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A Randomized Controlled Trial Comparing Glargine U300 and Glargine U100 for the Inpatient and Post-Hospital Discharge Management of Medicine and Surgery Patients with Type 2 Diabetes

Principal Investigator:

Guillermo E. Umpierrez, M.D.
Professor of Medicine, Endocrinology
Emory University School of Medicine
Director, Diabetes and Endocrinology Section
Grady Health System

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Principal Investigator:

Guillermo E. Umpierrez, M.D.
Professor of Medicine, Endocrinology
Emory University School of Medicine
Director, Diabetes and Endocrinology Section
Grady Health System

Co-Principal Investigator:

Francisco J Pasquel, MD, MPH
Assistant Professor of Medicine, Endocrinology
Emory University School of Medicine

Investigators:

Emory University, Atlanta
Priyathama Vellanki, MD
Maya Fayfman, MD
Sonya Haw, MD
Sol Jacobs, MD
Rodolfo J Galindo, MD

Minneapolis Medical Research Foundation-Hennepin Medical Center, Minneapolis
Ameer Ali Khowaja, MD

The Cleveland Clinic Foundation, Ohio
Cecilia Lansang, MD

I. RESEARCH OBJECTIVES AND SPECIFIC AIMS

A. Introduction:

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 hospital hypoglycemia rate was reported in 3% in medicine (16) and 12% in surgery (17) 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 (18-20).

The Food and Drug Administration and the European Commission recently approved Glargine U300 insulin for the treatment of patients with diabetes. Glargine U300 is long-acting insulin with duration of action longer than 24 hours (21, 22). The results of the Edition clinical trials with more than 3500 patients demonstrated that glargine U300 resulted in similar improvement in glycemic control and with a lower rate of nocturnal hypoglycemia compared to glargine U100 (23-27). The efficacy and safety of glargine U300 has been documented in patients with type 1 and type 2 diabetes (22-27); however, no previous studies have assessed the safety and efficacy of these new formulations in the inpatient (hospital) setting. In addition, certain features of glargine U300 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; and limited safety data in acutely ill patients with altered nutritional status. Accordingly, the present randomized clinical trial will compare the efficacy and safety of a basal bolus regimen with glargine U300 and glargine U100 (standard of care) in general medicine and surgery patients with T2D.

B. Specific Aims:

Aim 1. To determine differences in inpatient glycemic control, as measured by mean daily blood glucose concentration and frequency of hypoglycemia, in general medicine and surgery patients with T2D treated with basal bolus regimen with glargine U300 and U100 plus glulisine insulin before meals.

Hypothesis*:* Treatment with glargine U300 will result in equivalent glycemic control in hospitalized patients with T2D. Glargine U300 will result in lower number of hypoglycemia compared to glargine.

Aim 2: To determine differences in glycemic control after hospital discharge between treatment with glargine U300 and glargine U100 in medicine and surgery patients T2D. Patients with poorly controlled diabetes (HbA1c ≥7.5%) 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 7.5% and 10% will be discharged on preadmission oral antidiabetic agents plus glargine U300 and U100 once daily. Patients with an admission A1C ≥ 10% will be discharged on basal bolus regimen with glargine and glulisine insulin before meals.

Hypothesis: treatment with glargine U300 and U100 will result in a similar improvement in HbA1c levels after hospital discharge. Glargine U300 will result in lower number of hypoglycemia compared to U100.

II. BACKGROUND AND CURRENT STATUS OF WORK IN THE FIELD.

Inpatient glycemic control in non-ICU setting. A large body of evidence has shown that in hospitalized patients, the presence of hyperglycemia and diabetes is associated with increased risk of complications and death (1-6, 28-31). Several randomized multi-center trials have shown that the use of basal bolus insulin regimen result in improved glycemic control and reduced rate of hospital complications compared to sliding scale regular insulin (SSI) in patients with T2D (12-14). We have reported that treatment with basal and basal bolus regimens using glargine U100 results in greater improvement in BG control and a reduction in the frequency of hospital complications including postoperative wound infection, pneumonia, bacteremia, and acute renal and respiratory failure compared to SSI treatment.(16, 17, 32, 33) In addition, the use of basal bolus regimen with glargine U100 is safe with low rate of hypoglycemic events. Based on these studies and others, clinical practice guidelines for the management of hyperglycemia in non-ICU setting have favored the use of basal prandial insulin regimens with insulin analogs for most inpatients with T2D (6, 19, 31).

