Comparison of postprandial glycemic control in non-critically ill hospitalized patients with type 2 diabetes mellitus using Novolog vs. Fiasp insulin: a Randomized Controlled Open Label Trial

INVESTIGATOR-SPONSORED STUDY PROPOSAL

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Statistical Analysis Plan see pages 27-28

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Synopsis

Primary Objective

The primary objective of this trial is to determine if Fiasp® (insulin aspart injection) provides non-inferior postprandial glucose control compared with NovoLog® (insulin aspart injection) in non-critically ill hospitalized patients with type 2 diabetes (T2DM). Glycemic outcomes will be assessed using a continuous glucose monitoring system [Dexcom G6 Pro Continuous Glucose Monitoring (CGM) System]. The primary outcome will be time spent in sensor glucose (SG) target range 100-180 mg/dL (both inclusive) in all of the 4 hour postprandial periods during the study.

Secondary Objectives

The secondary objectives of this study will assess whether our Fiasp® intervention is superior to NovoLog® in terms of postprandial glucose control (time spent in SG target range of 100-180 mg/dL in all of the 4 hour postprandial periods).

We will also assess glycemic control during other time periods during the study, and examine differences in hyperglycemia and hypoglycemia between groups. We will also analyze glucose variability and differences in insulin dosing between groups. All glycemic outcomes will be assessed using data obtained from CGM.

Secondary outcomes will include:

1. Percentage of time spent in the glycemic target range of 100-180 mg/dL (both inclusive) during the duration of the study.
2. Percentage of time spent in the glycemic range of 70-140 mg/dL (both inclusive) in all of the 4 hour postprandial periods.
3. Percentage of time spent in nocturnal glycemic target range 100-180 mg/dL (both inclusive) during the nocturnal period (00:01 AM to 05:59 AM, both inclusive)
4. Percentage of time spent with hypoglycemia (<70 mg/dL, <54 mg/dL, and <40 mg/dL respectively) in all of the 4 hour postprandial periods, in the nocturnal period (00.01 AM to 05:59 AM, both inclusive), and during the combined period of sensor wear during the study.
5. Percentage of time spent with level 2 hyperglycemia (>240 mg/dL) in all of the 4 hour postprandial periods.
6. Percentage of time spent with level 1 hyperglycemia (181-239 mg/dL, both inclusive) in all of the 4 hour postprandial periods.
7. Mean SG glucose concentrations during the study.
8. Glucose variability as measured by standard deviation (SD) of glucose and coefficient of variation (CV).
9. Comparison of basal, prandial and correction insulin doses.

10. Patient reported adverse effects from wearing a CGM and their perception of the experience of wearing a CGM while in the hospital.

Study Duration

24 months: 18 months for recruitment, 6 months for analysis.

Study Design

Open-label, 1:1 randomization without placebo control.

Study Population

Inclusion criteria:

1. English-speaking or Spanish-speaking
2. Males and female adult subjects admitted to Boston Medical Center to a medical or surgical floor.
3. Age ≥ 21 and ≤ 80 years.
4. Diagnosed with type 2 diabetes at least 180 days prior to screening.
5. Hyperglycemia during admission, as defined by a point of care and/or venous blood glucose ≥ 140 mg/dL.
6. Prior to admission subjects must be using one of the following for outpatient diabetes management:
    a. Insulin
    b. ≥ 2 oral/injectable agents
    c. One oral/injectable agent with a HbA1c of ≥ 8% within 3 months of enrollment.
7. Patients who are expected to remain hospitalized for a minimum of 48 hours following CGM sensor placement.
8. BMI <45 kg/m^2.
9. Subjects must have insulin glargine dosing planned at bedtime for the duration of the study period. Morning and afternoon dosing of insulin glargine are exclusionary.

Exclusion criteria:

1. Patients with a history of type 1 diabetes or late-onset autoimmune diabetes (LADA).
2. Currently on glucocorticoids OR plan for treatment with glucocorticoids within the next 72 hours.
3. Female patients who are pregnant (tested during hospitalization or screening) or breast-feeding during the hospitalization.
4. Patients admitted with the following conditions: diabetic ketoacidosis, hyperosmolar hyperglycemic state, solid organ transplantation, or coronary artery bypass surgery.

5. Prior diagnosis of gastroparesis or cirrhosis.
6. Acute or chronic kidney disease with a serum creatinine of ≥ 2 mg/dL at the time of screening.
7. Clinically significant nausea and/or vomiting or unable to consume more than 30 grams of carbohydrate at each meal.
8. Patients expected to receive nothing by mouth (NPO) for >24 hours.
9. Use of continuous or intermittent enteral feeding or parenteral nutrition.
10. Patients receiving > 1 gram every 6 hours of acetaminophen (maximum dose of acetaminophen) and/or hydroxyurea during the hospitalization.
11. Any psychiatric condition rendering the subject unable to provide informed consent.
12. Patients currently incarcerated.
13. Patients using >1 unit/kg/day of insulin prior to admission.
14. Insulin pump usage within the 2 weeks prior to or during admission.
15. Patients currently using real-time continuous glucose monitoring (CGM) or personal flash glucose monitoring (FGM).
16. Patients with a history of an allergy to any of the types of insulin or one of the excipients in the insulin used in the study.
17. Patients who have tested positive for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in the past 30 days OR there is an ongoing clinical suspicion for COVID-19 infection.

Number of Participants

210

Number of Study Sites

Single site — Boston Medical Center

Primary Outcome Variables

All sensor glucose (SG) values collected by CGM during all of the 4 hour postprandial periods.

Secondary and Exploratory Outcome Variables

All SG values collected by CGM during the hospital stay, analyzed as detailed above, and insulin doses given in each group. Demographic information including age, sex, race, BMI, reason for hospitalization, creatinine, HbA1c and medications for diabetes prior to hospitalization.

Abbreviations

Abbreviation	Explanation
BG	Blood glucose
BMC	Boston Medical Center
BMI	Body mass index
BUMC	Boston University Medical Center
CGM	Continuous glucose monitoring device
CRF	Case report form
CT	Computerized tomography scan
CV	Coefficient of variation
DPP-4 inhibitor	Dipeptidyl peptidase-4 inhibitor
GLP-1	Glucagon-like peptide 1
HbA1c	Hemoglobin A1c
ICF	Informed consent form
ICU	Intensive care unit
IDS	Inpatient Diabetes Service
IRB	Institutional Review Board
IV	Intravenous
FBG	Fasting blood glucose
FGM	Flash glucose monitoring device
MRI	Magnetic resonance imaging
NPO	Nothing by mouth
OHRP	Office on Human Research Protection
PD	Pharmacodynamics
PK	Pharmacokinetics
PI	Principle investigator
PPBG	Postprandial blood glucose
SG	Sensor glucose
SGLT2-i	Sodium-glucose cotransporter-2 inhibitor
SPSS	Statistical Package for the Social Sciences
TDD	Total daily dose

Table of Contents

1 – Introduction

1.1. Introductory Statement

This document is a protocol for a human research study to be conducted according to applicable government regulations and institutional research policies and procedures.

