

Protocol
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Exenatide Inpatient Trial: A Randomized Controlled Pilot Trial on the Safety and Efficacy of Exenatide (Byetta®) Therapy for the Inpatient Management of General Medicine and Surgery Patients with Type 2 Diabetes

Principal Investigator:
Guillermo E. Umpierrez, M.D., C.D.E.
Professor of Medicine
Department of Medicine/Endocrinology
Emory University School of Medicine

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Statistical Support:

Limin Peng, Ph.D.; Associate Professor; Rollins School of Public Health; Emory University

I. RESEARCH OBJECTIVES AND SPECIFIC AIMS

The association between hyperglycemia and poor clinical outcomes in patients with and without diabetes is well established (1-5). Extensive data from observational and prospective randomized controlled trials in hospitalized patients have reported a strong association between hyperglycemia and poor clinical outcomes, such as mortality, morbidity, length of stay (LOS), infections and overall complications (1, 4, 6-8). Most clinical trials in critically ill and general medicine and surgery patients have reported that improvement of glycemic control reduces LOS, risk of multi-organ failure and systemic infections (9-11), as well as short- and long-term mortality (6, 11) in patients with hyperglycemia and diabetes.

Clinical guidelines from professional organizations (12-14) recommend the use of subcutaneous (SQ) insulin as the preferred therapy for glycemic control in general medical and surgical patients with type 2 diabetes (T2D). Prospective, randomized multi-center trials have shown that basal bolus insulin regimens improve glycemic control and reduce the rate of hospital complications compared to sliding scale regular insulin (SSRI) (15-18). In the Rabbit-2 medicine trial (18), patients with T2D were randomized to receive glargine once daily and glulisine before meals or SSRI four times daily. Patients treated with basal bolus had greater improvement in glucose control than SSRI (18). The Rabbit Surgery trial compared the safety and efficacy of a basal bolus insulin regimen to SSRI in patients with T2D undergoing general surgery. We observed a lower mean daily glucose concentration and a reduction in the frequency of hospital complications with basal bolus as compared with SSRI treatment (17). However, the use of basal bolus approach is labor intensive, requiring multiple daily insulin injections (4 to 6), and has a significant risk of hypoglycemia (17, 19) reported in up to 32% of hospitalized patients with T2D in non-ICU settings.

Increasing evidence indicates that the administration of native GLP-1 infusions and glucagon-like peptide-1 receptor agonists (GLP-1 RA) are safe and effective for the hospital management of patients with T2D. 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 (20), increasing left ventricular function in patients with heart failure (21) and in CABG surgery patients (21, 22), and reducing infarct size and preserving left ventricular myocardial performance in ischemic models (23, 24). The beneficial cardiac effects, low risk of hypoglycemia and the overall tolerability of the GLP-1 RA make them attractive considerations for use in hospitalized patients.

Exenatide is a GLP-1 analogue approved for the treatment of T2D. It has been shown to lower blood glucose (BG), stimulate endogenous insulin secretion, decrease plasma glucagon levels, inhibit gastric emptying, inhibit food intake, decrease body weight and improve beta-cell function (25, 26). Exenatide 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 GLP-1 has resulted in comparable reduction in HbA1c level, lower rates of hypoglycemia and less weight gain (27). No prospective randomized studies, however, have compared the efficacy and safety of exenatide alone or in combination with basal insulin in non-ICU patients or after hospital discharge.

II. Specific Aims:

Specific Aim 1: To determine whether in-hospital glycemic control, as measured by mean daily blood glucose concentration and frequency of hypoglycemic events, is different between treatment with exenatide (Byetta®) alone, exenatide in combination with basal insulin (glargine or detemir), and basal bolus regimen in general medicine and surgery patients with T2D. In this pilot study, patients with T2D treated with diet, oral antidiabetic drugs (OADs), or with low-dose

insulin (total daily dose < 0.5 units/kg) will be randomized to receive exenatide once daily (group 1), exenatide plus basal insulin (group 2), or basal bolus regimen (group 3). If needed, patients in all treatment groups will receive supplemental (correction) doses of rapid-acting insulin (lispro or aspart) before meals for BG > 140 mg/dl.

Hypothesis: Treatment with exenatide alone or in combination with basal insulin will result in a similar glycemic control and in a lower frequency of hypoglycemia than treatment with basal bolus in general non-ICU patients with T2D.

Specific Aim 2: To determine whether treatment with exenatide (Byetta®) will result in similar glycemic control compared to treatment with basal insulin (glargine or detemir) after hospital discharge in patients with T2D. Patients who participate in the in-hospital (Aim 1) arm with an Hb1C > 7% will be followed in the open label prospective outpatient study. The total duration of this outpatient part is 3 months. Patients will be discharged on their outpatient treatment of OAD plus exenatide or basal insulin once daily depending on the randomization group during the admission part. **Hypothesis:** Treatment with exenatide will result in a similar improvement in HbA1c levels and in lower number of hypoglycemic events compared to treatment with basal insulin in patients with T2D after hospital discharge.

III. BACKGROUND AND STATUS OF WORK IN THE FIELD.

A large body of evidence suggests that in hospitalized patients with and without diabetes, the presence of hyperglycemia is associated with poor clinical outcomes (1-6, 28-31). Evidence from observational studies indicates that development of hyperglycemia is associated with an increased risk of complications and mortality, a longer hospital stay, a higher admission rate to the ICU, and a higher likelihood that transitional or nursing home care after hospital discharge will be required (1, 2, 6, 32-36). Recent prospective, randomized multi-center trials have shown that basal bolus insulin regimens result in improved glycemic control and reduce the rate of hospital complications compared to sliding scale regular insulin (SSRI) in general medical and surgical patients with T2D (15-18). In the Rabbit-2 medicine trial, insulin naïve patients with T2D were randomized to receive glargine once daily and glulisine before meals or SSRI four times daily. Patients treated with glargine + glulisine had greater improvement in blood glucose control than SSRI (18). The Rabbit Surgery trial compared the safety and efficacy of a basal bolus insulin regimen with glargine once daily and glulisine before meals to SSRI in patients with T2D undergoing general surgery. We observed a lower mean daily glucose concentration after the 1st day and a reduction in the frequency of hospital complications with basal bolus as compared with SSRI treatment (17). The use of basal bolus approach, however, is labor intensive, requiring multiple daily insulin injections (4 to 6), and has a significant risk of hypoglycemia (17, 19), reported in up to 32% of hospitalized patients with T2D.

Hospital Use of native GLP-1 infusion. Increasing evidence indicates that the administration of native GLP-1 infusion is safe and effective for the hospital management of patients with T2D. The use of GLP-1 has been shown to improve glycemic control and to have a beneficial cardiovascular profile improving functional status and endothelial function (20), increasing left ventricular function in patients with heart failure (21) and in patients undergoing CABG surgery (21, 22), and to reducing infarct size and preserving left ventricular myocardial performance in ischemic models (23). These potentially beneficial cardiac effects and low risk of hypoglycemia of GLP-1 make it attractive for use in hospitalized patients.

Hospital Use of GLP-1 Receptor Analogs. Two previous uncontrolled studies have reported on the use of exenatide for the management of hyperglycemia in critically ill patients in the ICU. A pilot non-randomized, uncontrolled, prospective, open-label study evaluated the safety and efficacy of glucose

control with IV exenatide in cardiac ICU patients with admission glucose between 140-400 mg/dL (37). A total of 40 patients (age 65 years, 83% male, 63% acute coronary syndromes, 75% T2DM) received an initial bolus of 0.05 µg/min for 30 min followed by a fixed infusion of 0.025 µg/min for 24-48 hours. Compared to historic controls treated with IV insulin with a target 90-120 mg/dl (n=94) and 100-140 mg/dl (n= 39), the administration of IV exenatide resulted in similar glycemetic control and in a lower, but non-significant difference in hypoglycemic events in the cardiac ICU setting. The mean BG in the group treated with exenatide (139±41 mg/dl) was similar to those treated with IV insulin infusion with a target of 90-120 mg/dl (115±36 mg/dl) and a target of 100-140 mg/dl (147±52 mg/dl). Hypoglycemia BG <70 mg/dl was reported in 10% of patients treated with exenatide compared to 21% and 15% in patients treated with insulin to a target BG of 90-120 mg/dl and 100-140 mg/dl, respectively (p=0.27). A total of 8 patients (20%) experienced nausea due to exenatide and 6 patients (15%) requested early termination due to severe nausea.

