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Linagliptin Inpatient Trial: A Randomized Controlled Trial on the Safety and Efficacy of Linagliptin (Tradjenta®) Therapy for the Inpatient Management of General Surgery Patients with Type 2 Diabetes

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I. RESEARCH OBJECTIVES AND SPECIFIC AIMS

A. Introduction:

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 outcome, 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 multiorgan 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 T2D. The two most common SQ insulin regimens for inpatient glycemic management are sliding scale regular insulin (SSRI) and basal bolus insulin therapy in combination with correction insulin scale (15, 16). The use of basal bolus regimen results in better glycemic control and in lower rate of hospital complications compared to sliding scale regular insulin (SSRI) (16-19). The basal bolus regimen; however, requires multiple insulin daily injections and is associated with a significant risk of hypoglycemia reported in up to 32% of non-ICU patients with T2D (16, 18, 19).

We recently completed a randomized two-center pilot open label trial aiming to determine differences in glycemic control between treatment with sitagliptin (Januvia®) alone or in combination with glargine compared to a standard basal bolus regimen in general medicine and surgery patients with T2D (see preliminary result section). We found no differences in mean daily BG, number of BG readings within target, frequency of hypoglycemia, LOS and hospital complications. We also found that patients treated with sitagliptin alone required less insulin dose ($p < 0.001$) and lower number of insulin injections per day ($p < 0.001$) compared to treatment with basal bolus regimen. These results suggest that treatment with a DPP-4 inhibitor is safe and effective for the management of hyperglycemia in patients with T2D. These results are of great clinical importance and may represent a major improvement in management of hospitalized patients with T2D; however, they need to be confirmed by a large multicenter RCT. Accordingly, we propose to determine the safety and efficacy of DPP-4 inhibitor therapy for in-hospital and post-discharge management of general medicine and surgical patients with T2D.

B. Hypothesis:

We hypothesize that treatment with linagliptin (Tradjenta®) once daily plus correction (supplemental) doses with a rapid-acting insulin analog before meals will result in a similar glycemic control than treatment with glargine (Lantus®) once daily plus rapid-acting insulin before meals in general surgery patients with T2D.

C. 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 linagliptin (Tradjenta®) plus correction doses with a rapid-acting insulin analog before meals and a basal bolus regimen with glargine once daily and rapid-acting insulin analog before meals in general surgery patients with T2D. Surgery patients with T2D treated with diet, oral antidiabetic agents (OAD) or with low total daily dose insulin therapy (≤ 0.5 unit/kg/day) will be randomized to receive linagliptin (group 1) or basal bolus insulin regimen (group 2). If needed, patients in both groups will receive supplemental (correction) doses of rapid-acting insulin (lispro, aspart or glulisine) before meals for BG > 140 mg/dl.

Specific Aim 2: To determine the efficacy and safety of an HbA1c based discharge algorithm in controlling BG after discharge in surgery patients with T2D. Patients who participate in the in-hospital arm (Aim 1) will

be invited to enroll in this open label prospective outpatient study. The total duration of the study is 3 months. Patients with an admission HbA1c <7% will be discharged on their same outpatient antidiabetic regimen or linagliptin 5 mg once daily. Patients with an HbA1c between 7% and 9% will be discharged on their outpatient treatment plus linagliptin once daily. Patients with an admission A1C \geq 9% will be discharged on a combination of metformin plus linagliptin and 50% of basal insulin used in the hospital stay.

II. BACKGROUND AND CURRENT 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, 20-23). Evidence from observational studies indicates that 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, 24-28). Prospective randomized trials in critical care patients have shown that glycemic control reduces short- and long-term mortality, multiorgan failure and systemic infections, length of hospital and ICU stay [7, 9-11], and to lower total hospitalization cost (29). Similarly, attainment of targeted glucose control in the setting of cardiac surgery is associated with a significant reduction in deep sternal wound infections and mortality rate (9, 30, 31). Based on these observational and interventional studies, improved glycemic control is recommended in patients with critical illness (3, 6, 23, 26, 28, 32).

The importance of hyperglycemia also applies to adult patients admitted to general surgical and medical wards. In such patients, the presence of hyperglycemia is associated with prolonged hospital stay, infection, disability after hospital discharge, and death (1, 4, 6). Over the short-term, hyperglycemia can adversely affect fluid balance and immune function, and it can promote inflammation (26, 33). Our research group reported that inpatient hyperglycemia (defined as a fasting blood glucose \geq 126 mg/dl or random blood glucose \geq 200 mg/dl on two or more occasions) in subjects with and without history of diabetes was associated with longer length of hospital stay and increased hospital mortality (1). In general surgical patients, a serum glucose > 220 mg/dL on postoperative day one has been shown to be a sensitive predictor of the later development of postoperative nosocomial infection (4). In patients with hyperglycemia (BG > 220 mg/dL) on postoperative day one, the infection rate was 2.7 times that observed (31.3% versus 11.5%) in diabetic patients without hyperglycemia. These data strongly indicate that hyperglycemia from any etiology is a predictor of poor outcome in hospitalized patients in critical care units or in general medicine or surgical services, and that improvement in outcomes can be achieved with improved glycemic control.

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 (16, 18, 19). In the Rabbit-2 medicine trial (34), 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 (19). 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 (19). These results indicate that basal/bolus insulin regimen is a preferred regimen over SSRI alone in the hospital management of patients with T2D. The use of basal bolus approach; however, is labor intensive requiring multiple daily insulin injections (4 to 6), and have a significant risk of hypoglycemia (19, 35) reported in up to 32% of hospitalized patients with T2D in general wards.

We recently completed the first pilot study on the safety and efficacy of treatment with sitagliptin (Januvia®) alone or in combination with basal insulin in general medicine and surgery patients with T2D (see preliminary result section). In this study, 90 patients with T2D randomized to sitagliptin once daily,

sitagliptin and basal insulin and to a standard basal bolus regimen, we found similar improvement in glycemic control in all groups with no differences in mean daily BG, number of BG within target range, frequency of hypoglycemia, length of stay, hospital complications, or in the number of treatment failures. These results suggest that treatment with sitagliptin alone or in combination with basal insulin are safe and effective for the management of hyperglycemia in patients with T2D.

Linagliptin is a new orally active small-molecule inhibitor of DPP-4, licensed in the US in 2011 to improve glycemic control in adults with T2D (36). Linagliptin is rapidly absorbed after oral administration, with maximum plasma concentration (C (max)) occurring after approximately 90 minutes. Linagliptin exhibits concentration-dependent protein binding in human plasma in vitro and has a large volume of distribution into tissues. Linagliptin has a long terminal half-life (>100 hours); however, its accumulation half-life is much shorter ~ 10 hours, accounting for a rapid attainment of steady state. Linagliptin is eliminated primarily in feces, with only around 5% of the oral therapeutic dose excreted in the urine at steady state (37). There are no clinically relevant alterations in linagliptin pharmacokinetics resulting from renal impairment or hepatic impairment. Long-term safety and efficacy of linagliptin as monotherapy or in combination with other OAD has been demonstrated in in 24-week phase III trials followed by a 78-week open-label extension in patients with T2D (38, 39). Although the safety and effectiveness has not been tested in the inpatient setting, linagliptin has a unique pharmacokinetic and pharmacodynamic profile that makes it an attractive agent for the treatment of inpatients with T2D including: rapid-onset of action and efficacy in reducing fasting and postprandial glucose levels, low risk of hypoglycemia when used as monotherapy, large volume of distribution into tissues, and lack of relevant alterations in linagliptin pharmacokinetics in patients with renal or hepatic impairment.

