or oral antidiabetic agents including sulfonylureas, repaglinide, nateglinide, DPP4s, SGLT2, or metformin as monotherapy or in combination therapy or on low-dose insulin therapy (TDD ≤0.4 unit/kg/day) prior to admission. Subjects will be recruited from 5 medical centers in the United States. A total of 300 patients will be recruited at Grady Memorial Hospital, Emory University Hospital and Emory Midtown hospital.

Study Sites: This study will be performed at Grady Memorial Hospital, Emory University Hospital, Emory University Hospital at Midtown, and 3 institutions in the United States:

1. MetroHealth Medical Center, Cleveland (PI: Jorge Calles-Escandon, MD.)
2. State University of NY at Buffalo (PI: Ajay Chaudhuri, MD.)
3. University of Miami, Florida (PI: Gianluca Iacobellis, MD.)
4. Sanatorio Guemes, Buenos Aires -Argentina (PI: Javier Farias)

Inclusion Criteria

1. Males or females between the ages of 18 and 80 years discharged after hospital admission from non- ICU general medicine and surgical services (excluding gastrointestinal and cardiac surgeries).
2. Admission HbA1c between 7% and 10%
3. Patients with T2D treated with diet alone or with oral antidiabetic agents as monotherapy or in combination therapy (excluding GLP1 receptor agonists) or on low-dose insulin therapy (TDD ≤0.4 unit/kg/day) prior to admission.
4. Subjects with a hospital admission BG < 400 mg/dL without laboratory evidence of diabetic ketoacidosis (serum bicarbonate < 18 mEq/L or positive serum or urinary ketones).
5. BMI > 25 Kg/m^2 and ≤ 45 Kg/m^2

Exclusion Criteria

1. Age < 18 or > 80 years.
2. Subjects with stress hyperglycemia (BG > 140 mg/dL and HbA1c < 6.5%)
3. Subjects with a history of type 1 diabetes (1).
4. Treatment with GLP1 analogs during the past 3 months prior to admission.
5. Recurrent severe hypoglycemia or hypoglycemic unawareness.
6. Subjects with gastrointestinal obstruction, gastroparesis or those expected to require gastrointestinal suction.
7. History of medullary thyroid cancer or multiple endocrine neoplasias
8. Patients with acute or chronic pancreatitis, pancreatic cancer or gallbladder disease.
9. Patients with clinically significant hepatic disease (cirrhosis, jaundice, end-stage liver disease, portal hypertension) and elevated ALT and AST > 3 times upper limit of normal, or significantly impaired renal function (GFR < 30 ml/min).

10. Treatment with oral or injectable corticosteroid (equivalent or higher than prednisone 5mg/day), parenteral nutrition and immunosuppressive treatment.
11. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
12. Female subjects who are pregnant or breast-feeding at time of enrollment into the study.
13. Females of childbearing potential who are not using adequate contraceptive methods (as required by local law or practice).

Investigational drugs.

- Liraglutide 6.0 mg/mL solution for subcutaneous (s.c.) injection. The solution will be provided in 3 mL prefilled pen.
- Liraglutide will be provided to patients
- Glargine will be provided

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 diagnosed with acute pancreatitis by clinical and/or radiographic criteria.
4. If the fasting BG and average daily BG on 3 consecutive days exceeds > 15.0 mmol/L (240 mg/dL). If this occurs, the subject will be called for an unscheduled visit as soon as possible. A confirmatory FPG should be obtained and analyzed by the hospital laboratory. If this FPG exceeds 15.0 mmol/L (240 mg/dL), and no treatable intercurrent cause for the hyperglycemia has been identified, the subject must be withdrawn.
5. Pregnancy or intention to become pregnant.

Subject Replacement

There will be no replacement of subjects in this trial.