In one small open-label study of 24 severely burned pediatric patients randomly assigned to receive exenatide (n=6) or IV insulin infusion for glycemetic management, similar levels of glycemetic control were achieved in both groups (38). Daily average glucose was 130 ± 28 mg/dl in the exenatide group and 138 ± 25 mg/dl in the insulin group (p= 0.31); however, administered insulin was significantly lower in the exenatide group (22 ± 14 unit/patients/day vs. 76 ± 11 unit/patients/day in the insulin group (p= 0.01). The incidence rate of hypoglycemia was similar in both groups (0.38 events/patient-month). The authors of this study reported that exenatide was well tolerated and may offer an alternative to insulin therapy in pediatric patients in a critical care setting.

Hospital Use of DPP-4 Inhibitors. We recently completed (NCT01378117) a randomized two-center open label pilot trial aimed to determine differences in glycemetic control between treatment with sitagliptin alone or in combination with basal insulin in general medicine and surgery patients with T2D (39). In this pilot study, 90 general medicine and surgery patients with a BG between 140-400 mg/dl treated with diet, oral antidiabetic drugs or low-dose insulin were randomized to sitagliptin once daily (n=30), sitagliptin and basal insulin (n=30), or basal bolus insulin (n=30). All groups received correction doses of lispro before meals and bedtime for BG >140 mg/dl. Patients in the sitagliptin group received a single daily dose of 50-100 mg based on kidney function. The use of sitagliptin alone or in combination with basal insulin was well tolerated and resulted in no significant differences in daily BG, frequency of hypoglycemia or in the number of treatment failures compared to basal bolus regimen.

Exenatide (Byetta®) is a human GLP-1 analogue approved for the treatment of T2D. Exenatide has been shown to lower blood glucose, stimulate endogenous insulin secretion, decrease plasma glucagon levels, inhibit gastric emptying, inhibit food intake, decrease body weight and improve beta-cell function when administered subcutaneously (25). Exenatide increases insulin secretion in a glucose-dependent manner (i.e., only when plasma glucose levels are elevated), resulting in low-risk of hypoglycemia when use as monotherapy. In addition, during hypoglycemia exenatide does not impair glucagon action or the general counter-regulatory response, indicating a low risk of hypoglycemia (27). 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 (27). No prospective studies however, have compared the efficacy and safety of exenatide in general non-ICU settings or after hospital discharge.

Innovation and Rationale

The proposed pilot study will be the first RCT aiming to determine the safety and efficacy of exenatide treatment, alone or in combination with basal insulin, in patients with T2D admitted to general medicine and surgery wards will be randomized to basal bolus insulin regimen (standard of

care) or to exenatide alone or in combination with low-dose basal insulin (glargine or detemir). Despite the efficacy of previous studies on the use of basal bolus in the non-ICU setting, this regimen requires frequent injections, BG testing, and is associated with a risk of hypoglycemia (5% - 30%). Extensive preliminary data indicates that the administration of GLP-1 is effective in improving glycemic control and to have a beneficial cardiovascular profile improving functional status and left ventricular function in patients with heart failure (21) and in surgery patients undergoing CABG surgery (21, 22). These potentially beneficial effects and low risk of hypoglycemia of GLP-1 make it attractive for use in hospitalized patients with T2D. Few studies have investigated the use of GLP-1 receptor agonists in the hospital setting, but we anticipate that treatment with exenatide SC alone or in combination with basal insulin will result in similar improvement in glycemic control and in lower rates of hypoglycemic events compared to the use of basal bolus insulin therapy in patients with uncontrolled T2D. If effective, the use of exenatide will facilitate care by reducing the number of insulin injections and the risk of hypoglycemia that has been associated with higher rates of hospital complications and mortality in the hospital setting.

IV. PRELIMINARY RESULTS:

We recently reported the results of 3 prospective, randomized multi-center trials comparing the efficacy and safety of basal/bolus insulin regimens to SSRI and split-mixed regimen with NPH/regular in T2D patients.

In the Rabbit medicine 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 (16). Patients treated with glargine/glulisine had greater improvement in BG control than SSRI with a minimal risk of hypoglycemia (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/glulisine whereas only 38% of those treated with SSRI achieved target glycaemia.

In the Rabbit Surgery trial (17), we reported on the efficacy and safety of improving glycemic control with basal/bolus insulin compared to SSRI in general surgery patients. The Rabbit Surgery trial included 211 patients with T2D undergoing general surgery and compared differences in daily BG and a composite of complications including wound infection, pneumonia, respiratory failure, renal failure, and bacteremia. The basal bolus regimen resulted in significant reductions in daily BG as well as in the frequency of the composite outcome compared to SSRI (8.6%, and 24.3% p= 0.003), Table 1.

Sitagliptin Inpatient Pilot Study (39). In a two-center open label randomized pilot trial, we recently determined differences in glycemic control between sitagliptin alone or in combination with basal insulin and basal bolus regimen in medicine and surgery patients with T2D. In this study, 90 patients

Fig 1

Mean Blood Glucose Levels During Basal Bolus and SSRI

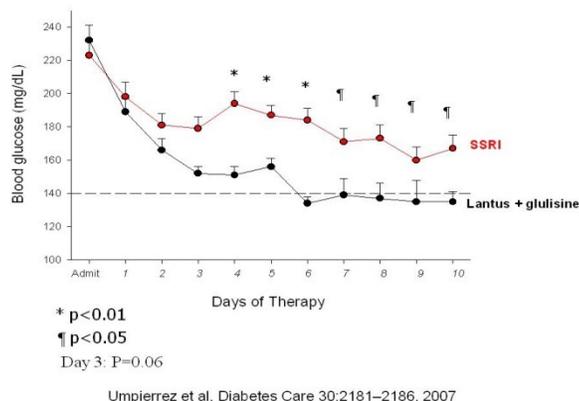
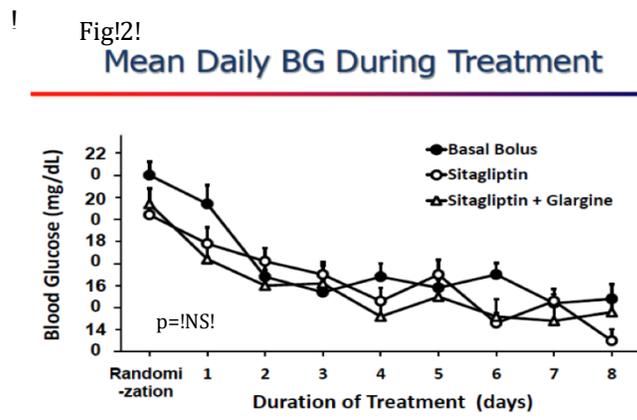


Table 1. Rabbit Surgery – Hospital complications.