III. 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 admitted to general medicine services.

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 (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 glycemia.

In the Rabbit Surgery trial (19), we reported on the efficacy and safety of improving glycemic control with a basal/bolus regimen compared to SSRI in general surgery. 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

Fig 1

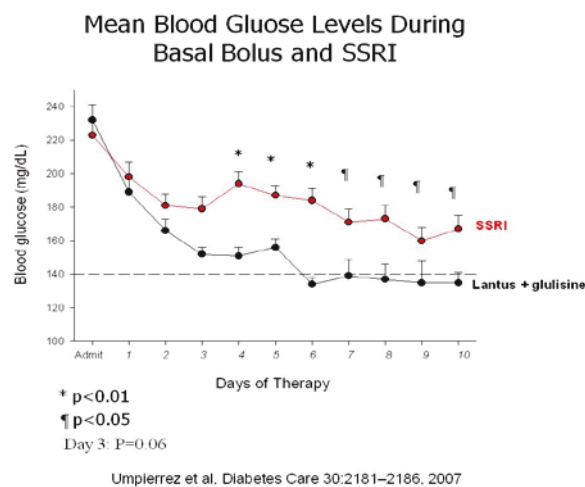


Table 1. Rabbit Surgery – Hospital complications.

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

failure, and bacteremia. The basal bolus regimen resulted in significant reduction in daily BG as well as in a significant reduction in the frequency of the composite outcome (24.3% and 8.6%, $p = 0.003$), Table 1.

Sitagliptin Inpatient Pilot Study (Table 2). In a two-center open label randomized pilot trial we recently determined differences in glycemic control between sitagliptin (Januvia®) alone or in combination with basal insulin and basal bolus regimen in medicine and surgery patients with T2D. In this study, 90 patients 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 ($n=30$) and 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.

Treatment with sitagliptin alone or in combination to glargine resulted in similar glycemic control compared to basal bolus regimen (Table 2 and Figure 3). There were no differences in 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 requirement and lower number of insulin injections, both, $p < 0.001$. These results indicate that treatment with a DPP-4 inhibitor alone or in combination with basal insulin is safe and effective in the management of patients with T2D.

Transition of Care after Discharge. In a recent preliminary study we assessed the efficacy of an HbA1c based algorithm for the management of patients with T2D (Fig. 5). Patients with an HbA1c $<7\%$ were discharged on their outpatient antidiabetic regimen (OAD and/or insulin). Patients with an HbA1c between 7% and 9% were discharged on a combination of OADs and basal insulin at 50%-80% of total daily hospital dose. Patients with an admission 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 admission HbA1c on admission of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge ($p < 0.01$). These data indicate that the admission HbA1c is beneficial in designing the discharge treatment algorithm after discharge in non-ICU patients with T2D.

Table 2. Glycemic control Among Treatment Groups

Glycemic Control	Sitagliptin	Sitagliptin + Glargine	Basal Bolus	P-Value
HbA1c, %	7.8 ± 2.2	8.4 ± 2.1	8.4 ± 2.1	0.51
Admit BG, mg/dl	209.4 ± 67	203.0 ± 48	224.9 ± 74	0.57
Randomization BG, mg/dl	193 ± 44	197 ± 44	211 ± 56	0.36
Mean BG, after 1 st day of therapy	168.4 ± 35	154.2 ± 29.2	158.3 ± 31	0.23
BG Control after 24hr Rx				
% BG 70-140 mg/dl	36 ± 30	43 ± 28	43 ± 26	0.53
% BG >140 mg/dl	64 ± 30	57 ± 27	55 ± 27	0.47
% BG >200 mg/dl	21 ± 21	13 ± 19	21 ± 18	0.23
Treatment failure*				
Treatment failures, n (%)	4 (14.8)	3 (10.3)	5 (19.2)	0.63

Data are mean ± SD

*Treatment failure was defined as having 2 consecutive BG readings > 240 mg/dl or a mean daily BG > 240 mg/dl after the 1st day of treatment

Fig 2 Mean Daily BG During Treatment

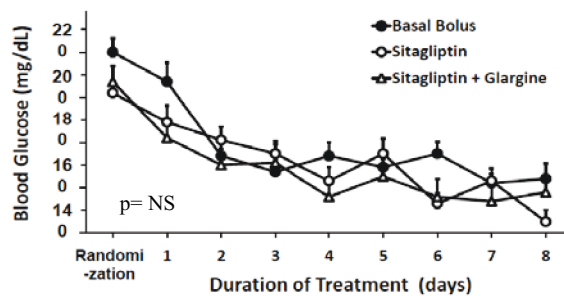


Fig 3 Mean blood glucose before meals and at bedtime during treatment

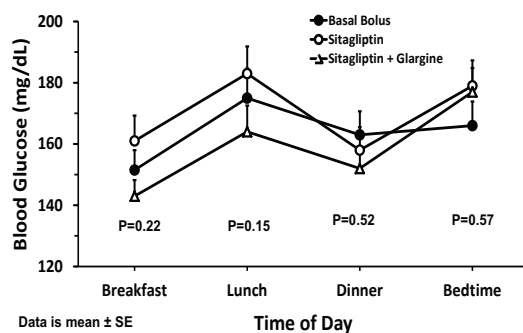
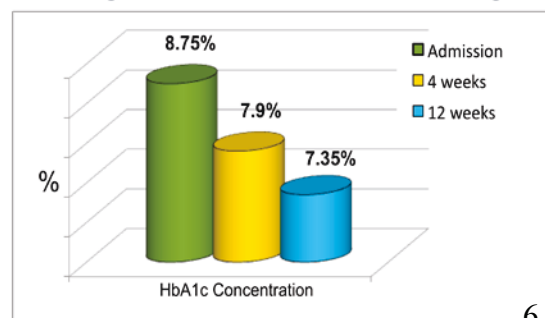


Fig 4 Change in HbA1c levels after discharge



In summary, our 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 SSRI 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 basal bolus insulin regimen for the management of hospitalized patients with T2D.

IV. EXPERIMENTAL PLAN.

Specific Aim 1: To determine whether in-hospital glycemic control, as measured by mean daily glucose concentration and frequency of hypoglycemic events, is different between treatment with linagliptin (Tradjenta®) plus correction doses with a rapid-acting insulin analog before meals and a basal bolus regimen with glargine once daily and rapid-acting insulin analog before meals in general surgery patients with T2D.

IV.a. Rationale. The result of several observational and interventional studies indicate that hyperglycemia is associated with poor hospital outcomes including prolonged hospital stay, increase rate of wound and systemic infections, disability after hospital discharge, and death (1, 26). Previous studies have shown that basal bolus regimens in patients with T2D result in a significant improvement in glycemic control and in lower rate of hospital complications compared to SSRI in patients with T2D (40-42). In our preliminary study, the use of sitagliptin alone or in combination with basal insulin was proven to be as effective in improving glycemic control compared to basal bolus insulin regimen.

Linagliptin 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, low risk of hypoglycemia when used as monotherapy, large volume of distribution into tissues, and lack of relevant alterations in linagliptin pharmacokinetics in patients with renal or hepatic impairment. Linagliptin is a new orally active small-molecule inhibitor of DPP-4, licensed in the US in 2011 to improve glycemic control in adults with T2D (36). Based on our preliminary experience and the proven efficacy of linagliptin in improving glycemic control, safety and excellent tolerance, we believe that linagliptin may represent an excellent alternative to basal bolus treatment in subjects with T2D.