Rationale for Study Population

We will recruit patients with poorly controlled T2D (HbA1c ≥7%-10%) treated with diet and/or oral antidiabetic agents or on low-dose insulin therapy (TDD≤0.4unit/kg/day)prior to admission. Patients will be treated with a basal bolus insulin regimen during the hospital stay (standard of care). Prior to hospital discharge, patients will be randomized to receive liraglutide or glargine as monotherapy in treatment of patients treated with low-dose insulin therapy (TDD ≤0.4 unit/kg/day) (or as add-on therapy to the subject's pre-admission OAD regimen.

We plan to analyze a total of 280 patients (who receive study medication) with T2D at the time of hospital discharge [liraglutide once daily in combination to OADs (n=140) or glargine once daily in combination to OADs (n=140)].

GROUP 1. Liraglutide Treatment Group.

- **Patients receiving no Therapy prior to admission:**
  - Discharge on liraglutide once daily.
  - Start metformin if A1C≥8% and no contraindications.

- **Patients receiving OAD prior to admission:**
- If no contraindication, restart pre-admission OADs according to standard of care and investigator's medical discretion (metformin, sulfonylureas, nateglinide, repaglinide, pioglitazone) in combination to liraglutide.
  - The total daily dose of insulin secretagogues (sulfonylureas, nateglinides and repaglinide) will be reduced to 50% of pre-admission dose to avoid risk of hypoglycemia.
  - DPP4-inhibitors will not be used in combination with liraglutide during the study period.

Liraglutide Titration:
Liraglutide will be administered once daily in accordance with a 3-4 week dose escalation regimen with weekly increments of 0.6 mg until the maintenance dose of 1.8 mg is reached. Liraglutide will be administered once daily by s.c. injections, either in the abdomen, thigh or upper arm. Injections can be done at any time of the day and irrespective of meals. It is recommended that the time of injection is consistent throughout the trial. Subjects will be instructed to perform an air shot before the first use of a new prefilled pen.

GROUP 2. Glargine Group

V.e. Treatment recommendations at discharge:

- **Patients receiving no Therapy prior to admission:**
  - Discharge on glargine once daily at 50% of total hospital dose
  - Add metformin if A1C≥8% and no contraindications.

- **Patients receiving OAD prior to admission:**

- If no contraindication, restart pre-admission OADs according to standard of care and investigator's medical discretion (metformin, sulfonylureas, repaglinide, nateglinide, pioglitazone) in combination to glargine at 50% of hospital dose.
- The total daily dose of insulin secretagogues (sulfonylureas, nateglinides and repaglinide) will be reduced to 50% of pre-admission dose to avoid risk of hypoglycemia.
- DPP4-inhibitors will not be used in combination with liraglutide during the study period

Algorithm for outpatient <u>glargine insulin dose adjustment</u>:

Insulin Glargine	
If mean **FBG > 180 mg/dL** for the last 2 consecutive days and no episodes of hypoglycemia (BG <70 mg/dL)	Increase daily dose by 4 IU
If mean **FBG > 140 mg/dL** for the last 2 consecutive days and no episodes of hypoglycemia (BG <70 mg/dL)	Increase daily dose by 2 IU
If mean **FBG between 100 to 140 mg/dL** for the last 2 consecutive days and no episodes of hypoglycemia (BG <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 < 70 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%

In hospital Diabetes Education. Prior to discharge, participants will be trained on:

1. Diabetes education if not received within 1 year of admission.
2. ADA targets for fasting and premeal BG between 70 to 130 mg/dL.
3. Use of glucose meters for home glucose self-monitoring (meters may vary at different institutions).
4. Keeping BG records, and will receive a log-book to record glucose tests results.
5. Hypoglycemia recognition and management (see VI.B.)
6. Insulin administration (if needed).

Follow-up Care:

- If baseline visit was not fully completed at the time of discharge, patients will be scheduled to return for a short in-person visit to complete (body measurements) study procedures within 7 days of discharge. Research team will call to verify correct administration of study medication and availability of medications and glycemic control monitoring supplies.