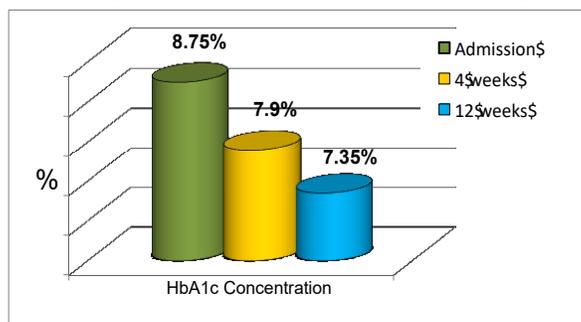
Hospital Complications				
Variable	ALL	SSI	Basal Bolus	P value
Wound infections	14	11	3	0.050
Pneumonia	3	3	0	0.247
Acute respiratory failure	6	5	1	0.213
Acute renal failure	15	11	4	0.106
Bacteremia	3	2	1	0.999
# patients with complications	35	26	9	0.003
Total # of complications	42	32	9	
Post-surg ICU admission	34	21	13	0.159
% post-surg ICU admission	16%	19.6%	12.5%	
ICU LOS	2.51±1.90	3.19±2.14	1.23±0.60	0.003

with a BG between 140-400 mg/dl treated with diet, OAD or low-dose insulin (≤ 0.4 U/kg/day) were randomized to sitagliptin once daily (n=30), sitagliptin and basal insulin (n=30) or to a basal bolus (n=30) regimen. Patients in the sitagliptin group received a daily dose of 100 mg or 50 mg as per renal function. Those in the sitagliptin plus glargine received sitagliptin and glargine starting at 0.25 U/kg once daily. Patients in the basal bolus group were started at 0.5 U/kg, given half as glargine once daily and half as lispro before meals. All groups received correction doses of lispro before meals and bedtime for BG >140 mg/dl. We found that treatment with sitagliptin alone or in combination with glargine resulted in similar glycemic control compared to basal bolus regimen (Figure 2). There were no differences in mean daily BG, number of BG readings within target, hypoglycemia, frequency of treatment failures, hospital LOS or complications. In addition, treatment with sitagliptin had less daily insulin requirements and lower number of insulin injections, both, $p < 0.001$.



Transition of Care after Discharge. In a recently published study (40), we assessed the efficacy of an HbA1c based algorithm for the management of patients with T2D (Fig. 3). Patients with an HbA1c <7% were discharged on their outpatient antidiabetic regimen. Patients with an HbA1c between 7% and 9% were discharged on a combination of OAD and basal insulin at 50%-80% of total daily hospital dose. Patients with an HbA1c $\geq 9\%$ were discharged on a combination of OAD and basal insulin at 80-100% of total daily hospital dose or on a basal bolus regimen. The overall admission HbA1c of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge ($p < 0.01$). A total of 29% of patients experienced ≥ 1 episode of hypoglycemia after discharge (Table 2). A higher frequency was observed in patients discharged on a combination of basal insulin and metformin (30%) and basal bolus regimen (44%). The frequency of severe hypoglycemia (BG <40 mg/dl) was low (3%). These data indicate that the admission HbA1c is beneficial in designing the discharge treatment algorithm for non-ICU patients with T2D.

Fig 3
Change in HbA1C levels after discharge



Umpierrez et al. ADA Scientific Meeting, Philadelphia 2012

Hospital Discharge Algorithm Based on Admission HbA1C for the Management of Patients with T2DM

Primary outcome: change in A1C at 4 wks and 12 wks after discharge

	All Patients	OAD	OAD + Glargine	Glargine+ Glulisine	Glargine
# patients, n (%)	224	81 (36)	61 (27)	54 (24)	20 (9)
A1C Admission, %	8.7 \pm 2.5	6.9 \pm 1.5	9.2 \pm 1.9	11.1 \pm 2.3	8.2 \pm 2.2
A1C 4 Wks F/U, %	7.9 \pm 1.7*	7.0 \pm 1.4	8.0 \pm 1.4 ψ	8.8 \pm 1.8 ψ	7.7 \pm 1.7
A1C 12 Wks F/U, %	7.3 \pm 1.5*	6.6 \pm 1.1	7.5 \pm 1.6*	8.0 \pm 1.6*	6.7 \pm 0.8*
BG<70 mg/dl, n (%)	62 (29)	17 (22)	17 (30)	23 (44)	5 (25)
BG<40 mg/dl, n (%)	7 (3)	3 (4)	0 (0)	3 (6)	0 (0)

In summary, these preliminary studies indicate that 1) treatment with basal bolus regimen results in better metabolic control and in a lower rate of hospital complications than treatment with SSI in patients with T2D, and 2) the use of a DPP-4 inhibitor alone or in combination with basal insulin may represent effective alternatives to a basal bolus insulin regimen for the management of hospitalized patients with T2D.

V. EXPERIMENTAL PLAN.

Aim 1. To determine whether in-hospital glycemic control, as measured by mean daily blood glucose concentration and frequency of hypoglycemic events, is different between treatment with exenatide (Byetta®) alone, exenatide in combination with basal insulin (glargine or detemir), and basal bolus therapy in general medicine and surgery patients with T2D.

V.a. Rationale. The result of several observational and interventional studies indicate that hyperglycemia is associated with poor hospital outcomes including prolonged hospital stay, increased rate of wound and systemic infections, disability after hospital discharge, and death (1, 34). Clinical guidelines from professional organizations (12-14) recommend the use of subcutaneous (SC) insulin as the preferred therapy for glycemic control in general medical and surgical patients with T2D. The use of basal bolus, however, is labor intensive requiring multiple daily insulin injections, and has a risk of hypoglycemia (17, 19) reported in up to 32% of hospitalized patients with T2D. Increasing evidence indicates that the administration of GLP-1 and glucagon-like peptide-1 receptor agonists (GLP-1 RA) are safe and effective for the hospital management of patients with T2D (27). The use of GLP-1 and its analogues have also been shown to improve glycemic control and to have a beneficial profile improving endothelial function (20), increasing left ventricular function in patients with heart failure (21) and in CABG surgery patients (21, 22), and reducing infarct size and preserving left ventricular myocardial performance in ischemic models (23). The potentially beneficial cardiac effects and low risk of hypoglycemia make them attractive for its use in hospitalized patients. Accordingly, this study will compare the efficacy and safety of exenatide alone or in combination with basal insulin to a basal bolus regimen on glycemic control in the inpatient setting and after hospital discharge.

V.b. STUDY DESIGN AND METHODS

A total of 150 subjects with T2D treated with diet, OADs or with low-dose insulin (<0.5 unit/kg/day) prior to admission will be included in this pilot randomized, open-label trial to compare the efficacy of exenatide twice daily (group 1), exenatide plus basal insulin (group 2), or basal bolus regimen (group 3) in general medicine and surgery patients with T2D. If needed, patients in both groups will receive supplemental (correction) doses of rapid-acting insulin (lispro, aspart) before meals for BG > 140 mg/dl.

The primary outcome of the study is to determine differences in glycemic control as measured by mean daily BG concentration (average of all blood glucose values by point-of-care and laboratory testing) during the hospital stay (up to 10 days) between exenatide arms and basal bolus therapy.

The secondary outcome is to compare differences between groups in any of the following measures:

Mean daily fasting and premeal glucose value up to 10 days of hospital stay.

Number of hypoglycemic events (<70 mg/dl) and severe hypoglycemic events (<40 mg/dl).

Number of episodes of hyperglycemia (BG > 300 mg/dl) after the first day of treatment.

1. Total daily dose of insulin.
2. Length of hospital stay.
3. Need for ICU care (transfer to ICU)
4. Differences between groups on a composite of hospital mortality and hospital complications including nosocomial pneumonia, bacteremia, respiratory failure, acute renal failure, and wound infections (surgery patients).

5. Acute kidney injury defined as an increment in serum creatinine > 0.5 mg/dL from admission value.
6. Difference in gastrointestinal adverse events including nausea, vomiting, diarrhea.