Efficacy and safety of new glargine U-300 insulin:

Glargine U300 insulin has a peakless pharmacodynamic profile with duration of action longer than 24 hours. Several clinical trials in the Edition clinical program, which included more than 3500 patients with type 2 diabetes treated with basal insulin or with oral agents demonstrated that glargine U300 treatment resulted in similar improvement in glycemic control (HbA1c reduction) compared to glargine U100 insulin (23-27). In addition, patients treated with glargine U300 experienced lower rates of hypoglycemia, in particular nocturnal hypoglycemia compared to glargine U100 (23-27). The safety profile of glargine U300 makes these new insulin formulations an attractive alternative to glargine U100, as hypoglycemia has been associated with increased risk of complications and mortality in the hospital setting (34, 35).

No previous studies have determined the safety and efficacy of glargine U300 compared to glargine U100 (current standard of care) in hospitalized patients with diabetes. Despite the benefit in improving glycemic control and in reducing hypoglycemia, there are potential concerns with the use of this new basal insulin formulation in the hospital due to its prolonged duration of action and time to achieve a steady-state concentration in patients with altered nutrition. The anticipated large number of patients who will be treated with glargine U300 in the future, makes this proposal timely and of great clinical interest.

Transition Care from Hospital to Home. Hospital discharge represents a critical time for ensuring a safe transition to the outpatient setting and reducing the need for emergency department visits and re-hospitalization. Few studies have addressed the management of patients with diabetes after hospital discharge in insulin treated patients with T2D. The Endocrine Society guidelines for the management of hyperglycemia recently recommended the use of HbA1c concentration during the hospital stay in tailoring the glycemic management of diabetic patients at discharge (19). In a recent study we assessed the efficacy of an HbA1c based algorithm using glargine insulin for the management of patients with T2D (see preliminary results section) (36). Patients with an HbA1c between 7% and 9% were discharged on a combination of OADs and glargine insulin at 50% of total daily hospital dose. Patients with an admission HbA1c $\geq$ 9% were discharged on a combination of OAD and glargine insulin at 80% of total daily hospital dose or on a basal bolus regimen with glargine and rapid-acting insulin analog before meals. The admission HbA1c on admission of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge ($p<0.01$). The rate of hypoglycemia was ~30% in patients treated with oral agents plus basal insulin and greater than 40% in patients treated with basal bolus insulin regimen. It is expected that

glargine U300, which is known to have lower rate of hypoglycemia compared to glargine U100, will reduce the rate of hypoglycemia after hospital discharge.

Significance and Innovation. Glargine U300 is a new generation basal insulin analog with a longer duration of action compared to insulin glargine (21, 22). Several outpatient trials have reported that treatment with glargine U300 results in comparable improvement in HbA1c levels and in lower rates of hypoglycemia compared to glargine U100 insulin (23-27). No previous studies; however, have compared the safety and efficacy of the long-acting glargine U300 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 glargine U300 in the inpatient setting and after hospital discharge in general medicine and surgery patients with T2D.

III. PRELIMINARY RESULTS:

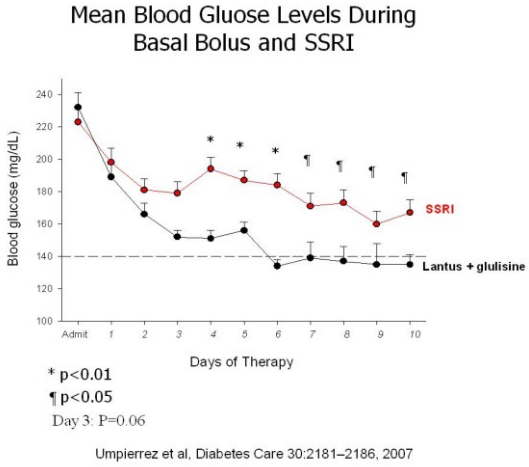
Our groups have reported the results of several observational and prospective, randomized multi-center trials comparing the efficacy and safety of basal/bolus insulin regimens to sliding scale regular insulin (SSI) and split-mixed regimen with NPH/regular in T2D patients admitted to general medicine services (16, 17).

In the Rabbit trial (Fig 1), 130 nonsurgical insulin naïve patients were randomized to receive glargine once daily and glulisine before meals or SSRI before meals and at bedtime. Patients treated with glargine/glulisine had greater improvement in BG control than SSRI with a minimal risk of hypoglycemia patients (3% of patients in each group had a BG < 60 mg/dL). A BG target of <140 mg/dL was achieved in 66% of patients treated with glargine and glulisine whereas only 38% of those treated with SSRI achieved target glycemia.

In the Rabbit-Surgery trial (Figure 2), 211 general non-cardiac surgery patients with T2D were randomized to a basal bolus (BB) with glargine once daily and glulisine before meals and to sliding scale regular insulin (SSI). Study outcomes included differences in daily BG levels and a composite of hospital complications including postoperative wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia. The mean daily glucose after the 1st day of BB and SSI was 145±32 mg/dl and 172±47 mg/dl, respectively, p<0.01. BG readings <140 mg/dl were recorded in 55% of patients in BB and 31% in the SSI group, p<0.001. There were reductions with BB as compared with SSI in the composite outcome (24.3% and 8.6%, OR: 3.39 (95% CI: 1.50-7.65); p=0.003). We concluded that treatment with BB improved glycemic control and reduced complications compared to SSI in surgery patients with T2D.