- After discharge, a member of the diabetes research team will contact patients via telephone call every 2 weeks for a total of 26 weeks.
- Patients will be asked to attend the next outpatient clinic visit at 4 weeks of hospital discharge. During this visit, patients will receive 8 weeks drug supply of liraglutide and will be asked to return to clinic at 12 weeks for the next outpatient visit. During this visit, patients will receive 12 weeks (3 months) drug supply of liraglutide and will be asked to return to a fourth and final visit at 26 weeks of hospital discharge.
- Recommendations on insulin adjustment will be provided to patients at each telephone and clinic visits by a licensed physician (fellow or study physician) (see section Vf).

During follow up we will collect the following information:

1. Glycemic control:
    a. Mean daily fasting and premeal blood glucose levels.
    b. HbA1c at 3 and 6 months of discharge
    c. Number of hypoglycemic events
        - **Symptomatic hypoglycemia** is defined as an event with typical symptoms (i.e., sweating, palpitation, and feeling of hunger) with or without confirmation by plasma glucose <70 mg/dl (3.9 mmol/L).
        - **Severe hypoglycemia** is defined as episodes necessitating assistance and associated with measured plasma glucose < 40 mg/dl (2.2 mmol/L) or with prompt recovery after administration of carbohydrates, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by low plasma glucose.

2. Diabetes treatment:
    a. Number of patients receiving insulin therapy, dosage and compliance.
    b. Use of liraglutide and other oral agents, dosage and compliance.
    c. Protocol adherence by PCP (diabetes clinic versus PCP)

3. Clinical Outcome:
    a. Hospital readmissions
    b. Emergency room visits

7-point self-measured blood glucose profile:

Subjects will be instructed to perform a 7-point SMBG profile three times during the trial within one week prior to site visit on a day where the subject do not anticipate unusual strenuous exercise.

Time-points for 7-point profile:

The blood glucose levels should be measured and recorded in the diary (including date, actual clock time and blood glucose value) at the following time points, always starting with measurement before breakfast.

- Before breakfast
- 90 min after the start of breakfast
- Before lunch
- 90 min after the start of lunch
- Before dinner
- 90 min after the start of dinner
- At bedtime

Body measurements

Body measurements consist of the parameters: Body weight, height, waist circumference, hip circumference and BMI

Body weight: Body weight should be measured in kilogram or pound, without shoes and only wearing light clothing.

Height: Height (without shoes) should be measured in centimeters or inches and recorded without decimals.

Waist and hip circumference: The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest. The hip circumference is defined as the widest circumference around the buttocks. Three consecutive measurements of waist and hip circumference should be taken and recorded. Mean values will be used for result analysis. The waist and hip circumferences will be measured to the nearest 0.5 cm (0.2 inches) using a non-stretchable measuring tape.

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist and hip. The tape should touch skin, but not compress soft tissue and twist in tape should be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

Body Mass Index (BMI): BMI will be calculated by the formula Body weight (Kg)/m^2.

Assessment for Safety

Potential Risks to the Subjects:

Hypoglycemia. It is possible that following the proposed protocol, patients receiving basal insulin or liraglutide may develop hypoglycemia. For the purpose of this analysis we **symptomatic hypoglycemia** is defined as an event with typical symptoms (i.e., sweating, palpitation, and feeling of hunger) with or without confirmation by plasma glucose <70 mg/dl (3.9 mmol/L). We expect that approximately 20% to 40% of subjects treated with basal insulin alone or in combination to OADs will experience one or more episodes of hypoglycemia during follow-up. We anticipate that less than 10% of patients taking liraglutide alone or in combination to OADs will experience hypoglycemic events.
Severe hypoglycemia is defined as episodes necessitating assistance and associated with measured plasma glucose < 40 mg/dl (2.2 mmol/L) or with prompt recovery after administration of carbohydrates, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by low plasma glucose. We anticipate that less than 5% of patients on insulin or liraglutide alone or in combination to OADs will experience severe hypoglycemic events.