V.c. Overall Design and Study Interventions

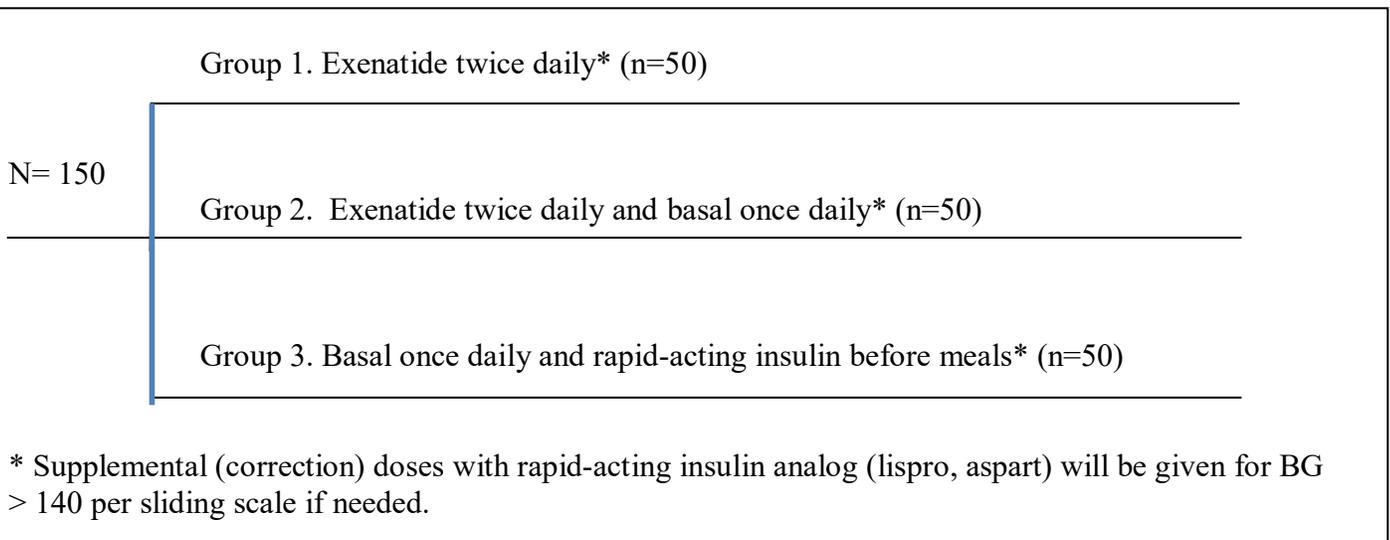
This open-label randomized clinical trial will include male or female subjects with known history of type 2 diabetes, age 18-80 years admitted to general medicine and surgery (non-ICU) services. Due to the design of this study (i.e. enrollment of subjects in need of acute care), there will be no run-in period. Upon arrival to the Emergency Department or general medicine or surgery services, subjects will be screened for the study. Patients with a known history of T2D treated with diet alone, with any combination of oral hypoglycemic agents prior to admission, or low-dose insulin with total daily dose <0.5 units/kg will be considered potential candidates in this study. The primary care physician will be approached asking for authorization to approach the study candidate. Then, a research coordinator and/or investigator will present the study details, review consent form, and discuss benefits and risk with participation in the study. When the patient has agreed to participate in the study, the research pharmacy will be notified and will proceed with randomization. A research pharmacist at each institution will follow a computer-generated block randomization table based on glucose levels ($BG \leq 200$ or $BG > 200$). The goal of therapy is to maintain fasting and pre-meal BG between 80 and <180 mg/dL while avoiding hypoglycemia. Diabetic patients will be randomized consecutively to receive:

- Group 1. Exenatide twice daily* (n=50).
- Group 2. Exenatide twice daily* plus basal insulin (n=50)
- Group 3. Basal bolus insulin regimen* (n=50).

* Supplemental (correction) doses rapid-acting insulin analog (lispro, aspart) will be given for BG > 140 per sliding scale if needed.

The primary care physician (PCP) will decide on the treatment for the medical problem(s) for which patients are admitted. At discharge, patients with HbA1C $>7\%$ will be invited to participate in a post-discharge trial to compare the efficacy and safety of exenatide and basal after hospital discharge (Aim 2).

V.d. Treatment Groups:



V.e. Treatment Protocols.

GROUP 1. Exenatide Alone (Group.1)

- Oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, pioglitazone, DPP4 inhibitors, metformin) or low-dose insulin will be discontinued on admission.
- Exenatide twice daily- (250 mcg/mL solution for subcutaneous (s.c.) injection provided in 1.2 mL prefilled pen).
- Exenatide will be administered twice daily starting at 5 mcg per dose, in the abdomen, thigh or upper arm.
- Exenatide injections will be given within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart between doses)
- Supplemental (correction) insulin. Rapid acting insulin analogs (lispro, aspart) will be administered following the “supplemental/sliding scale” protocol (Table 1).
 - If a patient is able and expected to eat all or most of his/her meals, supplemental (lispro, aspart) insulin will be administered before each meal and at bedtime following the “usual” dose of the sliding scale protocol.
 - If a patient is not able to eat, supplemental (lispro, aspart) insulin will be administered every 6 hours (6-12-6-12) following the “sensitive” dose of the sliding scale.
- **Blood glucose monitoring.** Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia or if requested by the treating physician.

GROUP 2. Exenatide plus Basal Insulin Group.

- Oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, pioglitazone, DPP4 inhibitors, metformin) or low-dose insulin will be discontinued on admission.
 - Exenatide twice daily-** recommended dosage adjustments:
 - Exenatide twice daily- (250 mcg/mL solution for subcutaneous (s.c.) injection provided in 1.2 mL prefilled pen).
 - Exenatide will be administered twice daily starting at 5 mcg per dose, either in the abdomen, thigh or upper arm.
 - Exenatide injections will be given within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart between doses)
 - Basal Insulin once daily - starting daily dose:**
 - Patients with BG between 140-200 mg/dL= 0.2 units per kg weight per day.
 - Patients with BG between 201-400 mg/dL= 0.25 units per kg weight per day.

- The starting insulin dose will be reduced to 0.15 units per kg of body weight in patients ≥ 70 years of age and/or with a glomerular filtration rate (GFR) < 60 ml/min.
- Basal insulin will be given once daily, at the same time of the day.
- Patients will receive the full-dose of basal insulin (even if NPO).

Supplemental (correction) insulin. Lispro/aspart insulin will be administered following the “supplemental/sliding scale” protocol (Table 1).

- If a patient is able and expected to eat all or most of his/her meals, supplemental (lispro, aspart) insulin will be administered before each meal and at bedtime following the “usual” dose of the sliding scale protocol.
 - If a patient is not able to eat, supplemental (lispro, aspart) insulin will be administered every 6 hours (6-12-6-12) following the “sensitive” dose of the sliding scale.
- **Insulin adjustment.** The basal insulin dose will be adjusted as follows:
 - Fasting and pre-meal BG between 100-140 mg/dl without hypoglycemia the previous day: no change
 - Fasting and pre-meal BG between 141-180 mg/dl: increase dose by 10% every day
 - Fasting and pre-meal BG >180 mg/dl: increase dose by 20% every day
 - Fasting and pre-meal BG between 70-99 mg/dl: decrease dose by 10% every day
 - If a patient develops hypoglycemia (BG <70 mg/dL), decrease dose by 20%.
 - If a patient develops hypoglycemia (BG <40 mg/dL), decrease dose by 30-40%.

If determined by the investigator or co-investigator that patient’s requirements differ from the above protocol, it would be to his/her clinical judgment to adjust doses of basal and rapid acting insulin based on patient’s needs.

Blood glucose monitoring. Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia or if requested by the treating physician.

Group 3. Basal Bolus Regimen (glargine or detemir) and Rapid-Acting Insulin Analogs (lispro, aspart)

Oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, pioglitazone, DPP4 inhibitors, or metformin) will be discontinued on admission.

Starting total daily insulin dose:

Insulin naïve (no insulin treatment on admission)

- Patients with BG between 140-200 mg/dL= 0.4 units per kg weight per day.
- Patients with BG between 201-400 mg/dL= 0.5 units per kg weight per day.
- The starting insulin TDD will be reduced to 0.3 units per kg of body weight in patients ≥ 70 years of age and/or with a glomerular filtration rate (GFR) < 60 ml/min.
- Patients treated with insulin injections prior to admission will receive 80% of total home daily insulin dose as basal bolus regimen.
- Half of total daily dose will be given as basal and half as rapid-acting insulin analogs
- Basal insulin will be given once daily, at the same time of the day.

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- Patients will receive the full-dose of basal insulin (even if NPO).
- Rapid-acting insulin (lispro, aspart) will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of lispro will be held.

Insulin adjustment. The basal insulin dose will be adjusted as follows:

- Fasting and pre-meal BG between 100-140 mg/dl without hypoglycemia the previous day: no change
- Fasting and pre-meal BG between 141-180 mg/dl: increase dose by 10% every day
- Fasting and pre-meal BG >180 mg/dl: increase dose by 20% every day
- Fasting and pre-meal BG between 70-99 mg/dl: decrease dose by 10% every day
- If a patient develops hypoglycemia (BG <70 mg/dL), decrease dose by 20%.
- If a patient develops a BG <40 mg/dL, decrease dose by 30-40%.