2 – Background

2.1 Background/scope of the problem

Hyperglycemia in hospitalized patients is associated with worse patient outcomes, including higher rates of infection, increase in morbidity, longer length of stay, and increased mortality (1, 2). Thus it is advised that blood sugar levels be maintained between 100-180 mg/dL in non-critically ill patients (2). Treatment with a regimen of basal, bolus and correction insulin is the recommended standard of care to manage inpatient hyperglycemia (3). Insulin doses are calculated based on the weight of the patient and other clinical factors to derive a total daily insulin dose (TDD). This dose is then divided into 50% basal insulin, and the remaining 50% is divided into 3 and given prior to each of 3 meals per day in patients consuming meals (2, 3). Despite this standard, management of hyperglycemia in hospitalized patients remains a challenge, with many patients experiencing hyper or hypoglycemia (4).

One challenge in managing diabetes with insulin replacement therapy is the relatively slow onset of action of rapid-acting insulin analogs such as NovoLog® (insulin aspart) or Humalog® (insulin lispro) compared with endogenous insulin secreted in response to carbohydrate consumption. This can lead to an excessive rise in blood glucose after meals. Fiasp® (insulin aspart) is a formulation of insulin aspart with the addition of vitamin B3 (Niacinamide) and an amino acid (L-Arginine). It is a faster-acting insulin which has been shown to better control the early rise in blood glucose (BG) levels after consuming carbohydrates in the outpatient setting (5, 6). Here we propose to compare postprandial BG control using a continuous glucose monitor in hospitalized patients receiving either NovoLog® or Fiasp®.

2.2 Prior Experience

At Boston Medical Center (BMC), basal/bolus insulin therapy has been the standard of care for more than a decade. As per recognized standard of care, we use tailored electronic orders to initiate and adjust insulin therapy in hospitalized patients. All nurses are trained in the correct administration of basal, bolus and correction insulin. Insulin is dosed based on the calculated TDD as above and adjusted based on BG response. Providers order a standard amount of carbohydrates for patients with diabetes, most commonly 75 grams per meal. A staff dietitian reviews the carbohydrate content of meals in the kitchen.

Since 2006 we have had a dedicated Inpatient Diabetes Service, consisting of an endocrinologist, an endocrinology fellow, and diabetes nurse practitioners who see patients in consultation and assist in the management of hyperglycemia. Our consult service typically manages the diabetes of 25-30 inpatients per day, with about 6 new consults per day. Dr. Sara Alexanian, the principal investigator (PI) of this protocol, is the Director of the Inpatient Diabetes Service at BMC, which is the primary academic teaching hospital of Boston University School of Medicine. Dr. Alexanian is also the Quality lead in the Endocrinology Section at Boston University School of Medicine. The sub-investigator Dr. Steenkamp is the Director of Clinical Diabetes at BMC and is a current investigator in various diabetes clinical trials including trials investigating insulin, FGM and non-insulin diabetes pharmacotherapies in both type 1 and type 2 diabetes. He has a particular interest in the use of technology in the management of diabetes. In 2015, 2 of the 3 investigators (Alexanian and Steenkamp) participated in a multi-center randomized controlled trial comparing basal/bolus insulin therapy to treatment with an oral DPP-4 inhibitor in hospitalized patients. We successfully recruited 70 patients over the course of the

study, which was recently published in 2018 (7). Nicole Spartano, PhD, is a Research Assistant Professor in the Endocrinology Section with expertise in continuous data collection and analysis methods. She is working with Dr. Steenkamp on a research project investigating the effectiveness of a continuous glucose monitoring intervention in the primary care setting leveraging electronic (e)-consultation with endocrinologists. Dr. Spartano also serves as PI on grants from the American Heart Association and Alzheimer's Association with recent publications in the JAMA Network, BMJ, Neurology, and Circulation.

3 – Rationale/Significance

3.1 Problem Statement

Hyperglycemia affects 30-40% of hospitalized patients (8, 9). Despite the fact that basal/bolus insulin therapy has been demonstrated to improve glycemic control and clinical outcomes in patients (10, 11), achieving good glucose control remains a challenge. Bolus insulin in a hospitalized patient is usually a rapid-acting insulin analog such as Humalog® or NovoLog®. The relatively slow onset of action of a rapid-acting insulin analog compared to endogenous insulin secretion can lead to an excessive rise in blood glucose after meals. Hyperglycemia in hospitalized patients is associated with worse patient outcomes, including higher rates of infection, increase in morbidity, longer length of stay, and increased mortality (1, 2).

3.2 Purpose of Study/Potential Impact

The purpose of this study is to compare the standard practice of dosing rapid-acting analog NovoLog® vs Fiasp® at the time of a standardized carbohydrate meal in hospitalized patients. If Fiasp® is shown to improve postprandial glycemic control, and in particular reduce hypoglycemia in the postprandial period, this could potentially have wide-ranging impacts on the management of all hospitalized patients with hyperglycemia.

3.2.1 Potential Risks

The potential risks of the study are similar to risks that would be incurred with usual treatment with basal/bolus insulin in the hospital. This includes both hyperglycemia and hypoglycemia, potential allergic reactions to insulin, and pain or bruising at the site of insulin injection.There is also the risk of a loss of confidentiality due to data collection.

Blood samples will be taken during the course of the study as per usual hospital care. In addition, routine point of care blood glucose monitoring through fingersticks by use of standardized bedside glucometers will continue per standard inpatient protocols. There will be no additional blood samples required by the study protocol.

Risks of CGM use include mild discomfort during sensor insertion, along with pain, redness, swelling, minor bleeding and minor infection at the sensor insertion site. Allergic reactions can develop in response to the sensor, the adhesive, and other parts of the CGM. There is a remote chance a sensor wire could break or detach and remain under the skin. Sterile broken or detached sensor wires usually don't pose a significant clinical risk.

Hypoglycemia: The risk of hypoglycemia in insulin-treated non-ICU patients can range from 7-23% in some studies (9, 12). We anticipate that 10-20% of patients receiving insulin during the study may experience hypoglycemia. The number of episodes of hypoglycemia and time spent

in the range of hypoglycemia will be analyzed statistically from CGM-captured data. Hypoglycemia that requires treatment will be defined as a BG < 70 mg/dL.

Hyperglycemia: Quele et al (9) reported that 40% of patients receiving insulin during a hospital stay experienced more than 1 episode of hyperglycemia (BG >300 mg/dL). For patients with ≥ 2 blood glucose values >250 mg/dL at separate times of a single day, these subjects will be discontinued from the study insulin titration algorithm and insulin will be adjusted at the discretion of the study team per standard of care.