Gastrointestinal side effects including nausea and vomiting are more common in patients treated with liraglutide compared to placebo. The frequency of nausea and vomiting is reported in up to 14% of patients receiving higher doses of liraglutide 1.8 mg in combination to metformin and sulfonylurea therapy compared to 3.5% in patients receiving placebo plus OADs (Victoza package insert). The number of adverse events will be collected at each telephone contact or clinic visit. There have been few reported events of acute pancreatitis. Subjects should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, liraglutide and other potentially suspect medicinal products should be discontinued. If the investigator suspects acute pancreatitis, all suspected drugs should be discontinued until confirmatory test have been conducted and appropriate treatment should be initiated. Subjects diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase >3xUNR or characteristic findings on CT scan/ MRI should be withdrawn from the study.

Protection against Risks:
We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor response to medical treatment every 2 weeks by telephone contact and every 3 months during clinic visits, b) women of reproductive age who are sexually active will undergo a urine pregnancy tests prior to participation in the study, c) female subjects whom are pregnant, breast-feeding, or not willing to use appropriate contraception at time of enrollment will not be included in the study, d) patients with significant comorbidities such as chronic kidney disease

greater than stage III, liver cirrhosis, gastroparesis, and pancreatic disorders will be excluded from the study.

Hypoglycemia: Patients will receive diabetes education prior to discharge and will be instructed on hypoglycemia sign/symptoms and treatment. Patients will be asked to call the diabetes center and/or PCP in the event of hypoglycemia. If a patient develops hypoglycemia, the dose of OAD will be reduced or discontinued and the daily dose of basal insulin will be reduced by 10% to 30% (see treatment algorithm).

Gastrointestinal side effects including nausea and vomiting may be expected, more commonly in patients treated with liraglutide. In subjects with suspected acute pancreatitis liraglutide and other potentially suspect medicinal products should be discontinued until confirmatory tests have been conducted and appropriate treatment initiated.

STATISTICAL CONSIDERATIONS:

This study is randomized multicenter, open-label controlled trial. The overall hypothesis is that patients with T2D discharged on liraglutide and glargine will experience similar improvement in glycemic control (HbA1c level at 26 weeks post-discharge). In addition, we anticipate that compared to patients treated with insulin glargine, patients on liraglutide will experience lower number of hypoglycemic events and less weight gain during follow-up.

Sample Size and Power Calculations: The primary endpoint in this study is glycemic control measured by HbA1c at 26 weeks after discharge between treatment groups. To show the non-inferiority of liraglutide to basal glargine insulin in terms of glycemic control, we set the equivalence margin as 0.5%, from a view that an HbA1c difference < 0.5% is usually not considered as clinically significant.
Based on preliminary discharge data, we assume the standard deviation of 26 week A1c is bounded about 1.5%. We set the margin of equivalence as 0.5% and assume the true difference between mean A1c is 0. A sample size of 124 for each treatment group would achieve 80% power to reject the hypothesis that the mean HbA1c in patients treated with liraglutide is < 0.5% more than that in patients treated with glargine based on a two-sample one-sided t test, with alpha=0.05. Accounting for 10% attrition rate, we would need 140 patients per treatment group. This leads to a final total sample size estimate of 280 patients that receive study medication.

The secondary outcome of major interest in this study is the difference in hypoglycemia (BG <70 mg/dl). Based on our preliminary discharge data, 30-40% of patients treated with basal insulin will have at least one hypoglycemia episode. Assuming a hypoglycemia rate of 20-35% in the insulin group in this study, given the sample size of 140 subjects per treatment group, based on a two sided Fisher's exact test with alpha=0.05, we would have 80% power to detect an odds ratio in hypoglycemia rate of 0.42 in liraglutide group (versus glargine group). In the following table,

we give the estimated power under different assumed group differences in hypoglycemia rate, represented by four hypothesized odds ratios.

Table: Estimated power with 140 subjects per group (before 10% attrition) and the anticipated hypoglycemia rate of 35% in the insulin group based on two-sided Fisher's exact test with alpha=0.05.

Odds Ratio	0.2	0.3	0.4	0.5
Power	>0.99	0.97	0.85	0.64

The above calculations show that we will have a good chance to achieve over 80% power for the secondary outcome of hypoglycemia rate.