Supplemental insulin. Supplemental (lispro, aspart) insulin will be administered following the “sliding scale” protocol (Table 1).

- If a patient is able and expected to eat all or most of his/her meals, supplemental (lispro, aspart) insulin will be administered before each meal and at bedtime following the “usual” dose of the sliding scale protocol.
- If a patient is not able to eat, supplemental (lispro, aspart) insulin will be administered every 6 hours (6-12-6-12) following the “sensitive” dose of the sliding scale.

If determined by the investigator or co-investigator that the patient’s requirements differ from the above protocol, it would be to his/her clinical judgment to adjust doses of basal and rapid acting insulin based on patient’s needs.

Blood glucose monitoring. Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter. In addition, blood glucose will be measured at any time if a patient experiences symptoms of hypoglycemia or if requested by the treating physician.

Aim 2. To determine whether treatment with exenatide (Byetta®) will result in a similar glycemic control and in a lower rate of hypoglycemic events compared to treatment with Basal (glargine or detemir) in patients with T2D after hospital discharge.

VI.a. Rationale. Our preliminary studies indicate that the use of basal insulin alone or in combination with OADs are effective in improving glycemic control after discharge with an HbA1c reduction ~1.5% in general medicine and surgery patients. We observed; however, a high rate of hypoglycemia (29%) during the following 12 weeks after discharge, with a higher frequency observed in patients discharged on the combination of basal insulin and metformin (30%) and basal bolus regimen (44%). Exenatide has a unique pharmacokinetic and pharmacodynamic profile that makes it an attractive agent for the treatment of inpatients with T2D including its rapid-onset of action in improving glycemic control without weight gain and its low risk of hypoglycemia. Based on the proven efficacy of exenatide in improving glycemic control, we believe that exenatide represents an excellent alternative to insulin therapy after discharge in subjects with T2D.

Study Outcomes:

The primary outcome of the study is to determine differences in HbA1c concentration at 12 weeks from discharge between exenatide and basal insulin therapy.

The secondary outcome is to compare differences between treatment groups in any of the following measures during the 12 weeks following hospital discharge in medicine and surgery patients with T2D:

1. Fasting and mean daily BG concentration
2. Incidence rate and number of hypoglycemic events (<70 mg/dl) and severe hypoglycemic events (<40 mg/dl).
3. Percent of patients with 12 week HbA1c <7.0% and no weight gain
4. Percent of patients with 12 week HbA1c <7.0% and no hypoglycemia
5. Change in body weight and BMI
6. Cardiovascular risk factors including changes in blood pressure and heart rate
7. Total daily dose of insulin
8. Incidence rate and number of emergency room visits and hospital readmissions
9. Acute renal failure during the 12 week follow-up defined as a clinical diagnosis with documented new-onset abnormal renal function (an increment > 0.5 mg/dL from baseline)
10. Number of gastrointestinal adverse events including nausea, vomiting and diarrhea

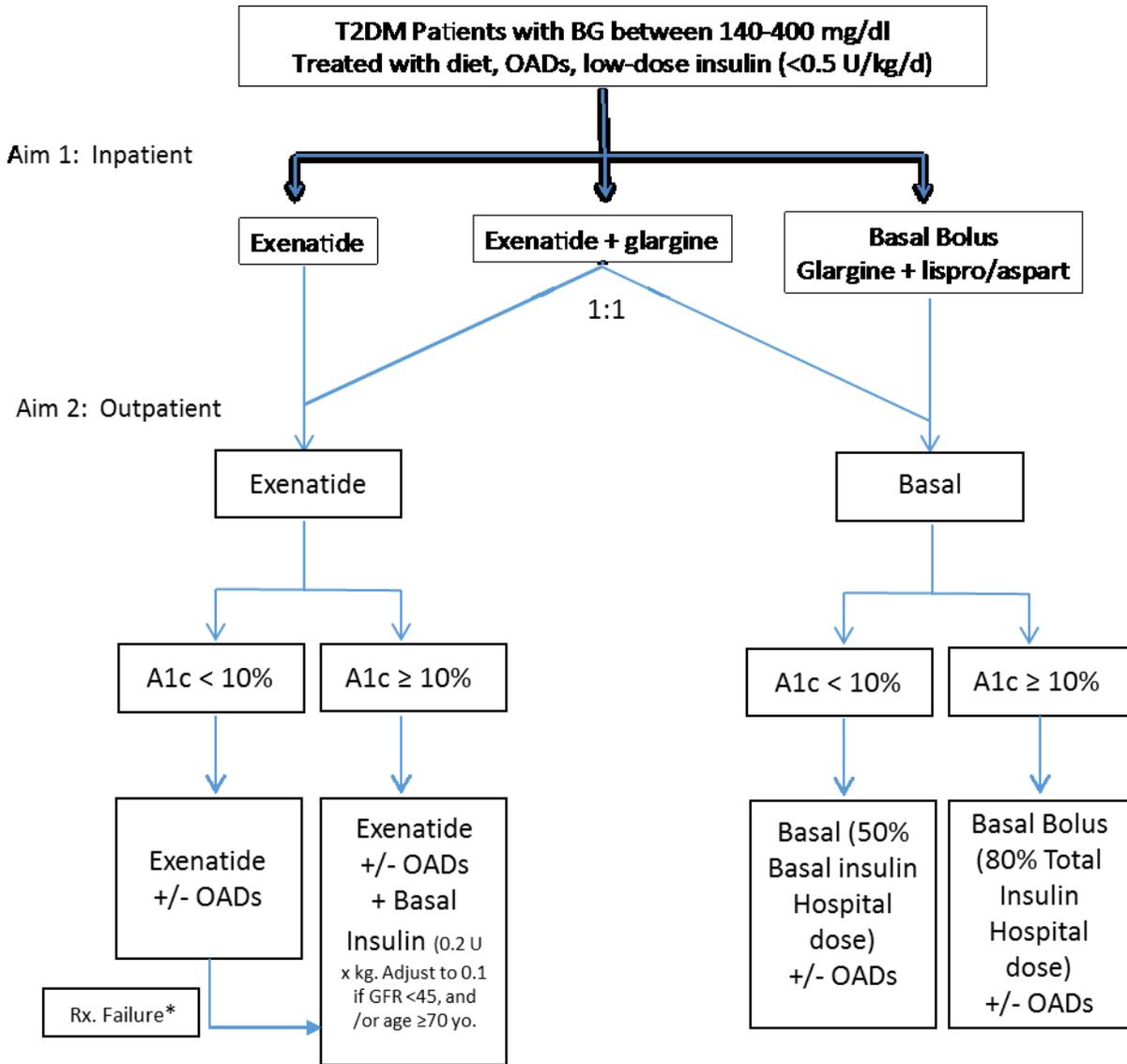
VI.b. STUDY DESIGN AND METHODS

The pilot trial is a 12-week, randomized, open label-controlled two-armed study investigating the efficacy and safety of exenatide versus basal insulin as add-on to existing oral antidiabetic drug (OAD) therapy in patients with T2D after hospital discharge.

Patients who participate in the in-hospital (Aim 1) arm and have an HbA1c > 7% will be followed in this open label prospective outpatient study. Patients will be randomized at the time of discharge to receive a twice-daily exenatide or once daily basal insulin alone or in combination to OAD therapy.

- 1) Patients treated with exenatide alone (inpatient group 1) in the hospital will be discharged with exenatide with or without oral agents with or without insulin (depending on patient's HbA1c and at investigator's discretion).
- 2) Patients treated with exenatide and basal insulin (inpatient group 2) in the hospital will be randomized in a 1:1 fashion to receive exenatide or basal (glargine or detemir) with or without oral agents.
- 3) Patients treated with basal bolus (inpatient group 3) in the hospital will be discharged with glargine or detemir with or without oral agents after discharge.