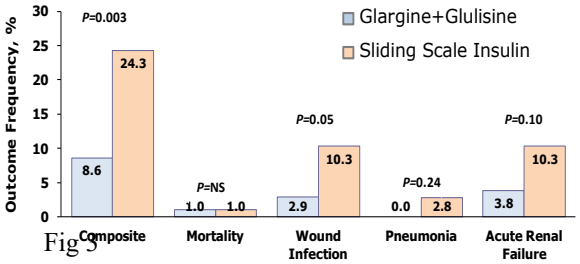
Basal insulin during Hospital Discharge.(36)

Fig 1



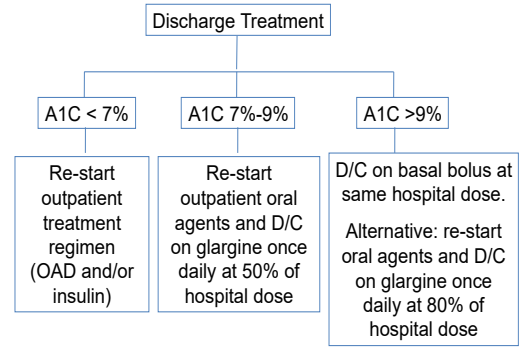
Umpierrez et al, Diabetes Care 30:2181–2186, 2007

Figure 3. Postoperative Complications



* Composite of hospital complications: wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia.

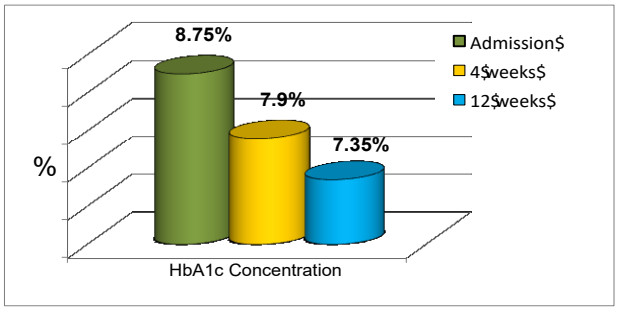
Fig 5



Umpierrez et al. ADA Scientific Meeting, Philadelphia 2012

In a recent preliminary study we assessed the efficacy of an HbA1c based algorithm for the management of non-ICU insulin treated patients with T2D (Fig. 4). A total of 214 general medicine and surgery patients with an admission HbA1c < 7% were discharged on their same outpatient antidiabetic regimen (oral antidiabetic drugs, OAD and/or insulin). Patients with an HbA1c between 7% and 9% were discharged on a combination of OADs and basal (glargine) insulin at 50% of total daily hospital dose. Patients with an admission HbA1c ≥ 9% were discharged on a combination of oral agents and basal insulin at 80-100% of total daily hospital dose or on a basal bolus regimen at the same hospital dosage. The admission HbA1c of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge respectively ($p<0.01$, Fig 5). Patients with higher HbA1c levels experienced a greater reduction as well as those treated with basal bolus insulin regimens. We concluded that the admission HbA1c concentration is beneficial in designing the discharge treatment algorithm after discharge in non-ICU patients with T2D.

Fig 4



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Our preliminary studies indicate that in general medicine and surgery patients with T2D 1) basal bolus or basal plus supplement regimens with glargine U100 are effective in improving glycemic control during the hospital stay, and 2) treatment with glargine U100 alone or in combination with oral agents or rapid-acting insulin (basal bolus) is effective in improving and maintain glucose control after hospital discharge. In addition, these results indicate our ability to design, recruit and complete clinical trials in hospitalized patients with T2D.

IV. EXPERIMENTAL PLAN

Aim 1. To determine differences in inpatient glycemic control, as measured by mean daily blood glucose concentration and frequency of hypoglycemia, in general medicine and surgery patients with T2D treated with basal bolus regimen with glargine U300 and U100 plus glulisine insulin before meals.

IV.a. Rationale. Several studies have shown improved clinical outcome with improved glycemic control in hospitalized patients with T2D (4, 5, 9, 11, 28, 37, 38). 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). Glargine U300 results in similar improvement but in lower rate of hypoglycemia than treatment with glargine U100. No previous studies; however, have compared the efficacy and safety of glargine U300 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.