Procedures for Protecting Against Risks

Hyperglycemia and Hypoglycemia: All glucose results obtained by the bedside glucose meter will be reviewed daily by the study team and insulin will be adjusted according to the study insulin titration protocol (Appendix 2).

Hypoglycemia: Subjects found to have hypoglycemia will be treated according to the hospital practice standard of care.

> For BG <70 mg/dL and patient is able to eat, give 16 g oral glucose, either juice or glucose tabs. Recheck BG in 15 minutes.
>
> For BG <70 mg/dL with altered mental status and/or NPO give 12.5 g of IV dextrose. Recheck BG in 15 minutes, call MD if still <70 mg/dL.

Insulin doses will be decreased as per study insulin titration protocol (Appendix 2) for a BG <70 mg/dL.

Hyperglycemia: Subjects with 2 or more BG >250 mg/dL at separate times in a single day will be removed from the study insulin titration protocol and insulin doses will be titrated as per the discretion of the study team.

Allergy: Patients with a known history of allergy to NovoLog®, Fiasp® or insulin glargine used in the study will be excluded.

Breach of Confidentiality: Only the PI, investigators and study personnel on this project will have access to the master code used to assign subject number. In addition, the investigators will be using password-protected computers and locked cabinets for data storage.

3.2.2 CGM risks

The sensor insertion site will be inspected by the research staff daily. If subjects develop an infection at the sensor insertion site or an allergic reaction develops in response to the sensor, the adhesive, and other parts of the CGM, it will be removed and subjects can anticipate that their symptoms will clear up within one week. Subjects can also request removal if they develop pain, redness, swelling or minor bleeding at the CGM insertion site.

3.2.3 Potential Benefits

Given the favorable postmeal pharmacokinetics of Fiasp®, this trial may demonstrate an alternative equivalent or superior way to dose meal insulin that mitigates hyperglycemia and/or hypoglycemia in hospitalized patients. If this is proven to be the case this would have landmark implications and likely shift national recommendations for inpatient diabetes care.

4 – Study Objectives

4.1 Hypothesis

We hypothesize that giving Fiasp® will result in superior postprandial glucose control with less time spent in the hyperglycemic range as determined by 4 hour post-bolus CGM data, when compared with NovoLog® based on standardized carbohydrate intake.

Pharmacokinetic and pharmacodynamic studies of Fiasp® vs NovoLog® showed significantly more rapid, earlier onset of the first appearance of Fiasp® in the circulation with approximately two times higher early insulin exposure, and 74-89% greater early glucose-lowering effect (5, 6, 13). Therefore, Fiasp® has the potential for improving postprandial glycemic control in comparison to older rapid acting analogs in both patients with type 1 and type 2 DM.

To the best of our knowledge, Fiasp® has not yet been evaluated in a hospitalized population with diabetes. CGM is the ideal tool to measure the effect of our intervention given the continuous measurement of glucose during a relatively short inpatient hospital admission and has the ability to accurately capture differences between groups.

4.2 Primary Objective

The primary objective of this trial is to determine if Fiasp® (insulin aspart injection) provides non-inferior postprandial glucose control compared with NovoLog® (insulin aspart injection) in non-critically ill hospitalized patients with type 2 diabetes (T2DM). Glycemic outcomes will be assessed using a continuous glucose monitoring system [Dexcom G6 Pro Continuous Glucose Monitoring (CGM) System]. The primary outcome will be time spent in sensor glucose (SG) target range 100-180 mg/dL (both inclusive) in all of the 4 hour postprandial periods during the study.

4.3 Secondary Objectives

The secondary objectives of this study will assess whether our Fiasp® intervention is superior to NovoLog® in terms of postprandial glucose control (time spent in SG target range of 100-180 mg/dL in all of the 4 hour postprandial periods).

We will also assess glycemic control during other time periods during the study, and examine differences in hyperglycemia and hypoglycemia between groups. We will also analyze glucose variability and differences in insulin dosing between groups. All glycemic outcomes will be assessed using data obtained from CGM.

Secondary outcomes will include:

1. Percentage of time spent in the glycemic target range of 100-180 mg/dL (both inclusive) during the duration of the study.
2. Percentage of time spent in the glycemic range of 70-140 mg/dL (both inclusive) in all of the 4 hour postprandial periods.
3. Percentage of time spent in nocturnal glycemic target range 100-180 mg/dL (both inclusive) during the nocturnal period (00.01 AM to 05:59 AM, both inclusive)

4. Percentage of time spent with hypoglycemia (<70 mg/dL, <54 mg/dL, and <40 mg/dL respectively) in all of the 4 hour postprandial periods, in the nocturnal period (00.01 AM to 05:59 AM, both inclusive), and during the study.
5. Percentage of time spent with level 2 hyperglycemia (>240 mg/dL) in all of the 4 hour postprandial periods.
6. Percentage of time spent with level 1 hyperglycemia (181-239 mg/dL, both inclusive) in all of the 4 hour postprandial periods.
7. Mean SG glucose concentrations during the study.
8. Glucose variability as measured by standard deviation (SD) of glucose and coefficient of variation (CV).
9. Comparison of basal, prandial and correction insulin doses between the two groups.
10. Patient reported adverse effects from wearing a CGM and their perception of the experience of wearing a CGM while in the hospital.

5 – Study Design

5.1 General Design Description

This is an open-label trial without blinding. Eligible subjects will be randomized to 2 groups in a 1:1 ratio to receive either Fiasp® or Novolog® at the start of the meal, which is our intervention. In addition to this, both groups will receive U100 insulin glargine dosed once daily for basal insulin, which is standard of care. Each subject will have a Dexcom G6 Pro CGM sensor inserted into the upper arm after signing consent and appropriate randomization by the study team. Subjects will remain in the study for 72 hours (3 days) of active sensor wear time in order to capture a minimum of 4 to a maximum of 6 insulin doses unless discharged from the hospital prior to that time, at which point the CGM sensor will be removed from the subject prior to discharge. If the minimum insulin doses for study completion have not been captured within the first 72 hours of sensor wear, the sensor wear period may be extended up to an additional 48 hours.

In both groups insulin glargine doses will be determined by one of the following methods: 1) calculating the total daily dose of insulin and providing 50% of the TDD as follows:

Determine initial TDD using baseline estimate and subtracting or adding for each risk factor:

Baseline TDD estimate	Start at 0.5 units/kg/day
Age >70 years old	-0.1 unit/kg/day
If renal insufficiency	-0.1 unit/kg/day
If pancreatic deficiency	-0.1 unit/kg/day
If Hemoglobin A1c >10%	+0.1 unit/kg/day
FINAL TDD ESTIMATE	=

2) continue with patient current insulin dose

The above algorithm is the standard approach to starting insulin in patients with hyperglycemia at BMC and is considered standard of care. Insulin glargine will be administered at bedtime to all study participants on the day of study entry (after signing informed consent). If a subject receives insulin glargine in the morning or afternoon, they will be excluded from the study.