Randomization scheme, Aim 2 (HbA1C>7%):



* Rx Failure: If the fasting BG and average daily BG on 3 consecutive days exceeds > 15.0 mmol/L (240 mg/dL).

GROUP 1. Exenatide Group.

Patients with A1C 7% < 10%:

- **Patients receiving no therapy prior to admission:**
 - Discharge on exenatide 5 mcg subcutaneously per dose twice daily within 60 minutes prior to morning and evening meals. The exenatide dose will be increased to 10 mcg twice daily after 1 month based on clinical response.
- **Patients receiving antidiabetic therapy prior to admission:**
 - If no contraindication, metformin should be started at the same preadmission total daily dose. The dose of insulin secretagogues (sulfonylurea, repaglinide, nateglinide) will be held (preferred) or reduced by 50% of preadmission daily dose.
 - DPP4 inhibitors will not be continued after discharge.

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Discharge on exenatide 5 mcg subcutaneously per dose twice daily within 60 minutes prior to morning and evening meals. The exenatide dose will be increased to 10 mcg twice daily after 1 month based on clinical response.

Patients with A1C \geq 10%:

▪ **Patients receiving no therapy prior to admission:**

- Discharge on exenatide 5 mcg subcutaneously per dose twice daily within 60 minutes prior to morning and evening meals. The exenatide dose will be increased to 10 mcg twice daily after 1 month based on clinical response.
- Start Basal insulin at 0.20 U/Kg/day (glargine or detemir) once daily. Adjust dose to 0.1U/Kg/day if age is >70yrs and/or GFR<45ml/min

▪ **Patients receiving antidiabetic therapy prior to admission:**

- If no contraindication, metformin should be started at the same preadmission total daily dose. The dose of insulin secretagogues (sulfonylurea, repaglinide, nateglinide) will be held (preferred) or reduced by 50% of preadmission daily dose.
- DPP4 inhibitors will not be continued after discharge.
- Discharge on exenatide 5 mcg subcutaneously per dose twice daily within 60 minutes prior to morning and evening meals. The exenatide dose will be increased to 10 mcg twice daily after 1 month based on clinical response.
- Start Basal insulin at 0.20 U/Kg/day (glargine or detemir) once daily. Adjust dose to 0.1U/Kg/day if age is >70 and/or GFR<45ml/min

Exenatide Titration:

Exenatide will be administered 5 mcg per dose twice daily within 60 minutes prior to morning and evening meals. The exenatide dose will be increased to 10 mcg twice daily after 1 month based on clinical response.

Exenatide will be administered in the abdomen, thigh or upper arm. 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.

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., acute renal failure or stable 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 dose of insulin secretagogues (sulfonylurea, repaglinide, nateglinide) will be held (preferable) or reduced by 50% of preadmission daily dose.

In the event of hypoglycemia, sulfonylurea and insulin secretagogues will be stopped.

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.

Treatment Failure: Defined as fasting BG and/or average daily BG on 3 consecutive days exceeds > 240 mg/dL. If patients are considered a treatment failure while treated only on Exenatide +/- OADs, basal insulin will be added at 0.2U/Kg/day. Adjust dose to 0.1U/Kg/day if age is >70 and/or GFR<45ml/min.

GROUP 2. Basal (glargine or detemir) Insulin Group

VI.c. Treatment recommendations at discharge:

Patients with A1C 7% < 10%:

- **Patients receiving no Therapy prior to admission:**
 - Discharge on glargine or detemir once daily at 50% of hospital basal dose.

- **Patients receiving antidiabetic therapy prior to admission:**
 - Discharge on glargine or detemir once daily at 50% of hospital basal dose.
 - If no contraindication, metformin should be started at the same preadmission total daily dose. The dose of insulin secretagogues (sulfonylurea, repaglinide, nateglinide) should be held or started at 50% of preadmission daily dose.
 - DPP4 inhibitors will not be continued after discharge.
 - The dose of OAD should remain unchanged throughout the trial.

Patients with A1C ≥ 10%:

- **Patients receiving no Therapy prior to admission:**
 - Discharge on basal bolus at 80% of hospital total insulin daily dose. Half of the dose as basal and the other half divided in 3 equal parts before meals.

- **Patients receiving antidiabetic therapy prior to admission:**
 - Discharge on basal bolus at 80% of total insulin hospital dose. Half of the dose as basal and the other half divided in 3 equal parts before meals.
 - If no contraindication, metformin should be started at the same preadmission total daily dose. The dose of insulin secretagogues (sulfonylurea, repaglinide, nateglinide) should be held or started at 50% of preadmission daily dose.
 - DPP4 inhibitors will not be continued after discharge.

VI.d. Primary care physicians will be provided with the following algorithm for outpatient glargine or detemir insulin dose adjustment:

Insulin Basal	
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%

The above algorithm provides recommended insulin doses and may be modified based on clinical judgement of the investigator or co-investigator.

VI.e. Inpatient Diabetes Education. Prior to discharge, participants will be trained on:

1. Diabetes education if not received within 1 year of admission. All patients will be instructed on insulin and exenatide administration.
2. Glucose targets for fasting and premeal BG between 90 to 140 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 logbook to record glucose tests results.
5. Hypoglycemia recognition and management (see VI.B.)
6. Insulin and exenatide administration.

VI.f. Follow-up Care:

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 1 and 3 months after hospital discharge.

- OADs and basal insulin are standard of care at discharge, therefore, they will not be provided to participants.
- At discharge, patients will receive a one-month supply of exenatide.
- After discharge, a member of the diabetes research team will contact patients via telephone call every 2 weeks for a total of 3 months. An optional telephone call or clinic visit may be done at one week following discharge to ensure that the patient is taking the medication(s) and has sufficient supplies.
- Patients will be asked to attend an outpatient clinic visit within one and three months of hospital discharge. Prior to the outpatient visits patients will perform one 7-point self-monitoring blood glucose (SMBG) within the week prior to visit (at 4 and 12 weeks). During this visit, patients will receive a 2-month supply of exenatide (5 or 10 mcg doses) and will be asked to return to clinic 2 months later (3 months after discharge visit).
- A licensed physician (fellow or study physician) will provide recommendations on exenatide and insulin adjustment to patients after each telephone contact and clinic visit (see section V.f).

VI.g. During follow up, we will collect the following information:

1. Glycemic control:
 - a. Mean daily fasting and pre-meal BG levels measured by POC testing between 2 – 4 times daily. Patients will be instructed to monitor blood glucose during fasting and before lunch or dinner.
 - b. HbA1c at 4 and 12 weeks of discharge
 - c. Hypoglycemic events (BG < 70 mg/dl and < 40 mg/dl)
 - d. Hyperglycemic events (BG > 300 mg/dl)
2. Clinical Outcome:
 - a. Hospital readmissions
 - b. Emergency room visits
 - c. Postoperative complications

7-point self-measured blood glucose profile:

Subjects will be instructed to perform a 7-point SMBG profile two times during the trial within one week prior to site visit on a day where the subject does 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
- 120 min (2hours) after the start of breakfast
- Before lunch
- 120 min (2hours) after the start of lunch
- Before dinner
- 120 min (2hours) after the start of dinner
- At bedtime

Body measurements:

- Body weight
- Height
- Waist circumference
- Hip circumference
- 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

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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 subject should be standing with arms down their side and feet together. 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. The measurements should be performed in the following order: waist, hip, waist, hip, waist, hip.

Body Mass Index (BMI): BMI will be calculated by the formula Body weight (Kg)/m².

Flow Chart:

Aim 1.

AIM 1. Exenatide 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 8	Hosp Day 10 or Visit at Discharge
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									
Incl/excl criteria	x									
Random	x									
Withdrawal criteria	x	x	x	x	x	x	x	x	X	x
Dose adjustment	x	x	x	x	x	x	x	x	X	x
Efficacy										
Vital signs	x	x	x	x	x	x	x	x	X	x
P. Examination	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
Trial material										
Drug dispense	x	x	x	x	x	x	x	x	x	x

* The expected length of hospital stay is 6 – days. Data for glycemic control analysis will be collected during the first 10 days of hospital stay. Patients requiring hospitalization longer than 10 days will continue to receive study medications (insulin-exenatide) during the entire hospitalization.