Analysis of Primary Endpoint:

The primary endpoint in this study is glycemic control measured by HbA1c concentration at 26 weeks post-discharge. 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 . Particularly, we will investigate center effect for the HbA1c outcome by stratified univariate analysis or multivariate linear regression. 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 in this study include rate of hypoglycemia, number of hypoglycemia events, change in body weight in kilograms, number of episodes of severe hyperglycemia, complications and Emergency Room or hospital readmissions. For hypoglycemia outcomes, we will first conduct nonparametric comparisons of the rate of hypoglycemia based on a two-sided Chi-square test (or Fisher's exact test in the presence of low incidence rates), followed by the Cochran-Mantel-Haenszel test which adjusts for the potential center effect. Univariate Poisson regression (or Negative Binomial regression) will be performed to assess whether there is any difference in the number of hypoglycemia events between the two treatment groups. We will further conduct multivariate Logistic regression, Poisson regression (or negative binomial regression) to estimate the difference in the rate and frequency of hypoglycemia while adjusting for relevant covariates. 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, such as deviance residual plot and Hosmer-Lemeshow test, will be applied to examine the fit of the developed models. Similar analyses will be conducted for severe hyperglycemia outcomes. For single measurement continuous outcomes, such as length of

hospital stay, we will use two-sample t-tests or nonparametric Wilcoxon tests to compare them between groups. Transformations will be applied if normality violation is detected. Multivariate linear regression will be further conducted to assess the difference in continuous secondary outcomes between the two groups with other relevant covariates. We will use standard model selection and model checking procedures for linear regression to decide the final models and assess their fits to the data. For repeated measurement continuous outcomes, such as fasting BG values, we will first conduct cross-section analysis following the same strategy for the single measurement continuous outcome. Then we plan to fit repeated measures ANOVA or linear models which can simultaneously account for multiple time points during the discharge follow-up. Model selection and model checking will follow the standard procedures.

DATA HANDLING AND RECORD KEEPING:

Data collection records with personal identifiers will be stored in locked file cabinets. 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.
All data will be entered electronically in Redcap by participating sites. Sponsor site expects data to be entered in Redcap within 10 days of phone call or outpatient visit.

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 enroll 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 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 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.

Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important and key

points of the study. One of the investigators or research coordinators will obtain a witnessed informed consent prior to inclusion of a patient into the study.

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.

STUDY SCHEDULE:

FIRST PATIENT IN	**2014 FEBRUARY**
SCREENING	**~2000**
RANDOMIZED	**280**
LAST PATIENT RECRUITED	**2020 MAY**
LAST PATIENT IN (COMPLETED)	**2020 DECEMBER**
DATA ANALYSIS	**DECEMBER 2020-JANUARY 2021**
SUBMISSION TO CONGRESS OR JOURNAL	**ADA 2021 MAJOR MEDICINE JOURNAL AND/OR DIABETES CARE**

548 Flow Chart

Visit Type	Baseline Visit Hosp-prior to D/C	TC	Clinic visit	TC	TC	TC	Clinic visit	TC	TC	TC	TC	TC	TC	Clinic visit
Time-wks.[1]	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Inf. consent	x													
Incl/excl criteria	x													
Random	x													
Withdrawal criteria		x	x		x		x		x		x		x	
Drug Compliance		x	x	x	x	x	x	x	x	x	x	x	x	x
Dose adjustment		x	x	x	x		x			x		x		x
Efficacy														
Vital signs	X		x				x							x
Phys Exam	X		x				x							x
Body wgt	x		x				x							x
Body measurements	X[2]		x				x							x
BMI	x		x				x							x
HbA1c	X[3]						x							x
Fasting BG	X[3]		x				x							x
Collect 7-point profile			x				x							x
Chemistry (BMP or CMP)							**x**							
Safety														
Adv events	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglyc.	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Trial material														
Drug dispense	x		x				x							
Drug account	x		x				x							x
Remind 7-point profile prior next visit		x				x							x	

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[1] TELEPHONE CALLS AND OUTPATIEN VISITS CAN BE COMPLETED ±7 DAYS.