IV.b. STUDY DESIGN AND METHODS

We will consent about 300 patients (for a total of 180 randomized subjects) with T2D treated with diet, oral hypoglycemic agents or insulin therapy, except long-acting GLP1-RA (albiglutide, albiglutide and weekly exenatide), prior to admission will be included in this prospective, randomized, open label trial to compare the safety and efficacy of a basal bolus regimen with glargine U300 and U100 in patients with T2D admitted to general medicine and surgery services.

IV.c. Primary and Secondary Research Outcomes:

The primary outcome of the study is to determine differences in glycemic control as measured by mean daily blood glucose concentration between treatment groups. For each subject, we will take the average of all pre-meal and bedtime glucose values collected after the first day of therapy during the hospital stay (up to 10 days).

Secondary outcomes include differences between treatment groups in any of the following measures:

1. Differences in mean daily glucose in patients admitted to medicine and surgery services.
2. Differences in mean daily glucose in patients with admission HbA1c lower than and higher than 8%.
3. Differences in mean daily glucose in patients with length of stay shorter and longer than 3 and 5 days.
4. Proportion of BG readings within target of 80 mg/dl and 180 mg/dl before meals.
5. Number of BG readings between 80 mg/dl and 180 mg/dl before meals without hypoglycemia.
6. Number of patients with hypoglycemia (defined as a BG < 70 mg/dl) and number of events adjusted by length of stay (event rate).
7. Number of patients with severe hypoglycemia (defined as a BG < 40 mg/dl) and number of events adjusted by length of stay (event rate).
8. Length of hospital stay.
9. Cardiac complications are defined as myocardial infarction, cardiac arrhythmia requiring medical treatment, or cardiac arrest.
10. Acute renal failure defined as a clinical diagnosis with documented new-onset abnormal renal function (increment in serum creatinine > 0.5 mg/dL from baseline).
11. Hospital mortality.

IV.d. Plan. This study will include male or female subjects > 18 years. Due to the design of this study, there will be no run-in period. 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 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. The goal of insulin therapy is to maintain fasting and pre-meal blood glucose levels between 80 mg/dl and 180 mg/dL while avoiding hypoglycemia.

A total of 180 patients with T2D with a blood glucose > 140 mg/dL and < 400 mg/dL will be randomized to receive:

Group 1. Basal bolus with glargine U300 once daily and glulisine insulin before meals (n=90).
Group 2. Basal bolus with glargine U100 once daily and glulisine insulin before meals (n=90)**.**

IV.d. Basal Bolus Insulin Protocol.

Patients will be treated with a basal bolus insulin regimen as previously reported (15, 16, 39). 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 200 mg/dL and 0.5 U/kg/day for BG between 201 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 (glargine U300 or U100) once daily and half as insulin glulisine 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 (32). Insulin dose will be adjusted daily to maintain a fasting and pre-dinner BG between 80 mg/dl and 180 mg/dl.

IV. e Treatment randomization. This is an open label randomized controlled trial. Patients will be randomized 1:1 consecutively using a computer generated randomization table provided by Dr. Limin Peng, statistician 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. A research pharmacist at each institution will follow a computer-generated block randomization table based on prior insulin use (yes/no).

IV.f TREATMENT PROTOCOL - Basal Bolus Insulin Regimen with Glargine Once Daily plus Glulisine 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**:

- Randomization BG <200mg/dl-give 80% of the TDD*
- Randomization BG>200mg/dl-give 100% of the TDD*

- Half of TDD will be given as basal (glargine U300 or U100) and half as rapid-acting insulin.
- Glargine U300 and U100 will be given once daily, at the same time of the day.
- Patients will receive the full-dose of glargine (even if NPO) the day of surgery or diagnostic procedure(s).
- Glulisine insulin will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, glulisine 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 Prior to Admission

- Discontinue oral antidiabetic drugs on admission.
- Starting total daily insulin dose:
  - 0.4 U/Kg/day when randomization BG between 140-200 mg/dL
  - 0.5 U/Kg/day when randomization BG between 201-400 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 U300 or U100 and half as glulisine.
- Glargine will be given once daily, at the same time of the day.
- Patients will receive the full-dose of glargine insulin (even if NPO) the day of surgery or diagnostic procedure(s).
- Glulisine 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 glulisine will be held.

Supplemental insulin. Glulisine insulin will be administered following the "supplemental/correction insulin scale" protocol (Appendix 1).

- 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 following the "sensitive" dose of the supplemental insulin scale protocol.

Basal Insulin adjustment.

- Daily basal (glargine U300 and U100) insulin dose will be adjusted as follow:

- If the fasting and pre-dinner BG is between 100 - 140 mg/dl in the absence of hypoglycemia the previous day: no change
- If the fasting and 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 pre-dinner BG is 181- 299 mg/dl in the absence of hypoglycemia the previous day: increase basal insulin (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%.