All insulin decisions will be directed by hospital bedside point of care glucose meter readings. The blood glucose data measured by the CGM will not be used to make insulin decisions.

Correction insulin (Fiasp® or NovoLog®) will be administered with each meal if premeal glucose is ≥ 150 mg/dL and at bedtime if glucose is ≥ 200 mg/dL by calculating an individualized insulin sensitivity factor for each subject per the following formula: 1500/total daily dose of insulin = sensitivity factor.

Group 1 will receive daily basal insulin glargine as per the calculation above, with a scheduled bolus of meal NovoLog®. As per the FDA approved labeling, NovoLog® should be given immediately (usually 5-10 minutes) prior to the start of a meal. Given that this is a hospital setting and insulin is administered by nursing, it is not practical to precisely time insulin injections and so meal NovoLog® will be dosed at the time the subject starts to eat (defined as: immediately prior to the first bite of the meal). NovoLog® doses will be determined using the above TDD calculation or continue with patient's previous insulin dose, with half of the TDD

being divided equally for each of the three meals. The dose of NovoLog® will be administered by the floor nurse as per usual standard of care. To prevent hypoglycemia, the subject will not be given prandial insulin if they do not eat, as per usual standard of care. As per usual hospital practice for prandial insulin, the dose of NovoLog® will be decreased by 2 units if the premeal blood sugar is between 70-100mg/dL. Additional correctional premeal NovoLog® will be added to the calculated prandial dose based on the ordered correctional (sliding) scale as appropriate. The bedtime NovoLog® correction scale (described above) will be given between 21:00 and 22:00.

Group 2 will similarly receive basal insulin glargine as dosed in Group 1. As per the FDA approved labeling, Fiasp® should be given at the start of or within 20 minutes of a meal. Given that this is a hospital setting and insulin is administered by nursing, it is not practical to precisely time insulin injections and so meal Fiasp® will be dosed at the time the subject starts to eat (defined as: immediately prior to the first bite of the meal). Meal Fiasp® dosing will be calculated the same way as NovoLog® dosing above. As per usual hospital practice for prandial insulin, the dose of Fiasp® will be decreased by 2 units if the premeal blood sugar is between 70-100mg/dL. If the premeal BG is ≥ 150 mg/dL, additional Fiasp® will be administered based off the correctional scale at the same time as the prandial insulin. The bedtime correctional scale (described above) will be given between 21:00 and 22:00 utilizing Fiasp® insulin.

See Appendix 1 for insulin initiation worksheet.

Both groups will be ordered for a standard carbohydrate diet as per usual hospital practice (75g carbohydrate with each meal).

Blood glucose levels will be monitored and insulin will be dosed using the standard hospital point-of-care glucose meters (Accucheck Inform II™ meter). This is standard for use in the hospital to monitor glucose and adjust insulin. The CGM data will not be visible to the subject, nurse, or study team in real time, but will be retrospectively downloaded to assess outcomes for the study. Current BMC practice aligns with that of other hospitals in the United States, which may allow patients to wear continuous glucose monitors in the hospital, however does not use them to make insulin dosing decisions. There have been some studies evaluating the accuracy and utility of CGM devices in non-critically ill patients (14, 15). These studies have not found a significant difference in mean hospital glucose when comparing to data obtained by point-of-care meters, but have shown a greater ability to detect hypoglycemia.

On the day of enrollment and after obtaining informed consent, the Dexcom G6 Pro CGM sensor will be placed in the afternoon, with the insulin protocol to be started with basal insulin that evening at bedtime and the meal insulin dosing to begin the next morning. Each individual subject will have CGM data for a minimum of 4 and maximum of 6 meals during the study, unless the CGM sensor needs to be removed as described per protocol.

Insulin doses will be titrated daily as per insulin titration protocol (Appendix 2).

Subjects would continue in the study until discharge, or would be withdrawn if transferred to a higher acuity level of care, if nutrition method was changed, or after the subject has received 4-6 meal doses within the 72 hours of active sensor wear time (3 days). If a subject does not receive the minimum 4 meal doses during the 72 hours, the sensor wear period may be extended up to an additional 48 hours in order to successfully complete the study.

Subjects will be educated to avoid unscheduled eating to prevent potential hyperglycemic events at the time of enrollment and additionally if needed.

5.1.1 Study Date Range and Duration

From the date of first subject screening, we plan to consent 210 subjects, randomize 178 subjects (89 per group) to achieve our target of 160 subjects (80 per group) who complete the study, over a period of 18 months. See section 6.7.3 for detailed power calculations. The active sensor wear time per subject will be 48-72 hours and maximum allowed active sensor wear time can be extended and additional 48 hours if needed to successfully complete the study. In the subsequent 6 months, the study team will analyze collected data and prepare for publication.

5.1.2 Number of Study Sites

Single site — Boston Medical Center

5.2 Primary Outcome Variables

All SG values collected by CGM during the postprandial study period.

5.2.1 Secondary and Exploratory Outcome Variables

All SG values collected by CGM during the hospital stay, analyzed as detailed above in Section 4.3 of the Study Objectives. Insulin doses given in each group will be analyzed. Demographic information including age, sex, race, BMI, reason for hospitalization, creatinine, HbA1c and medications prior to hospitalization.

5.3 Study Population

Participants with type 2 diabetes who are admitted to Boston Medical Center and who meet eligibility criteria.

5.3.1 Number of Participants

We anticipate that we will need to screen (consent) 210 patients to randomize 89 participants per group in order to achieve a sample size of 80 participants per group (expecting a 15% screen fail rate and a 10% rate of drop out or early hospital discharge). See section 6.7.3 for detailed power calcuations.

5.3.2 Eligibility Criteria/Vulnerable Populations

Participant eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's study team before subjects are included in the study.

Participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Inclusion criteria:

1. English-speaking or Spanish-speaking

2. Males and female adult subjects admitted to Boston Medical Center to a medical or surgical floor.
3. Age ≥21 and ≤80 years.
4. Diagnosed with type 2 diabetes at least 180 days prior to screening.
5. Hyperglycemia during admission, as defined by a point of care and/or venous blood glucose ≥ 140 mg/dL.
6. Prior to admission subjects must be using one of the following for outpatient diabetes management:
    a. Insulin
    b. ≥ 2 oral/injectable agents
    c. One oral/injectable agent with a HbA1c of ≥ 8% within 3 months of enrollment.
7. Patients who are expected to remain hospitalized for a minimum of 48 hours following CGM placement.
8. BMI <45 kg/m^2.
9. Subjects must have insulin glargine dosing planned at bedtime for the duration of the study period. Morning and afternoon dosing of insulin glargine are exclusionary.