[2] TO BE COMPLETED WITHIN 7 DAYS AFTER D/C (IF NOT COMPLETED AT TIME OF DISCHARGE)

[3] OBTAINED FROM MEDICAL RECORDS (HBA1C≤3MONTHS)

STUDY DRUGS AND MATERIALS:

Clinical trial materials will be labeled and should be handled and stored according to the respective hospital's regulatory requirements. After discharge, patients will be re-started on their pre-admission OADs (except for DPP4-inhibitors and selected drugs in the presence of contraindication, i.e., metformin and renal failure). Liraglutide or glargine will be provided during the study.

Study medication(s) / devices(s)
Liraglutide 6.0 mg/mL solution for s.c. injection, provided in 3 mL prefilled pen.

Storage and Drug Accountability of Study Medication(s)
Liraglutide will be stored and dispensed by the research pharmacy at each institution. The liraglutide prefilled pen and glargine 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), the liraglutide prefilled pen 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). The liraglutide prefilled pen must be protected from all sources of light and the pen cap should be kept on when the pen is not in use.

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 liraglutide and glargine insulin at each visit.

Randomization and Blinding
This is an open label randomized 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. Patient will be randomized (block randomization) based on glucose levels (BG>200 or BG<200). The randomization table will be mailed to each institution where a member of the research team will be in charge of the randomization process and group assignment.

CONCOMITANT ILLNESSES AND MEDICATIONS:

Background medications:

Metformin. Metformin is considered background medication (non-investigational medicinal product) and will not be provided during the trial. The total daily dose of metformin prior to admission will be restarted at hospital discharge (unless contraindicated = i.e., renal failure or eGFR < 45 ml/min) with no dose adjustments occurring during the trial.

Sulfonylurea and Insulin secretagogues. Sulfonylurea treatment is considered background medication (non-investigational medicinal product) and will not be provided during the trial. The total daily dose of sulfonylurea prior to admission will be decreased at hospital discharge. During the study, no up-titration of sulfonylurea dosage will be allowed. Dose reduction of SU due to hypoglycemia may be allowed at the investigators discretion. In the event of hypoglycemia, the dose of sulfonylurea can be reduced or the drug can be stopped at the investigator's discretion.

Pioglitazone. Pioglitazone is considered background medication (non-investigational medicinal product) and will not be provided during the trial. The total daily dose of pioglitazone prior to admission will be restarted at hospital discharge. No dose adjustment or up-titration will occur during the trial; however, in the event of peripheral edema or signs of volume overload, the dose of pioglitazone can be reduced or stopped at the investigator's discretion.

ADVERSE EVENTS:

Definition: An 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 as defined in the protocol.
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.

In this trial, an SAE is an experience that at any dose results in any of the following:
-Death
-A life-threatening experience
-Inpatient hospitalization
-Persistent or significant disability or incapacity
-Important medical events that may not result in death, be life threatening or require hospitalization
-Episodes of severe hypoglycemia will be captured as serious AEs.

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.

The presence of SAE will be reported to the Emory IRB and Novo Nordisk within 24 hours by fax or e-mail. A SAE is any adverse event from this study that results in one of the following outcomes: death, initial or prolonged inpatient hospitalization, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, and events considered significant by the investigator for any other reason.

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 in subjects who received liraglutide 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.

Medical Events of Special Interest (MESI)

Medical Events of Special Interest 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 acute pancreatitis, cardiovascular events (heart failure, acute myocardial infarction, and atrial fibrillation), malignancies, and medication errors (e.g., incorrect dose of liraglutide or insulin).

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 liraglutideat 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 your doctor requires as part of your usual medical care.

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 to the patient at the patient's own cost. The only exception is if it is proved that the injury or illness is directly caused by the negligence of an Emory or sponsor 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.

Publication Plan:

We anticipate completion of the study in October or November 2020. Data will be analysed in December 2020. One abstract will be submitted to the 2021 American Diabetes Association meeting and manuscript(s) will be submitted during the first six months of 2021.

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