Hosp: hospital; Inf. Consent= informed consent' Inc/excl = inclusion/exclusion; HbA1c= hemoglobin A1C; Adv= adverse

Flow Chart:

Aim 2.

Aim 2. Exenatide Discharge Arm – Flow Chart

Visit Type	Hosp Visit at D/C	Phone Visit	Clinic Visit	Phone Visit	Phone Visit	Phone Visit	Clinic Visit
Visit #	1	2	3	4	5	6	7
Time-wks.	0	2	4	5	8	10	12
Inf. Consent	x						
Inc/Excl Criteria	x						
Random	x						
Withdrawal Criteria			x				x
Drug Compliance		x	x	x	x	x	x
Dose Adjustment		x	x	x	x	x	x
Efficacy							
Vital Signs	x		x				x
P. Examination	x		x				x
Body weight	x		x				x
BMI	x		x				x
Waist circumference	x		x				x
Hip circumference	x		x				x
HbA1c	x		x				x
Fasting BG	x		x				x
7-SMBG			x				x
Safety							
Adv. Events	x	x	x	x	x	x	x
Hypoglycemia	x	x	x	x	x	x	x
Trial Material							
Drug dispense	x		x				
Drug account	x		x				
Remind 7-SMBG prior to next visit	X	X	X	X	X	X	X

VII. Methods and Procedures Applied to Human Subjects:

VII.a. Subject Population:

This study will analyze 150 (randomized) general medicine and surgery patients with a known history of T2D, age 18-80, treated with diet alone, OADS including sulfonylureas, repaglinide, nateglinide, DPP4 inhibitors or metformin as monotherapy or in combination therapy (excluding GLP1 receptor agonists), or low-dose insulin with total daily dose <0.5 unit/kg. Patients included within this study will be determined by the set of inclusion and exclusion criteria.

VII.b. Randomization and Blinding

Aim 1. 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. Patients will be randomized (block randomization) based on glucose levels (BG>200 or BG<200). The randomization table will be mailed to the research pharmacist at each institution who will be in charge of the randomization process and group assignment.

Aim 2. This is an open label randomized controlled trial. Patients who participated in Aim 1 (inpatient arm) will be randomized to receive a twice-daily exenatide or once daily glargine therapy alone or in combination to OAD therapy.

VII.c. Inclusion criteria

1. Males or females between the ages of 18 and 80 years discharged after hospital admission from general medicine and surgery services (non-ICU setting).
2. A known history of T2D receiving either diet alone or OAD including insulin secretagogues, pioglitazone, DPP4 inhibitors, or metformin as monotherapy or in combination therapy, or low-dose insulin at <0.5 unit/kg/day.
3. Subjects with a BG >140 < 400 mg/dL at time of admission and/or randomization without laboratory evidence of diabetic ketoacidosis (serum bicarbonate < 18 mEq/L or positive serum or urinary ketones).
4. BMI range: ≥ 25 Kg/m² and ≤ 50 Kg/m²

VII.d. Exclusion Criteria:

1. Age < 18 or > 80 years.
2. Subjects with increased BG concentration, but without a history of diabetes (stress hyperglycemia)
3. Subjects with a history of type 1 diabetes (suggested by BMI < 25 Kg/m² requiring insulin therapy or with a history of diabetic ketoacidosis and hyperosmolar hyperglycemic state, or ketonuria) (41).
4. Treatment with high-dose (>0.5 unit/kg/day) insulin or with GLP-1 RA during the past 3 months prior to admission.
5. Patients that required ICU care during the hospital admission.
6. Recurrent severe hypoglycemia or hypoglycemic unawareness.
7. Subjects with gastrointestinal obstruction, gastroparesis, and history of pancreatitis or those expected to require gastrointestinal suction.
8. Patients on tube feedings or TPN.
9. Patients with clinically relevant pancreatic or gallbladder disease.
10. Patients with unstable or rapidly progressing renal disease or severe renal impairment (creatinine clearance < 30 ml/min)
11. Patients with clinically significant hepatic disease (cirrhosis, jaundice, end-stage liver disease),
12. History of hypersensitivity to exenatide
13. Ongoing treatment with oral or injectable corticosteroid (equal to a prednisone dose ≥ 5 mg/day), parenteral nutrition and immunosuppressive treatment.

14. Patients with history of heavy alcohol use (female > 2 drinks per day, male > 3 drinks per day) or drug abuse within 3 months prior to admission.
15. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
16. Female subjects who are pregnant or breast-feeding at time of enrollment into the study.

VII.e. Withdrawal Criteria

VII.e.1. Aim 1. Withdrawal Criteria (inpatient arm)

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 and average daily BG on 3 consecutive days exceeds ≥ 15.0 mmol/L (240 mg/dL).
5. Pregnancy or intention to become pregnant.

VII.e.2. Aim 2. Withdrawal Criteria (outpatient arm)

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.

VIII. Study Sites: This study will be performed at Grady Memorial Hospital, Emory University Hospital, and Emory University Hospital at Midtown (PI: Guillermo Umpierrez, MD).

Additional sites: Temple University (PI: Daniel Rubin, MD.) and Vanderbilt University Medical Center (PI: Dara E. Mize, MD.).

IX. CLINICAL MANAGEMENT GUIDELINES

IX.a. Admission Laboratory Studies

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

IX.b. Treatment of Hypoglycemia (BG <70 mg/dL)

Hypoglycemia, defined, as a blood glucose level < 70 mg/dL will be treated following standard hypoglycemia protocols available at all institution.

IX.c. Assessment and Monitoring of Hospital Mortality

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

IX.d. Assessment and Monitoring of Nosocomial Infections

Nosocomial infections will be diagnosed based on standardized CDC criteria (42). New nosocomial infections will not be diagnosed until 48 hrs. 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 by the coordinators.

X. Statistical Analysis

AIM 1. This study is a three-arm randomized multicenter, open-label controlled trial. The overall hypothesis is that treatment with exenatide alone or in combination with basal insulin will result in a similar improvement in inpatient glycemic control and in a lower frequency of hypoglycemic events than treatment with basal bolus insulin regimen in hospitalized patients with T2D.

X.a. Sample Size and Power Calculations:

Sample size calculation is based on the plan to use average mean daily BG concentration as the primary measure for glycemic control. To show the non-inferiority of exenatide alone or in combination with basal insulin compared to basal bolus insulin regimen in terms of glycemic control, we set the equivalence margin as 20 mg/dl, from a view that a BG difference less than 20 mg/dl is usually not considered as clinically significant (15, 17, 18). Based on the preliminary data from Rabbit studies, 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 a one-sided, two-sample t-tests, we require 81 subjects for each treatment group to achieve 80% power. Accounting for 10% attrition rate, we would need 90 patients per treatment group, which means 270 subjects in total, to achieve >80% power in Aim 1.

X.b. Analysis of Primary Endpoint:

The primary endpoint for Aim 1 is glycemic control measured by mean daily blood glucose concentration among the three 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.

X.c. Analysis of Secondary Endpoints:

Secondary endpoints for Aim 1 in this study include incidence of hypoglycemia, number of hypoglycemic events, number of severe hyperglycemia, mean daily fasting BG, daily insulin dose, length of hospital stay, acute renal failure and hospital mortality. Blood glucose will be measured before each meal and at bedtime. For discrete outcomes (such as hypoglycemia outcomes), 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 univariate Poisson regression (or Negative Binomial regression) to assess the difference in the count outcome among the three treatment groups. We will further conduct multivariate Logistic regression, Poisson regression (or Negative Binomial regression) to account for the effects of relevant covariates on the discrete outcomes. 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. 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.

Aim 2: To determine whether treatment with exenatide (Byetta®) will result in lower number of hypoglycemia and similar glycemic control compared to treatment with basal insulin [glargine or detemir) after hospital discharge in patients with T2D.