Participant candidates must not be enrolled in the study if they meet any of the following criteria:

Exclusion criteria:

1. Patients with a history of type 1 diabetes or late-onset autoimmune diabetes (LADA).
2. Currently on glucocorticoids OR plan for treatment with glucocorticoids within the next 72 hours.
3. Female patients who are pregnant (tested during hospitalization or screening) or breast-feeding during the hospitalization.
4. Patients admitted with the following conditions: diabetic ketoacidosis, hyperosmolar hyperglycemic state, solid organ transplantation, or coronary artery bypass surgery.
5. Prior diagnosis of gastroparesis or cirrhosis.
6. Acute or chronic kidney disease with a serum creatinine of ≥ 2 mg/dL at the time of screening.
7. Clinically significant nausea and/or vomiting or unable to consume more than 30 grams of carbohydrate at each meal.
8. Patients expected to receive nothing by mouth (NPO) for >24 hours.
9. Use of continuous or intermittent enteral feeding or parenteral nutrition.
10. Patients receiving > 1 gram every 6 hours of acetaminophen (maximum dose of acetaminophen) and/or hydroxyurea during the hospitalization.
11. Any psychiatric condition rendering the subject unable to provide informed consent.
12. Patients currently incarcerated.

13. Patients using >1 unit/kg/day of insulin prior to admission.
14. Insulin pump usage within the 2 weeks prior to or during admission.
15. Patients currently using real-time continuous glucose monitoring (CGM) or personal flash glucose monitoring (FGM).
16. Patients with a history of an allergy to any of the types of insulin or one of the excipients in the insulin used in the study.
17. Patients who have tested positive for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in the past 30 days OR there is an ongoing clinical suspicion for COVID-19 infection.

Women of childbearing potential: A negative urine pregnancy test is required for all women of childbearing potential at screening, if one has not already been performed during the current hospitalization. Women in the postmenopausal state (defined as no regular menstrual bleeding for at least 1 year), women who have had their uterus removed (hysterectomy), both of their ovaries removed (bilateral oophorectomy), or who have undergone a bilateral tubal ligation are considered not of childbearing potential.

6 – Methods

6.1 Method of Assignment/Randomization

This is an open-label, 1:1 randomized trial. Treatment assigned will be determined by the study team through computer-generated randomization.

6.2 Assessments

The following assessments will be completed during the study:

Medical History: Study staff will obtain a prior history of diabetes and outpatient diabetes treatment medications. For women of non-childbearing potential, the reason should be documented.

Demographic/Medical information: Age, sex, BMI, vitals and reason for hospitalization will be obtained from the medical chart. Patients will be asked their self-identified race/ethnicity (white, black, Hispanic/Latino, Asian, or other). The most recent HbA1c if obtained during the index hospitalization or within 3 months prior to hospitalization will be collected from the medical chart. The serum creatinine at the time of randomization will be collected from the hospital record (note: serum creatinine is routinely obtained on all individuals admitted for inpatient care as part of the standard of care).

Blood Glucose Values/use of CGM: For insulin adjustment and treatment and monitoring of hypoglycemia, the standard hospital point of care meter will be used. At randomization a Dexcom G6 Pro CGM will be placed by the study team on the skin of the upper arm of the subject to collect blinded SG data during the study. The tiny sensor is under the skin and measures the interstitial glucose level, which is the glucose found in the fluid between the cells. The CGM device will be removed at the end of the study and the SG data from CGM will be used to assess glycemic outcomes.

If at any time the CGM becomes dislodged, a new device will be placed by the study team as soon as possible. If the patient must undergo a test during the study such as a CT scan or MRI where the CGM cannot be worn, the study team will remove the CGM prior to the test and place a new one as soon as possible immediately after the test.

Patient Reported Outcome (PRO) questionnaire: Study subjects will be asked to complete a questionnaire at the completion of the study (after sensor removal and before discharge). This questionnaire will assess the subject's perception of wearing a CGM device in the hospital and will also screen for adverse effects from wearing the CGM.

6.2.1 Safety/Pregnancy-related policy

Safety Measures: To ensure that the participant does not have any underlying health conditions, such as significant liver or kidney disease, the study team will review medical records from the hospitalization.

Hypoglycemia: Subjects will be monitored with bedside glucose meters 4 times daily as per usual standard of care. Subjects may have additional monitoring if hypoglycemia is noted, or if the patient complains of symptoms of hypoglycemia, or at the request of the treating physician. Hypoglycemia is treated as per standard of care at Boston Medical Center, with 16 grams of glucose given orally, followed by a repeat BG in 15 minutes for patients able to eat. For patients

not able to eat, 12.5 grams of dextrose will be administered from a 50% dextrose solution IV, followed by a repeat BG in 15 minutes.

Pregnancy: A negative urine pregnancy test is required for all women of childbearing potential at screening. The sponsor-investigator will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by sponsor-investigator will occur within the same timelines described for reporting of Adverse Events. Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

6.2.1.1 Storage and study Drug Accountability

Study insulins will be stored per institutional research standard procedures and in accordance with US product label instructions at the Investigational Pharmacy Service at BMC. Insulins used in the study will be administered as per usual standard of care by the hospital nursing staff and drug accountability will be performed by the study team and Investigational Pharmacy.

6.2.1.2. Adverse Events Definition and Reporting

Adverse Event: An Adverse Event (AE) is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events reported from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol, which in this study will be the last study visit. The following will not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures

Clinical Laboratory Adverse Event: A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE): A serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening* experience
- In-patient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening*, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Suspicion of transmission of infectious agents

*The term life-threatening in the definition of SAE refers to 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 was more severe.

Unanticipated Problem: An unanticipated problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents (such as the IRB-approved research protocol and informed consent document); and (b) the characteristics of the subject population being studied; AND
- is related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Adverse Drug Reaction (SADR): An adverse drug reaction (ADR) is an adverse event (AE) for which a causal relationship to the trial product is at least possible i.e. causal relationship is conceivable and cannot be dismissed. Serious adverse reaction (SAR): Adverse event which fulfils both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An SAE which is unexpected and regarded as possibly or probably related to the trial/study product by the investigator.

Medical Events of Special Interest (MESI): A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

Precautions/Overdosage: Include information concerning precautions and procedures to be observed in the event of overdose by any trial product provided during the study.

Non-Serious Adverse Event: A non-serious AE is any AE which does not fulfil the definition of an SAE.

Severity Assessment Definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

Relationship to study medication Assessment Definitions:

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial product

Outcome Categories and Definitions:

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent

- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown

Collection, Recording and Reporting of Adverse Events: All events meeting the definition of an adverse event must be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the posttreatment follow-up period as stated in the protocol, which will be the day of the last study visit.