IV.g. Data Analysis:

Aim 1. To determine differences in inpatient glycemic control, as measured by mean daily blood glucose concentration and frequency of hypoglycemia, in general medicine and surgery patients with T2D treated with basal bolus regimen with glargine U300 and U100 plus glulisine insulin before meals.

Due to the lack of efficacy and safety data with the use of glargine U300 in the inpatient setting, periodic conduct interim analyses will be conducted every 6 months to monitor the primary outcome and rate of hypoglycemia, and to modify the study design regarding interval of administration and dosage adjustment for basal insulin (see page 9, Data Safety Monitoring Plan, sections IV. f. and IV.g.).

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 glargine U300 and U100 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, 16). Based on the results from 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. Accounting for 10% 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 glycemic control measured by mean daily BG concentration among the two study groups. Blood glucose will be measured before each meal and at bedtime. We will first perform cross-sectional analyses using nonparametric Krustal-Wallis tests (or Wilcoxon tests) or one-way ANOVA, followed by repeated measures ANOVA to estimate and test the difference between the two treatment groups while simultaneously examining mean daily BG across multiple days during treatment. A mixed effect model may be used to further account center effect or other potential confounders for the BG outcome. 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 1in 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), if the outcome is binary (e.g. with or without hypoglycemia), we will first conduct nonparametric comparisons 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. If the discrete outcome is a count outcome (such as the number of hypoglycemic event), we will perform Poisson regression (or Negative Binomial regression) that adjusts for the length of hospital stay to assess the difference in the count outcome between the treatment groups. We also value the repeated measures analyses based on mixed effect models. This is because they will allow us to assess treatment effect fined tuned according to other confounders of the BG outcomes. By these considerations, we will conduct both types of analyses to provide a thorough evaluation of the hypothesis of interest. For continuous outcomes that are not repeated measures (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 while 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.

IV.f. Data and Safety Monitoring Board (DSMB):
The Data and Safety Monitoring Board (DSMB) will review unblended data on safety, treatment compliance, and evaluate the efficacy of the intervention being studied in this clinical trial. The DSMB will meet at 6-month intervals and report on study progress to the IRB.

IV.g. Interim Analysis and Stopping Rules: We plan to perform one interim analysis on the primary endpoint every 6 months and when half of the subjects have been randomized. The trial will be stopped if there is evidence beyond a reasonable doubt of a difference in the rate of death and hospital complications (two-sided alpha level, <0.01) between the treatment groups.

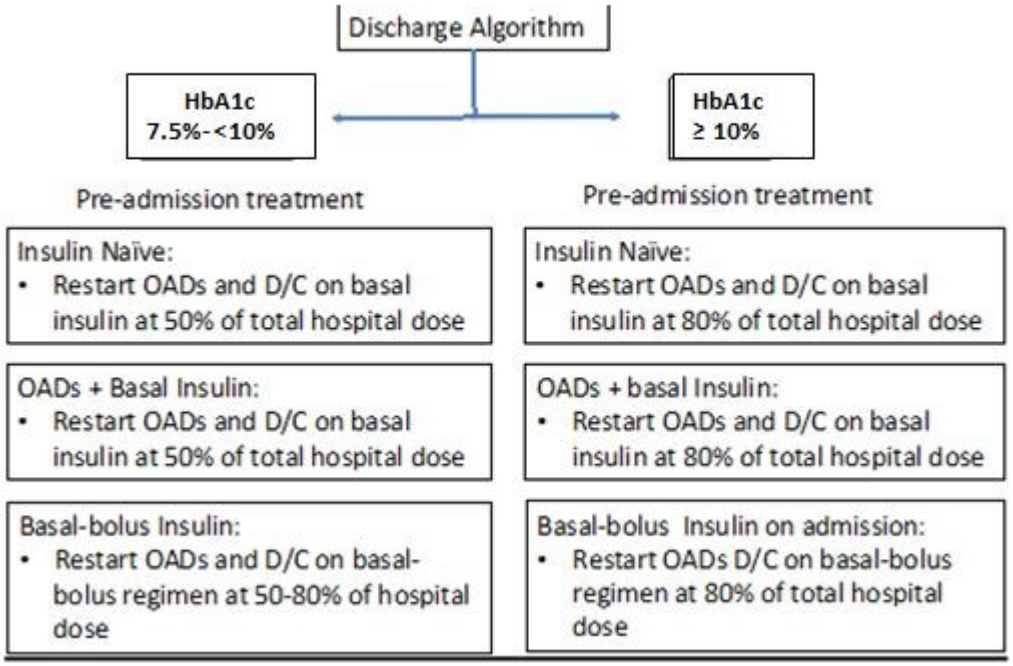
V. Aim 2: To determine differences in glycemic control after hospital discharge between treatment with glargine U300 and glargine U100 in medicine and surgery patients T2D.