IV.b. STUDY DESIGN AND METHODS

A total of 280 randomized (300 patients consented to account for screen failures) general surgery patients with T2D treated with diet, oral hypoglycemic agents, or low-dose (≤ 0.5 units/kg/day) insulin therapy prior to admission will be included in this prospective, randomized, open label trial to compare the safety and efficacy of linagliptin once daily versus basal bolus regimen with glargine once daily plus rapid-acting insulin before meals. Both treatment groups will receive corrective doses of rapid-acting insulin analogs (aspart, lispro or glulisine) before meals for BG > 140 mg/dl.

Study Outcomes:

The primary outcome of the study is to determine differences in glycemic control as measured by mean daily BG concentration between linagliptin and basal bolus therapy.

Secondary outcome is to compare differences between treatment groups in any of the following measures:

1. Number of hypoglycemic events (<70 mg/dl) and severe hypoglycemic events (<40 mg/dl).
2. Number of episodes of hyperglycemia (BG > 300 mg/dl) after the first day of treatment.
3. Total daily dose of insulin.
4. Length of hospital stay.
5. Need for ICU care (transfer to ICU)
6. Differences between groups on a composite of hospital mortality and perioperative complications including wound infections (deep and superficial), bacteremia, respiratory failure, acute renal failure, and major cardiovascular events (acute myocardial infarction, congestive heart failure, and cardiac arrhythmias).

7. Acute renal failure defined as a clinical diagnosis of acute renal failure with documented new-onset abnormal renal function (serum creatinine >2.2 mg/dL or an increment >0.5 mg/dL from baseline).
8. Hospital mortality. Mortality is defined as death occurring during admission.

IV.c. Overall Design and Study Interventions

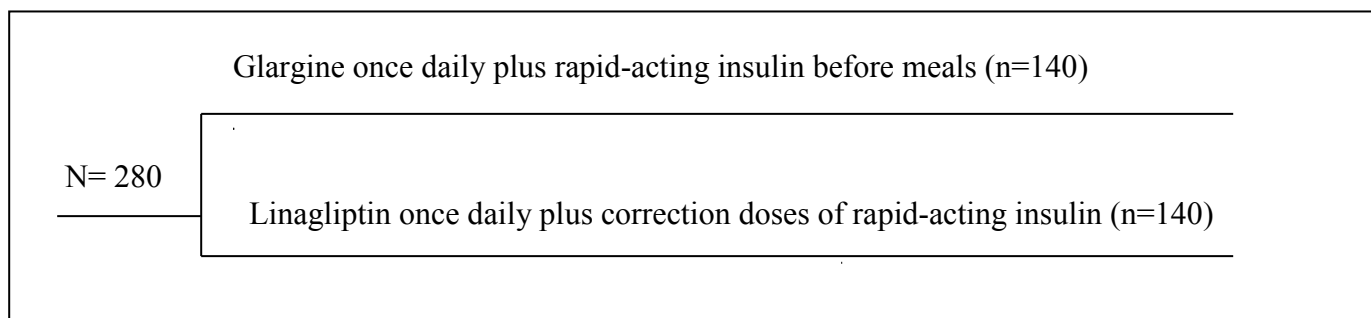
This multicenter randomized clinical trial will include male or female subjects with known history of diabetes between 18-80 years of age admitted to general surgery (non-ICU) service. Due to the design of this study (i.e. enrollment of subjects in need of acute care), there will be no run-in period. Upon arrival to the Emergency Department or surgery service, subjects will be screened for the study. Patients with a known history of T2D treated with diet alone, any combination of oral hypoglycemic agents or low-dose insulin therapy (≤ 0.5 unit/kg/day) prior to admission will be considered potential candidates in this study. The goal of therapy is to maintain fasting and pre-meal BG < 140 mg/dL while avoiding hypoglycemia. Treatment assignment will be coordinated by a research pharmacist at each institution following a computer-generated block randomization table. Diabetic patients with a BG > 140 mg/dL and < 400 mg/dL without ketosis will be randomized consecutively (using a randomization table) to receive:

- Group 1. Linagliptin once daily*
- Group 2. Basal bolus regimen with glargine once daily and lispro, aspart or glulisine before meals*

* Supplemental (correction) doses rapid-acting insulin analog (lispro, aspart or glulisine) will be given for BG > 140 per sliding scale if needed. Rapid-acting insulin may vary at different institutions.

The primary medical team (PMT) will decide on the treatment for the surgical and other medical problem(s) for which patients are admitted. The PMT will also decide patient's discharge orders for the treatment of their primary diagnosis. At discharge, patients will be followed by their primary care physician, surgery team, and the diabetes research team. The recommended insulin therapy at discharge will be based on the degree of glycemic control (HbA1c level) as described in Aim 2. After discharge, a member of the diabetes research team will contact patients via telephone call every 2 weeks for a total of 3 months. In addition, patients will be asked to attend an outpatient clinic visit within one month and after 3 months of hospital discharge to assess level glycemic control (fasting and premeal BG levels, presence of hypoglycemia), and to determine the presence of complications after discharge (wound or systemic infection, hospital readmission, cardiac events, etc).

IV.e. Treatment Groups:



GROUP 1. Linagliptin Group.

- Discontinue oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, metformin, pioglitazone), insulin and non-insulin injected antidiabetic medication (pramlintide, exenatide) on admission.
- Linagliptin 5 mg once daily
- **Supplemental (correction) insulin.** Supplemental (lispro, aspart or glulisine) 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 or glulisine) 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 or glulisine) insulin will be administered every 6 hours (6-12-6-12) following the “sensitive” dose of the sliding scale.
- **Insulin adjustment.** The supplemental (lispro, aspart or glulisine) insulin dose will be adjusted as follow:
 - If the fasting and pre-meal plasma glucose are persistently >140 mg/dl in the absence of hypoglycemia, the supplemental (lispro, aspart or glulisine) insulin scale could be increased from sensitive to usual, or from usual to resistant scale.
 - If a patient develops hypoglycemia, the supplemental (lispro, aspart or glulisine) insulin should be decreased from insulin resistant to usual scale or from usual to sensitive scale.
 - The attending physician may consider using the total supplemental insulin dose, patient’s nutritional intake, and results of blood glucose testing to adjust insulin regimen.
- **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. Basal Bolus Regimen with Glargine and Rapid-acting Insulin (Lispro, Aspart or Glulisine)

- Discontinue oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, metformin, pioglitazone), insulin and non-insulin injected antidiabetic medication (pramlintide, exenatide) on admission.
- **Starting total daily insulin dose:**
 - Patients with BG between 140-200 mg/dL= 0.4 units per kg weight per day.
 - Patients with BG between 201-400 mg/dL= Total insulin dose 0.5 units per kg
 - If GFR<45 ml/min reduce total daily dose by half (0.2 to 0.25 units per Kg per day)
 - Half of total daily dose will be given as glargine and half as lispro, aspart or glulisine.
 - Glargine insulin will be given once daily, at the same time of the day.
 - Patients will receive the full-dose of glargine insulin (even if NPO).
 - Prandial insulin (lispro, aspart or glulisine) will be given in three equally divided doses within 30 minutes before/after each meal. To prevent hypoglycemia, if a subject is not able to eat, the dose of lispro, aspart or glulisine will be held.
- **Insulin adjustment.** The total daily insulin dose will be adjusted as follow:
 - 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 glargine dose by 10% every day
 - Fasting and pre-meal BG >180 mg/dl: increase glargine dose by 20% every day
 - Fasting and pre-meal BG between 70-99 mg/dl: decrease glargine dose by 10% every day
 - If a patient develops hypoglycemia (BG <70 mg/dL), decrease glargine dose by 20%.
 - If a patient develops hypoglycemia (BG <40 mg/dL), decrease glargine dose by 30-40%.
- The attending physician may consider using the total supplemental insulin dose, patient's nutritional intake, and results of blood glucose testing to adjust insulin regimen.
- **Supplemental insulin.** Supplemental (lispro, aspart or glulisine) 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 or glulisine) 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 or glulisine) 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.