X.d. Sample Size and Power Calculations:

The primary endpoint in Aim 2 is difference in the frequency of hypoglycemic events after discharge between treatment groups. Based on the results from the Basal Plus study (reference 40), we anticipate about 30% subjects in the Glargine +/- OAD group would experience hypoglycemic events after hospital discharge. Treatment with GLP1-RA including exenatide as monotherapy is not associated with hypoglycemia. We estimate that the rate of hypoglycemia in the exenatide group after hospital discharge will be less than 10% if we avoid the use of sulfonylurea/insulin secretagogues agents (21,38). Given the sample size targeted by this pilot study, 150, accounting for 10% attrition rate, we would have 67 subjects per group for Aim 2. Based on two-sided Fisher's Exact test with $\alpha=0.05$, we would have 79%, 92% and 97% power to detect the group difference in the occurrence rate of hyperglycemia events, when the event rate in exenatide group is assumed to be 10%, 7% and 5%.

X.e. Analysis of Primary Endpoint:

The primary endpoint in this study is the rate of hypoglycemia after hospital discharge up to 12 weeks. Secondary outcomes include 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.

XI. Potential Risks to the Subject:

Hypoglycemia. It is possible that following the proposed protocol, patients receiving basal insulin or exenatide in combination to OAD will develop hypoglycemia ($BG < 70$ mg/dL). We expect that approximately 20% to 40% of subjects treated with basal insulin will experience one or more episodes of hypoglycemia during follow-up. The frequency of hypoglycemia in patients with T2D treated with exenatide is expected to be $< 10\%$.

The number of reports of hypoglycemia will be analyzed statistically. For the purpose of this analysis, hypoglycemia is defined as a capillary and/or laboratory $BG < 70$ mg/dL. Severe hypoglycemia is defined as an event with symptoms consistent with hypoglycemia in which the subject required the assistance of another person and blood glucose less than 40 mg/dL.

Gastrointestinal side effects including nausea and vomiting are more common in patients treated with exenatide compared to placebo. 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, exenatide 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 >3x UNR or characteristic findings on CT scan/ MRI) should be withdrawn from the study.

XII. ADVERSE EVENTS

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

XII.a. Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug

induced liver injury (DILI) is also considered an important medical event. (See Section 1.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 1.4 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

XII.b. Serious Adverse Event Collection and Reporting

The collection of AEs will start after the signing of the informed consent. All SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE that occurs after these time period and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on an SAE Report Form or similar form (e.g. CIOMS, MedWatch); pregnancies on a BMS Pregnancy Surveillance Form. Reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: AEMailboxClinicalTrialTCS@astrazeneca.com

SAE Facsimile Number: 302-886-4114

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

XII.c. Nonserious Adverse Events

A **nonserious adverse event** is an AE not classified as serious.

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

XII.d. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

XII.e. Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 1.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

XII.f. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 1.1.1 for reporting details.).

XII.g. Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 1.1.1 for reporting details).

Potential drug induced liver injury is defined as:

ALT or AST elevation > 3 times upper limit of normal (ULN) **AND**

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), **AND**

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

XII.h. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

XIII. 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) patients with significant comorbidities such as chronic kidney disease greater than stage III, cirrhosis, gastroparesis, and pancreatic disease will be excluded from the study.

Hypoglycemia: We expect that approximately 20% to 30% of subjects treated with basal insulin will experience one or more episodes of hypoglycemia and less than 10% of exenatide treated patients will experience hypoglycemia during follow-up. 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 and the daily dose of insulin will be reduced by 10% to 30%.

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

XIII.a. Treatment of Hypoglycemia (BG <70 mg/dL)

Hypoglycemia, defined as a BG < 70 mg/dL will be treated following standard hypoglycemia protocols available at both institutions.

Patients with hypoglycemia will be treated as per protocol:

For BG < 70 mg/dL, follow hypoglycemic orders below:

- If patient is alert and can tolerate oral intake, give 20 grams of fast-acting carbohydrate (6 oz. fruit juice or regular soda, crackers).
- If patient is not alert and cannot tolerate oral intake, give 1 ampule (50 mL) of D₅₀.
- Check finger stick BG q 15 minutes and repeat above treatment until BG > 100 mg/dL.
- Once BG > 100 mg/dL, repeat finger stick BG 1 hour later and treat as follows:
 - If BG < 70 mg/dL, call MD and follow y hypoglycemia orders (above)
 - If BG 70 – 100 mg/dL, give snack/scheduled meal and check BG q 1 h until BG >100 mg/dl
 - If BG > 100, no further treatment needed.

XIV. Potential Benefits to the Subject:

We believe that all subjects will benefit greatly from this study. Improved glycemic control may significantly reduce complications after discharge and reduce the risk of hyperglycemia and hypoglycemia.

XV. Potential Benefits to Society:

This study will provide important information on the benefits of exenatide and insulin therapy after discharge for the management of patients with type 2 diabetes. We will determine whether glycemic control is different among insulin and exenatide therapy after hospital discharge.

XVI. Risk/Benefit Assessment:

Insulin therapy is the mainstay of diabetes management in hospitalized patients with diabetes. There are no prospective, randomized studies to assess the efficacy and safety of exenatide for the management of diabetes after hospital discharge. This study will test the efficacy of exenatide versus insulin therapy in combination to oral antidiabetic agents after hospital discharge in medicine and surgery patients with type 2 diabetes.

XVII. Therapeutic Alternatives:

Patients can be treated with other insulin formulations (regular insulin, NPH, glargine, lispro, aspart or glulisine) and oral agents (glyburide, glipizide, DPP4 inhibitors and GLP1 analogs) currently available for the treatment of type 2 diabetes.

XVIII. Inclusion of women.

We anticipate that ~50% of the study subjects will be female. No patients under the age of 18 and no pregnant women will be included in the study. Absence of pregnancy must be demonstrated by blood or urine testing prior to randomization (in female subjects of childbearing potential only).

XIX. Inclusion of minorities.

Patients will not be excluded based on race or ethnic origin. We anticipate that half of patients will be African Americans, 10% Hispanics, and the rest Caucasians.

XX. Inclusion of children.

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

XXI. Confidentiality

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. 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.

XXII. Payment for Participation.

Participation in this study is voluntary. Patients will receive one hundred dollars (\$100.00) during the hospital stay and seventy- five dollars (\$75, 00) after each clinic visit at 1 and 3 months after discharge. Total compensation will be two hundred and fifty dollars (\$250).

XXIII. Financial Obligation.

No additional cost to patients or to the institution will be incurred for research purposes. Research studies will be performed at no cost to study subjects. Exenatide will be provided by Astra Zeneca at no cost to participants.

XXIV. Research Injuries.

If a patient is injured because of taking part in this study, Dr. Umpierrez and investigators, along with the medical facility will make medical care available to the patient at the patient's own cost. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

XXV. Financial Conflict of Interests.

None of the investigators in this study has any outside activities that may represent a conflict of interest. None of the investigators has an economic interest in an outside entity, or act as officers, directors, employees or consultants with such an entity, whose financial interest may be affected by this research study.

XXVI. Informed Consent.

After identification of eligible patients, these individuals will be provided basic information regarding the study and, if interested, they will then be screened by research staff using the inclusion/exclusion criteria delineated elsewhere in this protocol. 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 any questions, and research staff will answer these 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.

XXVII. Medical Device Research.

Not applicable.

XXVIII. References

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XXIX. Table 1.

Supplemental Insulin Aspart or Lispro

BEFORE MEALS Add Supplemental Sliding Scale Insulin dose (# of units) from table below to the scheduled Insulin dose.

BEDTIME. Supplemental Sliding Scale Insulin dose at bedtime starting at BG > 220 mg/dL

Check appropriate column and cross out other columns

Sliding scale before meals:

BG (mg/dL)	<input type="checkbox"/> Insulin Sensitive	<input type="checkbox"/> Usual	<input type="checkbox"/> 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:

BG (mg/dL)	<input type="checkbox"/> Insulin Sensitive	<input type="checkbox"/> Usual	<input type="checkbox"/> 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 lispro or aspart insulin per dose.

“Supplemental” dose is to be added to the scheduled dose of lispro or 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.

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 180 mg/dl will receive 2 U of supplemental insulin.