V.a. Rationale. 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 bA1c 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 glargine U300 and U100 after hospital discharge. The total duration of the study is 3 months. Several outpatient insulin trials have shown that treatment with glargine U300 results in similar improvement in glycemic control, but in significant reduction in hypoglycemia compared to glargine U100 (23-27). Thus we expect that glargine U300 will be a safer alternative to current use of glargine U100 formulation.

V.b Insulin Discharge algorithm:
Patients with poorly controlled diabetes (HbA1c $\geq$7.5%) 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 admission Hba1c < 7.5% will be discharged on their preadmission antidiabetic regimen and will not be included in the Aim 2 outpatient study.
- Patients with no previous pharmacological treatment prior to admission will be discharged on 50% of daily basal insulin (glargine U300 or glargine U100) hospital dose.
- Patients on oral agents prior to admission with an HbA1c between 7.5% and <10% will be discharged on oral agents plus glargine U300 or glargine U100 at 50% of the daily hospital dose.
- Patients on oral agents prior to admission with an admission A1C ≥ 10% will be discharged on their oral agents plus glargine U300 or glargine U100 at 80% of daily hospital dose. If previous basal bolus only therapy or contraindications to previous oral therapy, discharge on basal bolus at 100% of daily hospital dose.
- Patients on oral agents plus basal insulin (NPH, glargine, detemir) prior to admission with HbA1C between 7.5% and <10% will be discharged on their oral agents plus glargine U300 or glargine U100 at 50% of daily hospital dose.
- Patients on oral agents plus basal insulin (NPH, glargine, detemir) prior to admission with an admission A1C ≥ 10% will be discharged on their oral agents plus glargine U300 or glargine U100 at 80% of daily hospital dose. If contraindications to previous oral therapy, discharge on basal bolus at 100% of daily hospital dose.

Patients treated with basal or basal bolus regimen prior to admission will be discharged on 50%-80% of their preadmission TDD with glargine once daily and glulisine before meals.



Concomitant 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 with no dose adjustments occurring during the trial. Patients with eGFR between 30-45 ml/min will be discharged at a max-dose of 500 mg twice daily. Patients with eGFR < 30 ml/min will not be allowed to receive metformin.

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 reduced by 50% or stopped at hospital discharge 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.

DPP4-inhibitors. DPP4-i treatment is considered background medication (non-investigational medicinal product) and will not be provided during the trial. The total daily dose of DPP4-I will be adjusted as per renal function (eGFR). No dose adjustment or up-titration will occur during the trial.

GLP1-RA. GLP1-RA treatment is considered background medication (non-investigational medicinal product) and will not be provided during the trial. No dose adjustment or up-titration will occur during the trial.

SGLT2-i. The use of SGLT2-I is considered background medication (non-investigational medicinal product) and will not be provided during the trial. No dose adjustment or up-titration will occur during the trial.

V.c. Hospital Diabetes Education. Prior to discharge, participants will be trained in:

1. Diabetes education if not received within 1 year of admission
2. Recommended targets for fasting and premeal blood glucose between 90 to 130 mg/dL
3. Use of glucose meters for home glucose self-monitoring
4. Keeping BG records, and will receive a logbook to record glucose tests results.
5. Hypoglycemia prevention, recognition and management
6. Insulin administration

V.d. Follow-up Care:

- Provide glargine insulin 1-month 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 1 and 3 month after hospital discharge.
- Recommendation on insulin adjustment to be provided after each telephone contact and/or clinic visit by a licensed physician (fellow or study physician) (section V.f).

V.e. 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 (BG < 70 mg/dl and < 40 mg/dl)
    d. Hyperglycemic events (BG > 240 mg/dl)
2. Diabetes treatment:
    a. Insulin dosage (unit/day)
    b. Use of oral agents

c. Protocol adherence

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

V.f. Primary care physicians will be provided with the following algorithm for outpatient <u>basal insulin dose adjustment every 2 weeks</u>:

Basal Insulin (glargine U300 and glargine U100)	
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 no RBG <70 mg/dL	**Increase daily dose by 2 IU**
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%**

V.g. Aim 2. Statistical Analysis:

V.g.1. 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% attrition rate, we would need 90 patients per treatment group (total # of patients to be recruited: 180 subjects, 90 per treatment group), to achieve >80% power.

V.g.2. 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 in kilograms, 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.

<u>DATA HANDLING AND RECORD KEEPING:</u>

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.

VI. Methods and Procedures Applied to Human Subjects:

VI.a. Subject Population:

We plan to study a total of 180 randomized patients with a known history of T2D, age > 18 years, treated with diet alone, any combination of oral antidiabetic agents, GLP1-RA (except long-acting agents: albiglutide, albiglutide and weekly exenatide) or insulin therapy (except degludec or glargine U300). Patients included within this study will be determined by the set of inclusion and exclusion criteria.