V. Specific Aim 2: To determine the efficacy and safety of an A1C based discharge algorithm in controlling BG after discharge in patients with T2D.

Patients who participate in the in-hospital arm (Aim 1) will be invited to enroll in this open label prospective outpatient study. The total duration of the study is 3 months.

V.a. Rationale. Few studies have addressed the efficacy of insulin or oral antidiabetic agents after hospital discharge. In a recent pilot study we assessed the efficacy of an HbA1c based algorithm for the management of patients with T2D (see preliminary results section, Fig. 5). Patients with a high HbA1c were discharged on a combination of OADs and basal insulin or on a basal bolus regimen. The admission HbA1c on admission of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge ($p < 0.01$). These data indicate that the admission HbA1c is beneficial in designing the discharge treatment algorithm after discharge in non-ICU patients with T2D. Linagliptin has a unique pharmacokinetic and pharmacodynamic profile that makes it an attractive agent for the treatment of with T2D including its rapid-onset of action in improving glycemic control without weight gain and the low risk of hypoglycemia. Based on our preliminary experience and the proven efficacy of linagliptin in improving glycemic control, we believe that linagliptin may represent an excellent alternative to insulin therapy after discharge in subjects with T2D.

IV.a. Study Outcomes:

The primary outcome of the outpatient arm is to explore the safety and efficacy of linagliptin after hospital discharge. Differences from baseline (hospital admission) in HbA1c concentration will be assessed at 4 weeks and 12 weeks after discharge.

Secondary outcome will include:

1. Fasting and postprandial BG concentration
2. Number of hypoglycemic events (< 70 mg/dl) and severe hypoglycemic events (< 40 mg/dl).
3. Number of patients with HbA1c $< 7.0\%$
4. Total daily dose of insulin.
5. Number of emergency room visits and hospital readmissions
6. Number of complications: wound infection, pneumonia, acute renal failure and mortality.

IV.b. STUDY DESIGN AND METHODS

The trial is a 12-week, open label trial investigating the efficacy and safety of linagliptin as add-on to existing oral antidiabetic drug (OAD) or insulin therapy in patients T2D after hospital discharge.

V.a. Inhospital Diabetes Education. Prior to discharge, participants will be trained on:

1. Diabetes education if not received within 1 year of admission or if discharge on insulin therapy.
2. ADA targets for fasting and premeal BG between 90 to 130 mg/dL.
3. Use of glucose meters for home glucose self-monitoring (meters may vary at different institutions).
4. Keeping BG records, and will receive a log-book to record glucose tests results.
5. Hypoglycemia recognition and management (see VI.B.)
6. Insulin administration (if needed).

V.b. Follow-up Care:

- Insulin therapy is the standard of care at discharge, therefore, glargine or rapid-acting insulin analogs will not be provided to participants. The choice of rapid-acting analogs will be based on formulary availability at each institution.
- Patients to be discharged on linagliptin will receive 1-month supply by the research hospital pharmacy.

- After discharge, 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 an outpatient clinic visit within one month of hospital discharge. During this visit, patients will receive a 2 month supply of linagliptin and will be asked to return to clinic 2 months later (3 month after discharge visit).
- Recommendation on insulin adjustment will be provided to patients and their PCP after each telephone contact and clinic visit by a license physician (fellow or study physician) (see section Vf).

V.c. During follow up we will collect the following information:

1. Glycemic control:
 - a. Mean daily fasting and premeal blood glucose levels
 - b. A1C at 3 months of discharge
 - c. Hypoglycemic events (BG < 70 mg/dl and < 40 mg/dl)
 - d. Hyperglycemic events (BG > 300 mg/dl)
2. Diabetes treatment:
 - a. Number of patients receiving insulin and linagliptin therapy
 - b. Use of linagliptin and other oral agents
 - c. Protocol adherence by PCP (diabetes clinic versus PCP)
3. Clinical Outcome:
 - a. Hospital readmissions
 - b. Emergency room visits
 - c. Postoperative complications

V.d. Treatment recommendations at discharge:

V.d.1. Admission A1C < 7%:

- Discharge on same pharmacologic regimen (oral agents, insulin therapy) or linagliptin 5 mg/day.
- If contraindication to OADs, discharge on linagliptin once daily.

V.d. 2. Admission A1C between 7% and 9%:

- **V.d.2.a. Patients receiving no pharmacologic agents prior to admission:**
- Assure there are no contraindications to metformin therapy.
- If no contraindication to metformin, discharge on the combination of linagliptin daily and metformin twice daily.
- If contraindication to metformin, discharge patient on linagliptin once daily.
- **V.d.2.b. Patients treated with OADs prior to admission:**
- Assure there are no contraindications to metformin therapy.
- If no contraindication to metformin, discharge on linagliptin daily and metformin 500 mg twice daily. If patients were on metformin 1000 mg twice a day prior to admission, may restart on the same dose if A1C > 8%. May use previous OADs, but consider stopping or reducing dose of sulfonylureas.
- If contraindication to metformin, discharge patient on linagliptin once daily plus previous OADs. May consider linagliptin plus basal if HbA1c > 8% as follows:
 - If in basal bolus group during the inpatient arm, can start basal insulin at 50% of hospital dose.
 - If in the linagliptin group during the inpatient arm, can start basal insulin at 0.2 units/kg/day

V.d.2.c. Patients treated with insulin (with or without OADs) prior to admission:

- Assure there are no contraindications to metformin therapy.
- If no contraindications to metformin, discharge patient on linagliptin daily and metformin 500 mg twice daily and basal insulin as follows:
 - If in the basal bolus group during the inpatient arm, can start basal insulin at 50% of hospital dose.
 - If in the linagliptin group during the inpatient arm, can start basal insulin at 0.2 units/kg/day
- If contraindication to metformin, discharge on linagliptin once daily and basal insulin as follows:
 - If in the basal bolus group during the inpatient arm, can start basal insulin at 0.2 units/kg/day.

V.d.3. Admission A1C \geq 9%:

V.d.3.a. Patients receiving no treatment or on OADs treatment prior to admission:

- Assure there are no contraindications to metformin therapy.
- If no contraindications to metformin, discharge patient on linagliptin daily and metformin 500 mg twice daily and basal insulin as follows:
 - If in the basal bolus group in the inpatient arm, can start basal insulin at 80% of hospital dose.
- If in the linagliptin group in the inpatient arm, can start basal insulin at 0.2 units/kg/day If contraindication to metformin, discharge on linagliptin once daily and basal insulin as follows:
 - If in the basal bolus group in the inpatient arm, can start basal insulin at 80% of hospital dose.
 - If in the linagliptin group in the inpatient arm, can start basal insulin at 0.2 units/kg/day.
- Consider stopping or reducing dose of sulfonylureas
- **Alternative:** Discharge on basal bolus regimen at same inpatient total daily insulin dose.
 - Basal insulin once daily and rapid-acting insulin before meals.