At each contact with the participant, the investigator or study staff will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded in the source document, and also in the appropriate adverse event form of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document. All adverse events occurring during the study period must be recorded. The information reported to the sponsor will include at a minimum the study name, patient identification (subject number, initials, sex, age), event and diagnosis if available, trial drug, reporter, causality, and outcome.

Unanticpated Problems should be reported to the BUMC IRB within 7 days of the PI learning of event. Adverse Events that are not Unanticipated Problems should be submitted during the annual continuing review.

All SAEs, SUSARs, and SADRs need to be recorded and reported to Novo Nordisk within 24 hours of investigator’s knowledge of the SAE. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Post-study Adverse Event: All unresolved adverse events should be followed by the study team until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. In the rare circumstance that a subject has experienced an adverse event directly related to being in this study, which has not resolved by the time of discharge, the study team will contact the patient by telephone daily until the adverse event has resolved. We anticipate that the only adverse event related to the study that could persist by the time of discharge would be CGM related risks. Due to the nature of the study, no delayed toxicities or withdrawal effects are expected after a participant has discontinued participation in the study. Therefore, no collection of new safety information will be done after participant's discontinuation from the study.

6.3 Study Procedures

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the Investigator or their designee. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. Subjects agreeing to participate in the study will sign the ICF and be given a duplicate copy before undergoing any screening procedures. A unique ID number will be issued at the time of consent by the study team.

- Informed consent must be obtained before any study related activity.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- The investigator or their designee will maintain a screening log to record details of all participants screened and to confirm eligibility or record reason for screen failure, as applicable.

6.3.1 Informed Consent

All eligible and willing subjects will be consented prior to any procedures being performed. Subjects will be given the opportunity prior to the consent process to read and review the consent form. During the informed consent process, a study staff member, who is also a physician, will review main areas of the study design, address all subject concerns, reinforce the study's commitment to the subject and reinforce the commitment needed from the subject to be in the study. Subjects will be allowed as much time as they need prior to signing the consent form. If the subject is limit- or non-reader, a “teach back” method will be used at consent to ensure the subject understand the study.

6.3.2 Screening

Pre-screening: Potentially eligible participants will be identified from the list of inpatients with diabetes in Epic. Patients who meet the preliminary study criteria (determined by completion of the Pre-Screen Form, Appendix 3 by the research staff) will be approached to consent for the trial.

Screening Visit: Participants will first be asked to give written, informed consent. A screening visit from the study team to the patient bedside will be completed to confirm subject eligibility. Assessments and procedures at the Screening Visit include:

- Informed consent will be obtained from the patient
- Medical history will be obtained from the hospital chart and will be reviewed with the patient
- Antihyperglycemic therapy prior to hospitalization will be obtained from the hospital chart and will be reviewed with the patient
- Medications currently being administered in the hospital (to review for exclusion criteria) will be obtained from the hospital chart
- Demographics (self-reported and obtained from hospital chart) will be reviewed with the patient
- Vitals and anthropometrics (height, weight, BMI) will be obtained from hospital chart
- Laboratory tests available in medical record (HbA1c and serum creatinine) will be reviewed
- Urine pregnancy test will be administered to women of child-bearing potential who have not had a pregnancy test in the current hospitalization.

6.3.3 Recruitment and Enrollment

Recruitment: Subjects will be recruited by reviewing the list of inpatients with diabetes from Epic. The study team will review the patient's sex, age, medical history, medications, ability to speak English or Spanish and BMI from Epic Systems Corporation (EPIC) medical records. Patients meeting the study criteria will be introduced to the study by a clinician who may also be an investigator. These patients will be screened in-person by the study team.

Enrollment: Participants are enrolled in the study when they have signed the ICF. Patients who enroll will receive $25 dollars per day of participation, with a maximum of $75 per subject. Payment will occur via ClinCard (a reloadable debit card), which subjects will receive after the consent process. After completion of participation, the study coordinator will add $25 to the card for each day of participation up to a maximum of $75. At the onset of the study, participants will be enrolled on 4 regular inpatient floors only (Menino building floors 6 East, 6 West, 7 East, 7 West), but this will be expanded to all other regular med-surg inpatient floors and stepdowns after the recruitment of 10 participants OR two months from study onset (whichever occurs first).

During the study: Please refer to section 5.1 General Design Description for a detailed review of what will happen once patients are recruited in the study.

6.3.4 End of Study and Follow-up

When participants have been in the study for three days the study will be completed. At study completion, participants with complete a Patient Reported Outcome (PRO) Questionnaire (Appendix 4). Patients may also be discontinued prior to 3 days if they withdraw consent, are transferred to a higher level of care, die during admission, are started on > 1 gram of acetaminophen and/or hydroxyurea by the primary medical/surgical team or are discharged from the hospital.

6.3.5 Removal of subjects

Every effort should be made to conduct all protocol-required procedures to complete the study. Participants may be removed from the study for the following reasons:

- Withdrawal of Consent: Participant wishes to exercise the right to withdraw from the study as stated in the ICF (all participants reserve the right to withdraw from the study without prejudice). We will still use the data obtained up until the time of withdrawal.
- Adverse Event: Participant experiences an adverse event that, in the investigator's opinion, necessitates withdrawal from the study.
- Investigator Decision: Investigator feels it is in the participant's best interest to terminate participation for reasons other than an adverse event.
- Protocol Violation: Participant is noncompliant with protocol procedures, violates study entry criteria, or starts an exclusionary concomitant medication. Examples of this include: started on > 1 gram of acetaminophen and/or hydroxyurea by the primary medical/surgical team while wearing the CGM sensor
- Administrative Reason: The study sponsor or other regulatory authority discontinues the study protocol or the clinical study site discontinues participation.

Any withdrawal must be fully documented in the participant's source records and recorded on the disposition page of the CRF. The documentation must include the reason for the withdrawal

and details of any sequelae (followed until symptoms resolve or improve, as appropriate). Withdrawals due to an adverse event must be documented on both the disposition page and the adverse event page of the CRF.

6.3.6 Statistical Design

The design is a randomized, open-label study. In order to reduce bias we propose stratified randomization per ward, whereby separate randomization lists will be developed for each individual ward.

The Dexcom G6 Pro CGM sensor will store four measurements per hour. If each subject remains in the study after sensor placement for a minimum of 48 hours, each subject will have 192 glucose measurements and a minimum of 4 postmeal periods of data. We will discard data from the first 12 hours after sensor placement given concerns about data accuracy during this time period, leaving a minimum of 144 measurements/subject. As the CGM will be placed the afternoon prior to starting the prandial insulin dosing, we anticipate that discarding the first 12 hours of data will have minimal impact on the study.

6.3.7 Sample Size Considerations

Although our primary objective is to assess the non-inferiority of our intervention, we calculated power based on our secondary analysis in which we assess the superiority of our intervention because a much lower sample size is required for the non-inferiority analysis given our anticipated results.