VI.b. Inclusion Criteria:

1. Males or females between > 18 years admitted to a general medicine or surgical service.
2. Known histories of T2D treated with either diet alone, oral monotherapy, any combination of oral antidiabetic agents, short-acting GLP1-RA (exenatide, liraglutide) or insulin therapy with the exception of degludec and glargine U300.
3. 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).

VI.c. Exclusion Criteria:

1. Subjects with increased BG concentration, but without a known history of diabetes.
2. Admission or pre-randomization BG≥400 mg/dl
3. Patients treated with degludec or glargine U300, or with long-acting weekly GLP1-RA (weekly exenatide, dulaglutide or albiglutide).
4. Patients with acute critical or surgical illness admitted to the ICU or expected to require admission to the ICU.
5. Patients with clinically relevant hepatic disease (diagnosed liver cirrhosis and portal hypertension), corticosteroid therapy, or impaired renal function (eGFR< 30 ml/min).
6. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
7. Female subjects who are pregnant or breast-feeding at time of enrollment into the study.

VI.d. **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. If needed, subjects will be started on continuous insulin infusion.

VII. Study Sites: This study will be performed at Grady Memorial Hospital, Emory University Hospitals, Atlanta, GA, Minneapolis Medical Research Foundation-Hennepin Medical Center, Minneapolis, and The Cleveland Clinic Foundation, Ohio.

VIII. CLINICAL MANAGEMENT GUIDELINES

VIII.a. Admission Laboratory Studies

Standard of care laboratory studies including glucose, HbA1C, and chemistry will be measured on admission and as determined by the treating physician.

For **research purposes** a blood sample will be obtained to measure HbA1C at 1 month and 3 months after discharge. In addition, a urine pregnancy test will be performed, when clinically indicated prior to randomization (in female subjects of child bearing potential only).

VIII.b. Assessment and Monitoring of Hospital Mortality

The investigators and research team will follow study subjects daily and the presumed cause of death will be recorded. Information on the attending physician's summary of events surrounding subject's demise will also be documented.

VIII.c. Assessment and Monitoring of Nosocomial Infections

Nosocomial infections will be diagnosed based on standardized CDC criteria (40). New nosocomial infections will not be diagnosed until 48 hours after study initiation to minimize the chance that the infection was actually present (but undiagnosed) prior to study initiation.

The investigators will review each subject's records regarding potential new infection diagnosis daily on each weekday from Monday to Friday. Data from the weekends will be collected on the following Monday. The coded infection diagnosis and the presumed causative microorganism will be determined daily on a Monday to Friday basis, with weekend data entered on the following Monday.

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[1]	x									x
Phys Exam[1]	x									x
Body weight	x									x
BMI	x									x
HbA1c	x									
Fasting BG	x	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									x
Trial material										
Drug dispense[2]	x									

[1]At time of study enrollment and hospital discharge [2]As needed

Flow Chart: Aim 2, Outpatient Study

Visit Type	Hospital Day 1	TC	Clinic visit	TC	TC	TC	Clinic visit
Visit #	1	2	3	4	5	6	7
Time-wks	0	2	4	6	8	10	12
Inf. consent	x						
Incl/excl criteria	x						
Randomization	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				x
Fasting BG	x		x				x
Safety							
Adv events	x	x	x	x	x	x	x
Hypoglycemia	x	x	x	x	x	x	x
Urine pregnancy test	x		x				
CMP or BMP	x		x				x
Trial material							
Drug dispense	x		x				
Drug account	x		x				x

IX. Potential Risks to the Subject:

IX.a. Hypoglycemia. It is possible that following the proposed protocol, patients receiving insulin glargine U300 and U100 may develop hypoglycemia. The risk of hypoglycemia in non-ICU patients treated with subcutaneous insulin is between 5–30% (12, 17, 41, 42). The number of hypoglycemia will be analyzed statistically. For the purpose of this analysis, hypoglycemia is defined as a BG < 70 mg/dL. Severe hypoglycemia is defined as BG < 40 mg/dL.

X. 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, renal impairment or cardiac failure will be recruited in this study.

X.a. Hypoglycemia: 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: 0.3 units

per kg of body weight) in patients ≥ 70 years of age and/or eGFR < 60 ml/min. 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.

XI. Inclusion of women.

We anticipate that ~50% of the study subjects will be female. Absence of pregnancy must be demonstrated by blood or urine testing prior to randomization (in female subjects of child bearing potential only). Glargine U300 and U100 have not been approved during pregnancy.

XII. Inclusion of minorities.

Patients will not be excluded based on race or ethnic origin. We anticipate that approximately one-third of patients will be African Americans, Hispanics, and Caucasians.

XIII. Inclusion of children.

No patients under the age of 18 will be recruited in this study.