V.d.3.b. Patients treated with insulin (with or without OADs) prior to admission:

- Assure there are no contraindications to metformin therapy.
- If no contraindications to metformin, discharge patient on linagliptin daily and metformin 500 mg twice daily and basal insulin as follows:
 - If in the basal bolus group during the inpatient arm, can start basal insulin at 80% of daily hospital dose.
 - If in the linagliptin group during the inpatient arm, can start basal insulin at 0.2 units/kg/day.
- If contraindication to metformin, discharge on linagliptin once daily and basal insulin as follows:
 - If in the basal bolus group during the inpatient arm, can start basal insulin at 80% of hospital dose.
 - If in the linagliptin group during the inpatient arm, can start basal insulin at 0.2 units/kg/day.

- **Alternative:** Discharge on basal bolus regimen at same inpatient total daily insulin dose. Basal insulin once daily and rapid-acting insulin before meals.

V.e. Primary care physicians will be provided with the following algorithm for outpatient glargine insulin dose adjustment:

Insulin Glargine	
If mean FBG > 180 mg/dL for the last 2 consecutive days and no episodes of hypoglycemia (BG <70 mg/dL)	Increase daily dose by 4 IU
If mean FBG > 140 mg/dL for the last 2 consecutive days and no episodes of hypoglycemia (BG <70 mg/dL)	Increase daily dose by 2 IU
If mean FBG between 100 to 140 mg/dL for the last 2 consecutive days and no episodes of hypoglycemia (BG <70 mg/dL)	No Change
If any FBG between 70 – 99 mg/dl	Decrease by 4 IU or 10% of total daily dose
If any FBG or RBG < 70 mg/dl	Decrease by 8 IU or 20% of total daily dose
If any FBG or RBG < 40 mg/dl	Decrease total daily dose by 30%

V.f. Primary care physicians will be provided with the following algorithm for the outpatient prandial (lispro, aspart or glulisine) insulin dose adjustment (Basal Bolus regimen):

Prandial insulin (lispro, aspart or glulisine)		
Mealtime Dose, U	BG 70 – 100 mg/dl*	BG 141-180 mg/dl**
≤ 10 U	Decrease by 1 U	Increase by 1 U
>11- 19 U	Decrease by 2 U	Increase by 2 U
≥ 20 U	Decrease by 3 U	Increase by 3 U
Mealtime Dose, U	BG 40-70 mg/dl	BG 180-240 mg/dl
≤ 10 U	Decrease by 2 U	Increase by 2 U
>11- 19 U	Decrease by 3 U	Increase by 3 U
≥ 20 U	Decrease by 4 U	Increase by 4 U
Mealtime Dose, U	BG < 40 mg/dl***	BG > 240 mg/dl
≤ 10 U	Decrease by 4 U	Increase by 3 U
>11- 19 U	Decrease by 6 U	Increase by 4 U
≥ 20 U	Decrease by 8 U	Increase by 5 U

* If > ½ of the pre-prandial BG values for the week were below target

**If > ½ of the pre-prandial BG values for the week were above target

*** Decrease by 30-40% in the event of severe hypoglycemia (pre-prandial BG < 40 mg/dl)

VI. Methods and Procedures Applied to Human Subjects:

a. Subject Population:

This will include 280 randomized general surgery patients with a known history of T2D, age 18-80, treated with diet alone, oral antidiabetic agents: sulfonylureas, repaglinide, nateglinide, or metformin, pioglitazone as monotherapy or in combination therapy (excluding DPP4 inhibitors), or on low-dose insulin therapy (TDD ≤ 0.5 unit/kg/day). Patients included within this study will be determined by the set of inclusion and exclusion criteria.

b. Inclusion Criteria:

1. Males or female surgical non-ICU patients ages between 18 and 80 years
2. A known history of T2D > 1 month, receiving either diet alone, oral antidiabetic agents: sulfonylureas and metformin as monotherapy or in combination therapy (excluding DPP-4 inhibitors) or low-dose (≤ 0.5 units/kg/day) insulin therapy.
3. Subjects with a BG >140 mg and < 400 mg/dL without laboratory evidence of diabetic ketoacidosis (serum bicarbonate < 18 mEq/L or positive serum or urinary ketones) at randomization.

c. 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 requiring insulin therapy or with a history of diabetic ketoacidosis and hyperosmolar hyperglycemic state, or ketonuria) (43).
4. Treatment with DPP4 inhibitor or GLP1 analogs during the past 3 months prior to admission.
5. Acute critical illness or CABG surgery expected to require admission to a critical care unit.
6. Subjects with gastrointestinal obstruction or adynamic ileus or those expected to require gastrointestinal suction.
7. Patients with clinically relevant pancreatic or gallbladder disease.
8. Patients with previous history of pancreatitis
9. Patients with acute myocardial infarction, clinically significant hepatic disease or significantly impaired renal function (GFR < 30 ml/min).
10. Chronic use of steroid with total daily dose (prednisone equivalent) >5 mg/day
11. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
12. Pregnancy or breast-feeding at time of enrollment into the study.
13. Patients who received supplemental sliding scale insulin >72 hours prior to randomization
14. Patients who received basal insulin > 48 hours prior to randomization

VII. Study Sites: This study will be performed at Grady M. Hospital: Guillermo Umpierrez, M.D. (Principal investigator), Dawn Smiley, M.D., Emory University Hospital: Francisco Pasquel, M.D. (Site PI); University of Colorado: Neda Rasouli, M.D. (Site PI); Boston University, Boston, MA (Site PI: Marie McDonnell); and Rush University, Chicago, IL (site PI: David Baldwin, MD).

VIII. CLINICAL MANAGEMENT GUIDELINES

VIII.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.

VIII.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 both institutions. Patients with hypoglycemia will be treated as per protocol: For blood glucose < 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 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 q1 h until BG > 100 mg/dl
 - If BG > 100 , no further treatment needed.

VIII.c. Assessment and Monitoring of Hospital Mortality

All study subjects will be followed daily by the investigators 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.

VIII.d. Assessment and Monitoring of Nosocomial Infections

Nosocomial infections will be diagnosed based on standardized CDC criteria (44). New nosocomial infections will not be diagnosed until 48 hr 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.

IX. STATISTICAL ANALYSIS

This study is randomized multicenter, open-label controlled trial. The overall hypothesis is that in non-ICU patients with T2D, treatment with linagliptin once daily will result in a similar improvement in glycemic control and in a lower frequency of hypoglycemic events than treatment with basal bolus insulin regimen with basal bolus insulin regimen.

IX.a. Sample Size and Power Calculations: The primary endpoint in this study is glycemic control measured by mean daily BG concentration between treatment groups. To show the non-inferiority of linagliptin to basal bolus in terms of glycemic control, we set the equivalence margin as 18mg/dl, from a view that a BG difference less than 18 mg/dl is usually not considered as clinically significant. Based on the preliminary data from Rabbit medicine and Rabbit Surgery trials, it may be reasonable to assume the standard deviation of mean daily BG is bounded above by 50 mg/dl. With two-sample t tests or Wilcoxon tests, one sided, $\alpha=0.05$, 121 subjects for each treatment arm would be needed to ensure 80% power to reject the hypothesis that the mean daily BG in patients treated with linagliptin is no more than 18 mg/dl higher than that in patients treated with Basal Bolus. In our calculation, we applied Bonferroni correction to adjust for multiple comparisons across four time points during follow-up. Accounting for 10-15% attrition rate, we would need 140 patients per treatment group. This leads to a final total sample size estimate of 280 randomized patients.