Powering non-inferiority of our primary outcome: Using a one-sided (alpha=0.025) power calculation, we estimate that we would need a sample size of 63 participants per group to have 80% power to detect non-inferiority of Fiasp® compared to NovoLog® in postmeal time in glycemic range (100-180 mg/dl), assuming we set our non-inferiority margin at 5% less time in glycemic range and a standard deviation of 10%. A 5% non-inferiority margin was set according to an international consensus report stating that changing time in range by 5% increments would be clinically relevant. It is important to note that we have no true reference for a standard deviation of postmeal time in range for our study population, so we chose a conservative (higher than expected) standard deviation. These calculations are also conservative because they assume no hypotheses about superiority of Fiasp® (using sealedenvelope.com to calculate power).

We also estimated requiring only 63 participants to have 80% power (alpha=0.05) to detect a 2.5% greater time in glycemic range (superiority) for participants randomized to Fiasp®, compared to NovoLog® (with a 5% standard deviation of the outcome), however, we expect a greater change in percent time in range.

We will be sufficiently powered for non-inferiority (and superiority) of our primary outcome because we have chosen to power our study in order to be able to execute our secondary analysis, described below.

Powering for secondary analysis: We estimate that 80 participants per group will provide 80% power (alpha=0.05, two sided) to detect a 20 mg/dL difference in mean 24 hour (day 2) glucose between groups, assuming a standard deviation for mean glucose of 45 mg/dL, which was reported previously in a study of inpatient prandial insulin dosing (16). Previous intervention studies using CGM have reported larger differences (treatment vs. control) for time in target

glycemic range compared to differences in mean glucose (17), and we also expect larger differences (treatment vs. control) for glucose variability. Therefore, we expect to have greater power to detect differences in our primary outcome (percentage of time in the glycemic target range) because these measures have proved to be a sensitive measure of glycemic control which leverage the full granularity of CGM data (18, 19).

We anticipate that we will need to screen 210 patients to randomize 89 participants per group in order to achieve a sample size of 80 participants per group (expecting a 15% screen fail rate and a 10% rate of drop out or early hospital discharge).

6.3.7.1 Primary Analyses

The percentage of time spent in various glycemic target range will be calculated as the number of measurements in each glycemic range divided by the total number of recorded measurements. We will compare the percentage of time spent in range (100-180 mg/dL, both inclusive) in the postprandial period using Student t tests, among those randomized to NovoLog® vs. Fiasp®. Non-inferiority of Fiasp® can be confirmed if participants randomized to Fiasp® demonstrate <5% lower amount of time spent in glycemic target range compared to NovoLog®.

6.3.7.2 Secondary Objectives Analyses

We will compare percentage of time spent in other ranges of interest as detailed in the Study Objectives using Student t tests between NovoLog® vs. Fiasp® groups. We will explore other demographic factors in modeling procedures (including age, sex, and BMI) using analysis of covariance.

In additional sensitivity analysis, we will repeat all analysis using only data from the first three meals for each patient in order to partially account for differences in hospitalization duration.

6.3.7.3 Safety/Pregnancy-related policy

See Section 7.12 Data Safety Monitoring Plan.

6.3.7.4 Analysis of Subject Characteristics

Descriptive subject variables are age, sex, race, serum creatinine and HbA1C.

6.3.7.5 Interim Analysis

There is no planned interim analysis for this study.

6.3.8 Handling of Missing Data

We anticipate minimal time periods of missing sensor data due to insufficient device attachment or device removal. These periods will be excluded from analysis. Only non-missing data will be analyzed.

7 – Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Informed Consent: Study will be conducted in accordance with ICH GCP guidelines and Declaration of Helsinki. Sponsor-investigator will comply with all applicable regulatory and legal requirements in obtaining and documenting the informed consent. Sponsor-investigator will ensure that participants or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding this clinical trial.

The preparation of the ICF(s) used for this study is the responsibility of the PI and must include all elements required by applicable regulatory requirements. Prior to beginning the study, the ICF(s) will be approved by the IRB. The consent form(s) used will bear the IRB stamp on all pages.

7.2 Institutional Review Board (IRB) Review

Before study initiation, the PI must have written and dated approval/favorable opinion from an IRB for the protocol, consent form/s, and any other written information provided to participants. The PI should also provide the IRB with product labeling.

The PI will provide the IRB with reports, updates and any other information according to regulatory requirements or IRB procedures.

7.3 Subject Confidentiality

Only the PI, investigators and study personnel on this project will have access to the master code. In addition, the investigators will be using password-protected computers and locked cabinets for document storage.

7.4 Deviations/Unanticipated Problems

The study shall be conducted as described in this approved protocol. Deviations or changes to the protocol shall be made only after amendment approval/favorable opinion by the IRB, except where necessary to eliminate immediate hazard to study participants. Any significant deviation will be documented in the study team progress notes and reported to the IRB per regulations.

If an amendment substantially alters the study design or increases potential risk for study participants, the Informed Consent should be revised and submitted to the IRB. Once the IRB has approved the revised Informed Consent, all study participants currently enrolled in the study must sign the amended consent, and the new consent will be used for all new participants prior to enrollment.

7.5 Data Collection

The site will perform all data management activities, including the writing of a data management plan outlining the systems and procedures to be used. Data will be collected directly from study participants or their medical records after receiving written informed consent. Data will be collected onto paper source documents and then transcribed into the study database. Study data will be accessible to study staff who are approved to work on this protocol.

Destruction of Identifiers: Paper participant records will be kept in a locked office and electronic study data will be stored in a computer database that will be password-protected and

kept on the Endocrinology shared drive. A password-protected master code list will be created that links the subjects study number to the subjects' identity. The office will be locked at all times when charts are not in use and will only be accessible to study staff. Coded data will be kept indefinitely after completion of the study.

7.6 Data Quality Assurance

The study team is responsible for the data management of this trial including quality checking of the data. For data analysis, all data will be downloaded from the electronic databases and reformatted into SPSS data sets.

7.7 Study Records

The investigator and their team will maintain adequate and accurate records that fully document the conduct of the study and enable study data to be verified. These documents should be classified into separate categories: (1) investigator's study file, and (2) participant clinical source documents.

(1) The investigator's study file includes the original protocol, protocol amendments, official data capture forms and query forms, IRB approval with correspondence, approved informed consent form, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

(2) Participant clinical source documents include patient hospital/clinic records, physician's and nurse's notes, screening and enrollment log, etc.

The investigator and their team is required to prepare and maintain adequate and accurate case histories for each participant involved in the study. Source documents and electronic records entered in the study database must be consistent with each other, and discrepancies explained.

Corrections must be made by striking incorrect data with single line and entering correct information followed by authorized person's initials and date.