XIV. Payment for participation.

Participation in this study is voluntary. Patients will receive one hundred dollars ($100.00) during the hospital stay. If a participant should stop participation before completion, the payment will be prorated at $10.00 per day. Participants will receive 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).

XV. Financial conflict of interests.

This study receives support from Sanofi. Dr. Umpierrez serves as a consultant to Sanofi and receives compensation for these services. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

XVI. Pharmacovigilance specifications

1. DEFINITIONS

Serious adverse event (SAE): any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening, (Note: the term “life-threatening” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or results in prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or

- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Related Adverse Event, i.e. Adverse Drug Reaction (ADR): There is a reasonable possibility according to the ISS sponsor that the product may have caused the event.

Unexpected Adverse Event, i.e. Adverse Drug Reaction (ADR): An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary of product characteristics for an approved product). An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

Adverse Event of Special Interest (AESI): An adverse event of special interest (AESI) is an adverse event (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.

New safety finding : Any (other than reportable individual case safety report (ICSR)) safety issue that may require expedited reporting because providing information that may lead to a change in the known risk-benefit balance for the product and as mentioned, but not limited to, in the following regulatory texts: Europe: Volume 9A of the Rules Governing Medicinal products in the European Union (September 2008) Section 4.1; and US: FDA: 21 CFR Parts 312 Investigational New Drug Application- Section 312.32, (c) (1) IND safety reports.

2. OBLIGATIONS AND RESPONSIBILITIES OF THE ISS SPONSOR

- The ISS sponsor warrants that the study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.
- The ISS sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.
- The sponsor shall be responsible for ensuring submission of required expedited and periodic reports to the appropriate Regulatory Authority (RA), the Ethics Committee and investigators of each country participating in the ISS (based on applicable regulations).
- Any Periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to Regulatory Authority must first be transmitted to Sanofi for review and comment.
- The study reports of any ISS must contain a section describing safety review and conclusion and must be reviewed by Sanofi before finalization.
- *New Safety Findings in a study pertaining to safety of product must be transmitted within 1 business day. (e.g., Data Safety Monitoring Board recommendations)*

  The ISS sponsor must provide to Sanofi upon request results of any relevant complementary exams performed to obtain the final diagnosis of any SAE (e.g., hospital discharge summary, autopsy, consultation).

- The Institution must report the following information in English to the Sanofi group entity Pharmacovigilance contact:

- Routine transmission of all Serious Adverse Events (SAEs) including pregnancy, overdose and Adverse Events of Special Interest (AESI), if any. These events must be transmitted within 1 business day of the Institution's awareness or identification of the event.
- Routine transmission of SAEs related to the use of the Sanofi product must be transmitted within 1 business day of the Institution's awareness or identification of the event. The reference safety information to be used by the Institution for evaluation of expectedness of adverse events shall be the current approved product label available in the country *for an approved indication or the Investigator Brochure for an unapproved indication*.
- Any Periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to Regulatory Authority must be transmitted to Sanofi at the time of submission.
- *New Safety Findings* in a study pertaining to safety of product must be transmitted within 1 business day. (e.g., Data Safety Monitoring Board recommendations)
- The study reports of any ISS must contain a section describing safety review and conclusion and must be reviewed by Sanofi before finalization.

- *The reference safety information to be used by the ISS sponsor for evaluation of expectedness of adverse events shall be the current approved product label available in the country (for an approved indication)*

3. SANOFI GROUP ENTITY PHARMACOVIGILANCE CONTACT

These reports may be sent by **GPE-PV E-MAIL to:**
Reports by **E-MAIL** should be sent to: CL-CPV-Receipt@sanofi.com or **Fax**: 908-547-8000, within 24 hours of receipt by investigator/sponsor. **E-Mail or Fax transmission should include the following:**
Investigator-Sponsored (IST #) study number: SA-2016-11517
Study Title: _ **Glargine U300 Hospital Trial:** A Randomized Controlled Trial Comparing Glargine U300 and Glargine U100 for the Inpatient and Post-Hospital Discharge Management of Medicine and Surgery Patients with Type 2 Diabetes
Name of Principal Investigator: Guillermo Umpierrez, MD, CDE.

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

<u>BEFORE MEAL,</u> Supplemental Sliding Scale – Glulisine 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

The numbers in each column indicate the number of units of glulisine 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 = half of premeal insulin dose. Example, a patient with blood glucose of 260 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 200 mg/dl will receive 3 U of supplemental insulin.
The patient's inpatient primary medical or surgical team may change insulin dose at their discretion in the presence of hypoglycemia (BG <70 mg/dL) or severe hyperglycemia (BG >350 mg/dL). In addition, the attending physician may consider using the total supplemental insulin dose, patient's nutritional intake, and results of BG testing to adjust insulin regimen.