Secondary outcomes of major interest in this study are outcomes on hypoglycemia (BG <70 mg/dl) and the composite of hospital mortality and perioperative complications. The assessment of group difference in hypoglycemia will mainly be based on the comparison of proportions of patients who have any hypoglycemia event during the study between the two treatment groups. Based on the Rabbit Surgery trail, 23% of patients that received Basal Bolus had at least one hypoglycemia episode. Assuming the same rate of hypoglycemia in the Basal Bolus group in this study, given the sample size of 121 subjects per treatment

group, based on a two sided Fisher's exact test with $\alpha=0.05$, we would have 80% power to detect an odds ratio in hypoglycemia rate of 0.33 in linagliptin group (versus Basal Bolus group), which corresponds to a smaller difference in hypoglycemia rate than that observed in Rabbit Surgery study. In the following table, we give the estimated power under different assumed group differences in hypoglycemia rate, represented by four hypothesized odds ratios.

Table: Estimated power with 121 subjects per group (after attrition) and the anticipated hypoglycemia rate of 23% based on two-sided Fisher's exact test with $\alpha=0.05$.

Odds Ratio	0.1	0.2	0.3	0.4
Power	>0.99	0.96	0.85	0.67

For the composite outcome of hospital mortality and perioperative complications, we consider complications including wound infection, bacteremia, acute renal failure, respiratory failure, and major cardiovascular events. Based on the Rabbit Surgery trial, the rate of the composite outcome is about 10% in the Basal Bolus group. Assuming the same rate for patients receiving Basal Bolus in this study, we would have 80% power to detect an odds ratio in the composite outcome of 0.09 in linagliptin group (versus Basal Bolus group).

IX.b. Analysis of Primary Endpoint:

The primary endpoint in this study is glycemic control measured by mean daily BG concentration. We will first perform cross-sectional analyses using 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.

IX.c. Analysis of Secondary Endpoints:

Secondary endpoints in this study include rate of hypoglycemia, number of hypoglycemia events, number of episodes of severe hyperglycemia, length of hospital stay, hospital mortality and differences between groups on a composite of hospital mortality and perioperative complications including wound infections (deep and superficial), bacteremia, respiratory failure, acute renal failure, and major cardiovascular events (acute myocardial infarction, congestive heart failure, and cardiac arrhythmias). For hypoglycemia outcomes, we will first conduct nonparametric comparisons of the rate of hypoglycemia based on a two-sided Chi-square test (or Fisher's exact test in the presence of low incidence rates), followed by the Cochran-Mantel-Haenszel test which adjusts for the potential center effect. Univariate Poisson regression (or Negative Binomial regression) will be performed to assess whether there is any difference in the number of hypoglycemia events between the two treatment groups. We will further conduct multivariate Logistic regression, Poisson regression (or negative binomial regression) to estimate the difference in the rate and frequency of hypoglycemia while adjusting for relevant covariates. Stepwise, backward, or forward model selection strategy will be adopted to determine the variables to be included in the final model. Standard diagnostic and model checking procedures, such as deviance residual plot and Hosmer-Lemeshow test, will be applied to examine the fit of the developed models. Similar analyses will be conducted to severe hyperglycemia, composite of hospital mortality and perioperative complications. For continuous outcomes, such as length of hospital stay, we will use two-sample t-tests or nonparametric Wilcoxon tests to compare them between the intensive BG control group and the conventional BG control group. 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.

X. Potential Risks to the Subject:

Hypoglycemia. It is possible that following the proposed protocol, patients receiving basal bolus insulin regimen or linagliptin in combination to insulin may develop hypoglycemia (BG < 70 mg/dL). The risk of hypoglycemia in non-ICU patients treated with subcutaneous insulin in previous RCT has varied between 4% and 32%. We expect that approximately 10-20% of subjects treated with basal bolus protocol will experience one or more episodes of hypoglycemia. The frequency of hypoglycemia in patients with T2D treated with linagliptin is similar to placebo, thus, we expect to have a frequency of hypoglycemia similar to that reported during SSRI alone (< 5%).

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.

Hyperglycemia. In the Rabbit Trial, 14% of patients treated with SSRI remained with blood glucose of > 240 mg/dL despite increasing the SSI dose to the maximal or insulin resistant scale. In such patients, glycemic control rapidly improved in all of the SSI failure subjects after starting basal bolus insulin, and the glucose target of < 140 mg/dL was achieved within 4 days of initiating basal bolus insulin therapy. Queale et al (15) reported that more than 25% had more than 1 episode of hyperglycemia during the first 4 days of hospitalization. We expect that approximately < 20% of subjects treated with insulin glargine or with linagliptin plus lispro, aspart or glulisine insulin will have severe hyperglycemia. The number of reports of severe hyperglycemia will be analyzed statistically. For the purpose of this analysis, severe hyperglycemia is defined as a capillary and/or laboratory BG >300 mg/dL.

Blood samples will be taken. Risks associated with drawing blood are pain, bruising at the site of the needle stick, bleeding, and on rare occasions, fainting, light-headedness and infection.

XI. Protection against Risks:

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor capillary blood glucose 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 that may result with the use of insulin, no patients with significant liver and renal impairment will be recruited in this study.

Hypoglycemia: We expect that approximately 20% of subjects treated with basal bolus insulin will experience one or more episodes of hypoglycemia and less than 5% of linagliptin patients will experience 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. 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. If a patient develops hypoglycemia, the total daily insulin dose will be decreased by 10% to 30% in the basal bolus group and by moving to a less sensitive supplemental insulin column (see appendix 3).

Hyperglycemia: supplemental insulin will be given up to 4 times daily to cover for BG >140 mg/dl (see appendix 2). Patients with persistent hyperglycemia (≥ 2 glucose readings ≥ 400 mg/dl, ≥ 3 consecutive glucose readings >240 mg/dl, or with a mean daily blood glucose concentration ≥ 240 mg/dl) will be considered as failure and discontinued from the study. Patients receiving linagliptin therapy will be switched to basal bolus insulin or continuous insulin infusion. Dose of insulin will be adjusted and if needed, patients treated with basal/bolus insulin will be started on continuous insulin infusion.

Acute renal failure: the total daily dose of insulin will be adjusted as per serum creatinine concentration. The total daily insulin dose will be reduced to 0.3 unit/kg in patients with creatinine >2.0 mg/dl. The dose of linagliptin does not need to be adjusted in patients with renal dysfunction.

XII. DATA handling and record keeping:

Data collection records with personal identifiers will be stored in locked file cabinets. Blood samples drawn and stored in conjunction with this study will not be labeled with information that could directly identify study subjects. Blood samples will be stored at Dr Umpierrez Research Laboratories in the Grady Diabetes Clinic. 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.

XIII. Study drugs and materials:

Clinical trial materials will be labeled and should be handled and stored according to the respective hospital's regulatory requirements. After discharge, patients will be re-started on their pre-admission OADs (except for DPP4-inhibitors, GLP-1, and selected drugs in the presence of contraindication, i.e., metformin and renal failure).

Storage and Drug Accountability of Study Medication(s)

Linagliptin will be stored and dispensed by the research pharmacy at each institution. Linagliptin will be dispensed to each subject as required according to treatment group. The research/clinical staff will perform drug accountability by asking patients to return all unused, partly used and unused at each visit.

Stock bottles of linagliptin will be stored at the hospital research pharmacy at a controlled room temperature between 59 to 86° Fahrenheit. A daily room temperature will be documented (Monday - Friday) as well as the minimum and maximum daily temperature reached. The minimum and max temperatures during weekends will be recorded on Monday morning.

Study drug will be stored at the Investigational Drug Office inside the hospital pharmacy, and will be kept locked when not in use. For the inpatient trial, unit-dose bottles would be stored in a pharmacy Pyxis. The room temperature is also captured for drug kept in the pharmacy pyxis.

Drug received for investigational use will be logged by Lot number specific log per study. All drug received and dispensed will be recorded on the study specific / drug specific / lot specific log.

XIV. Randomization and Blinding

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

XV. Adverse events:

XV.a. Definitions of adverse events

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

XV.b. Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical

event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Patients may be hospitalised for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site,). These and other hospitalisations planned at the beginning of the study do not need to be reported as a SAE in case they have been reported at screening visit in the source data and have been performed as planned.

XV.c. Adverse Events of Special Interest

Based on regulatory recommendation that is based on the experience with other compounds in the DPP-4 inhibitor class, the following events should be defined as adverse events of special interest.

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis
- Skin lesions such as exfoliative dermatitis, and exfoliative rash
- Renal adverse events (e.g. renal failure, $\geq 2x$ increase of creatinine from baseline)
- Pancreatitis
- Hepatic adverse events such as hepatitis, liver injury, and increased liver enzymes. Hepatic injury is defined by the following alterations of liver parameters: For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline an elevation of AST and/or ALT >3 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample.

Refer to the appendix 1 for a list of preferred terms (PT's) that are considered as AEs of Special Interest.

Protocol-specified significant events are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria.

XV.d. Intensity of adverse event

The intensity of the AE should be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or to perform usual activities

XV.e. Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

XV.f. Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S) AE in the (e) CRF.

XV.g. Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S) AE in the (e) CRF, if they are judged clinically relevant by the investigator.

XV.h. Responsibilities for SAE reporting

The Sponsor shall report (i.e., from signing the informed consent onwards through the trial defined follow-up period) all SAEs and non-serious AEs occurring at the same time and/or which are medically related to the

SAE and Adverse Events of Special Interest by fax or other secure method to the BI Unique Entry Point in accordance with timeline specified in the pharmacovigilance agreement

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Boehringer Ingelheim's (BI's) Investigator Brochure for the Product or BI Drug Information e.g. Summary of Product Characteristics (SmPC) or Product Information (PI) for the authorized Study Drug provided by BI.

XVI. Ethics

XVI.a. Informed Consent.

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

Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important and key points of the study. One of the investigators or research coordinators will obtain a witnessed informed consent prior to inclusion of a patient into the study.

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

XVI.b. Potential Benefits to the Subject: We believe that all subjects will benefit greatly from this study. Intensified blood glucose monitoring and blood glucose control may significantly reduce hospital complications associated with hyperglycemia and hypoglycemia.

XVI.c. Potential Benefits to Society: This study will provide important information on the benefits of oral antidiabetic agents (linagliptin) in the inpatient management of patients with type 2 diabetes. We will determine whether glycemic control is different among insulin and linagliptin therapy.

XVI.d. 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 oral antidiabetic agents for the inpatient management of diabetes. Most patients with type 2 diabetes are treated with a sliding scale or basal bolus insulin therapy. This study will test the efficacy of the inpatient use of oral antidiabetic agents and to determine whether glycemic control is different between linagliptin and basal bolus regimen in surgical patients with type 2 diabetes.

XVI.e. Therapeutic Alternatives: Patients can be treated with other insulin formulations (regular insulin, NPH, glargine, lispro, aspart or glulisine currently available at Grady Hospital, Emory University Hospital and other Medical centers for the treatment of T2D.

XVI.f. 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 of child bearing potential only).

XVI.g. 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.

XVI.h. Inclusion of children: No patients under the age of 18 will be recruited in this study.

XVII. 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. Blood samples drawn and stored in conjunction with this study will not be labeled with information that could directly identify study subjects. Blood samples will be stored at Dr Umpierrez Research Laboratories in the Grady Diabetes Clinic. 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.

XVIII. Payment for Participation.

Participation in this study is voluntary. Patients will receive one hundred dollars (\$100.00) prior to discharge. If a participant should stop participation before completion, the payment will be prorated at \$10.00 per day to a maximum of one hundred dollars (\$100.00). Patients participating in the discharge study (Aim 2) will also receive seventy-five dollars (\$75.00) after each clinic visit at 1 and 3 months after discharge. Total compensation for participation in the study is two-hundred and fifty (\$250.00).

XIX. 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. Linagliptin tables will be provided by Boehringer Ingelheim Pharmaceuticals, Inc.

XX. 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 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.

XXI. Financial Conflict of Interests.

None of the investigators in this study have any outside activities that may represent a conflict of interest. None of the investigators have 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.

XXII. 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 these questions will be answered by research staff. 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.

XXIII. Medical Device Research.

Not applicable.

XXIV. DSMB and Monitoring.

All adverse events (AEs) will be graded as to their attribution (unrelated to protocol, or possibly, probably, or definitely related to protocol). Any AE that is reported to either the PI or her designated research associates by a study subject or medical staff will document caring for the subject and which meets the criteria as such. This study will be entered into the Emory GCRC computerized database system to permit tracking of adverse events. This system will then be used by all investigators to report “expected” AEs (predefined AEs which will be monitored over the course of the trial – see below), “observed” AEs (AEs which occur but which may or may not have been anticipated), and all serious adverse events (SAEs, see below); this system will be used in this trial. Serious adverse events are predefined as: any experience that suggests a significant hazard, such as events which: a) are fatal, b) are life threatening, c) result in permanent disability, d) require inpatient hospitalization, or e) involve cancer, a congenital anomaly, or drug overdose.

Any AEs will be reported to the Emory GCRC Research Safety Advocate (RSA), within 15 days of the event and any SAEs will be reported to the RSA and the Emory IRB within 24-48 hours of the event. The standard Emory IRB reporting guidelines for AE and SAE reporting will also be followed. The investigators and staff will enter all AEs into the RSA database, and evaluate the SAEs, in close coordination with the Emory IRB. The IRB annual report from the P.I. will also be transmitted to the RSA and stored both in the RSA database and as a hard copy file. The P.I. will also personally discuss the study and any observed AEs or SAEs on a regular basis with the RSA (at least once a year and more often as indicated).

The Emory PI will be monitoring all sites (including non-Emory sites). The Emory PI and Emory study team will have a teleconference at the beginning to introduce the protocol, specific aims, plan and methods, and statistical analysis.

The PI will ensure that each site will have a regulatory binder that contains the following documents and forms;

Contact info, and CVs of all the study members.

Delegation of authority form

Financial disclosure form

Recruitment plans, and study procedure forms

Key inclusion/exclusion criteria checklist

Attendance log / Informed Consent Procedure

Randomization / Data Collection (CRF)

Electronic Data Capture (Red Cap)

Protocol deviation log

DSMP activities

Investigational product (package insert)

Linagliptin Inpatient_07.19.2016

The PI will also have a weekly teleconference with the sites to monitor the study process, recruitment and adverse events.

XXIV. References

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Appendix 1.

Table 1.

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

BEDTIME. Give half of Supplemental Sliding Scale Insulin for BG > 220 mg/dl.

Blood Glucose (mg/dL)	<input type="checkbox"/> Insulin Sensitive	<input type="checkbox"/> Usual	<input type="checkbox"/> Insulin Resistant
>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

** Check appropriate column below and cross out other columns

The numbers in each column indicate the number of units of lispro/aspart insulin per dose. Supplemental” dose is to be added to the scheduled dose of lispro/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 at BG > 220 mg/dl. Example, a patient with blood glucose of 240 mg/dl will receive 8 U before a meals or 2-4 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 240 mg/dl will receive 4 U of supplemental insulin.

Appendix 2.

Following preferred terms are considered as Adverse Event of Special Interest

Hepatic events

Acute graft versus host disease in liver
Acute hepatic failure
Alanine aminotransferase abnormal
Alanine aminotransferase increased
Ammonia abnormal
Ammonia increased
Ascites
Ascites
Aspartate aminotransferase abnormal
Aspartate aminotransferase increased
Asterixis
Autoimmune hepatitis
Bacterascites
Bacterascites
Bile output abnormal
Bile output decreased
Biliary cirrhosis
Biliary cirrhosis primary
Biliary fibrosis
Bilirubin conjugated abnormal
Bilirubin conjugated increased
Bilirubin excretion disorder
Biopsy liver abnormal
Blood bilirubin abnormal
Blood bilirubin increased
Blood bilirubin unconjugated increased
Caput medusae
Child-Pugh-Turcotte score increased
Cholaemia
Cholestasis
Cholestatic liver injury
Cholestatic liver injury
Cholestatic pruritus
Chronic hepatic failure
Chronic hepatitis
Coma hepatic
Cryptogenic cirrhosis
Cytolytic hepatitis
Duodenal varices
Foetor hepaticus
Galactose elimination capacity test abnormal
Galactose elimination capacity test decreased
Gamma-glutamyltransferase abnormal
Gamma-glutamyltransferase increased
Gastric varices
Gastric varices haemorrhage

Guanase increased
Hepaplastin abnormal
Hepaplastin decreased
Hepatectomy
Hepatic artery flow decreased
Hepatic atrophy
Hepatic calcification
Hepatic cirrhosis
Hepatic congestion
Hepatic encephalopathy
Hepatic encephalopathy prophylaxis
Hepatic enzyme abnormal
Hepatic enzyme decreased
Hepatic enzyme increased
Hepatic failure
Hepatic fibrosis
Hepatic function abnormal
Hepatic hydrothorax
Hepatic hydrothorax
Hepatic infiltration eosinophilic
Hepatic lesion
Hepatic mass
Hepatic necrosis
Hepatic pain
Hepatic sequestration
Hepatic steatosis
Hepatic vascular resistance increased
Hepatitis
Hepatitis acute
Hepatitis cholestatic
Hepatitis cholestatic
Hepatitis chronic active
Hepatitis chronic persistent
Hepatitis fulminant
Hepatitis fulminant
Hepatitis toxic
Hepatobiliary disease
Hepatobiliary scan abnormal
Hepatocellular foamy cell syndrome
Hepatocellular injury
Hepatomegaly
Hepatopulmonary syndrome
Hepatorenal failure
Hepatorenal syndrome
Hepatosplenomegaly
Hepatotoxicity
Hyperammonaemia
Hyperbilirubinaemia
Hyperbilirubinaemia

Hypercholia
Hypertransaminasaemia
Icterus index increased
Ischaemic hepatitis
Jaundice
Jaundice cholestatic
Jaundice hepatocellular
Kayser-Fleischer ring
Liver and small intestine transplant
Liver disorder
Liver function test abnormal
Liver induration
Liver injury
Liver operation
Liver palpable subcostal
Liver scan abnormal
Liver tenderness
Liver transplant
Lupoid hepatic cirrhosis
Lupus hepatitis
Mitochondrial aspartate aminotransferase increased
Mixed liver injury
Mixed liver injury
Molar ratio of total branched-chain amino acid to tyrosine
Nodular regenerative hyperplasia
Ocular icterus
Oedema due to hepatic disease
Oedema due to hepatic disease
Oesophageal varices haemorrhage
Perihepatic discomfort
Portal hypertension
Portal hypertensive enteropathy
Portal hypertensive gastropathy
Portal triaditis
Portopulmonary hypertension
Radiation hepatitis
Renal and liver transplant
Retrograde portal vein flow
Retrograde portal vein flow
Reye's syndrome
Subacute hepatic failure
Total bile acids increased
Transaminases abnormal
Transaminases increased
Ultrasound liver abnormal
Urine bilirubin increased
Urobilin urine present
Varices oesophageal
X-ray hepatobiliary abnormal

**Following preferred terms are considered as
Adverse Event of Special Interest**

Hypersensitivity reactions

Allergic bronchitis
Allergic cough
Allergic oedema
Allergic respiratory disease
Allergic respiratory symptom
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Bronchial hyperreactivity
Bronchospasm
Circulatory collapse
Circumoral oedema
Conjunctival oedema
Corneal oedema
Cough
Drug eruption
Drug hypersensitivity
Epiglottic oedema
Erythema
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
First use syndrome
Gingival oedema
Gingival swelling
Gleich's syndrome
Hereditary angioedema
Hypersensitivity
Idiopathic urticaria
Kounis syndrome
Laryngeal oedema
Laryngotracheal oedema
Lip oedema
Lip swelling
Oculorespiratory syndrome
Oedema mouth
Oropharyngeal swelling
Palatal oedema

Periorbital oedema
Pharyngeal oedema
Pruritus
Pruritus allergic
Pruritus generalized
Rash
Rash erythematous
Rash generalized
Rash pruritic
Scleral oedema
Shock
Small bowel angioedema
Swelling face
Swollen tongue
Tongue oedema
Toxic skin eruption
Tracheal oedema
Type I hypersensitivity
Type I hypersensitivity
Urticaria
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria papular
Urticaria papular
Wheezing

**Following preferred terms are considered as
Adverse Event of Special Interest**

Pancreatitis

Cullen's sign
Hereditary pancreatitis
Ischaemic pancreatitis

Oedematous pancreatitis
Pancreatic abscess
Pancreatic necrosis
Pancreatic phlegmon
Pancreatic pseudocyst
Pancreatic pseudocyst drainage
Pancreatitis
Pancreatitis acute
Pancreatitis chronic
Pancreatic haemorrhage
Pancreatitis haemorrhagic
Pancreatitis necrotizing
Pancreatitis relapsing
Pancreatorenal syndrome

**Following preferred terms are considered as
Adverse Event of Special Interest**

Renal events

Acute phosphate nephropathy
Acute prerenal failure
Anuria
Azotaemia
Continuous haemodiafiltration
Dialysis
Haemodialysis
Neonatal anuria
Nephropathy toxic
Oliguria
Peritoneal dialysis
Renal failure
Renal failure acute
Renal failure neonatal

Renal impairment
Renal impairment neonatal

**Following preferred terms are considered as
Adverse Event of Special Interest**

Skin lesions

Acute generalized exanthematous pustulosis
Cutaneous vasculitis
Dermatitis bullous
Dermatitis exfoliative
Dermatitis exfoliative generalized
Drug eruption
Epidermal necrosis
Erythema multiforme
Exfoliative rash
Lip exfoliation
Mucocutaneous ulceration
Mucosal exfoliation
Oral mucosal exfoliation
Penile exfoliation
Skin erosion
Skin exfoliation
Skin necrosis
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Toxic skin eruption
Vaginal exfoliation

Vaginal ulceration

Vulvar ulceration

Vulvovaginal ulceration