7.8 Access to Source

Clinical study data will be reported (captured) by study site personnel on paper source documents then transcribed into an electronic database.

There is no external monitor for this study. In accordance with BUMC IRB guidance, an internal quality assurance study monitor, if one is needed, will have direct access to the investigator's source documentation as needed throughout the study, in order to document compliance with the protocol and verify the completeness and accuracy of the data recorded in the official data capture forms. The Investigator and their team will cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved in a reasonable period of time.

7.9 Data Storage/Security

Paper subject records will be kept in a locked office and electronic study data will be stored in a computer database that will be password protected and kept on the Endocrinology shared drive. This storage meets BMC requirements for secure storage of PHI. A password-protected master code list will be created that links the subjects study number to the subjects' identity. The office

will be locked at all times when charts are not in use and will only be accessible to study staff. The database master code list will be deleted after completion of the study.

7.10 Retention of Records

The PI will retain all study records including the electronic database files and source documents after completion of the study. The database master code list will be kept for 7 years after completion of the study, after which it will be deleted, and coded data will be maintained indefinitely. Paper files may be stored on-site at BMC or at a secure off-site facility. The study team does not need permission from the sponsor to move or destroy the records.

7.11 Study Monitoring

An internal medical monitor (who is NOT a part of the study team) will be appointed by the PI who will review for safety (see section 7.12). Apart from this, no external or third party monitoring of this study will occur. If an internal audit is requested, the study team will cooperate per Section 7.8 Access to Source.

7.12 Data Safety Monitoring Plan

Per the OHRP Guidelines, this study is defined as "greater than minimal risk". Basal/bolus insulin regimen is the standard of care for patients with diabetes admitted to the hospital. The bolus insulin used routinely in our hospital is Humalog®. In this study, we are evaluating the effects of Fiasp® vs NovoLog®, which are being used as bolus insulin instead of Humalog®. The risks involved with administration of these two insulins are not different from the risks involved with Humalog®. Application of a CGM is a low risk procedure with minimal adverse effects. Therefore overall, this study does not have a significantly higher risk compared to the standard of care and we will not establish a Data Safety and Monitoring Board (DSMB). Study investigators will meet on a monthly basis to review study data and reported adverse events and given the risk level of the study, safety can be adequately monitored by the PI and study team.

The PI will uphold the following responsibilities:

- An internal medical monitor (who is NOT a part of the study team) will be appointed who will review for safety after the enrollment of 10 and 40 patients. Point-of-care and continuous glucose monitoring data will be reviewed. The monitor will review for any unacceptably high rates of hyper or hypoglycemia, or excessive need to deviate from the study insulin titration protocol, as well as any unexpected and/or severe events that warrant a change to the protocol.
- The PI and members of the staff will be responsible for reporting all new clinical experiences, exacerbations, and/or deterioration of any existing clinical condition occurring after a study subject has entered the study.
- The PI will be responsible for reporting Serious Adverse Events (SAEs) and Unanticipated Problems (UPs) to the BMC IRB. Per OHRP Guidelines all UPs should be reported to appropriate institutional officials (as required by an institutions written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.
- The PI will be responsible for determining the causality of all AEs/SAEs subject to review by the BMC IRB.

- The PI and staff will be responsible for follow-up information on all AEs until resolution or an appropriate endpoint is reached.

The PI in concert with BUMC IRB and other study investigators will be responsible for reviewing all reports of SAEs that occur in this study and for determining whether any corrective actions need to be taken regarding: management decisions of the PI and staff, whether protocol violations are congruous with patient welfare taking precedence over protocol, whether there are any issues among the research staff that need to be addressed, etc. The study investigators will be responsible to determine if the results of its review require a revision/modification of the protocol and/or the consent form. An independent reviewer may be considered if there is potential for conflict of interest.

If any expected event listed in the consent form/protocol exceeds what it expected in terms of incidence or severity and is thought to be related to study procedures, the study will stop any procedures until more can be known about the cause of the excess.

7.13 Study Modification

The study shall be conducted as described in this approved protocol. Deviations or changes to the protocol shall be made only after amendment approval/favorable opinion by the IRB, except where necessary to eliminate immediate hazard to study participants. Any significant deviation will be documented in the study team progress notes.

If an amendment substantially alters the study design or increases potential risk for study participants, the Informed Consent should be revised and submitted to the IRB. Once the IRB has approved the revised Informed Consent, all study participants currently enrolled in the study must sign the amended consent, and the new consent will be used for all new participants prior to enrollment.

7.14 Study Discontinuation

The treatments used in this study fall within accepted clinical practice. However, if severe unanticipated adverse events do occur, then the study will be stopped.

7.15 Study Completion

Data collection is expected to be completed by the end of 2022. When all data and sample analyses are completed, the study will be closed with the BUMC IRB per local guidelines.

7.16 Conflict of Interest Policy

Per BMC policy number 09.04.000, all study investigators are required to disclose any relationships that may create a potential conflict of interest to BMC using an approved institutional Conflicts of Interest form. This occurs at least once per year. Any actual or perceived conflicts of interest are managed by the BMC Compliance Department.

7.17 Funding Source

This study is funded by Novo Nordisk, Bagsvaerd, Denmark.

7.18 Publication Plan

We will submit study results for oral presentation at national conferences in Endocrinology as well as for publication in a major high impact peer-reviewed journals in that same area after

embargo has been lifted. All presentations and publications will acknowledge the funding source.

Appendix 1. Insulin initiation protocol

Initial insulin dose:

Determine initial TDD using baseline estimate and subtracting of adding for each risk factor:

Baseline TDD estimate	Start at 0.5 units/kg/day
Age >70 years old	-0.1 unit/kg/day
If renal insufficiency	-0.1 unit/kg/day
If pancreatic deficiency	-0.1 unit/kg/day
If HbA1c >10%	+0.1 unit/kg/day
FINAL TDD ESTIMATE	=

Basal dose: Give 50% of dose as insulin glargine every 24 hours.

Prandial dose:

Divide the remaining 50% of TDD by 3 and order for each meal. Round up (for decimals 0.6 and above) or down (for decimals 0.5 and below) to nearest whole number.

For Group 1: Order prandial insulin as NovoLog®

For Group 2: Order prandial insulin as Fiasp®

Correction dose:

Take 1500/TDD = correction factor. Patients will have correctional scales built for BG 150-300 mg/dL starting at 150 mg/dL premeal and at 200 mg/dL before bedtime. Doses will start at 2 units.

For Group 1: the correction dose will be given as NovoLog® insulin in addition to the patients' scheduled premeal prandial dose.

For Group 2. The correction dose will be given as Fiasp® insulin in addition to the patients' scheduled premeal prandial dose.

At the discretion of the study team, patients with fasting hypoglycemia or judged to be at risk for fasting hypoglycemia may have an additional correction scale ordered for 2AM.

BG monitoring: BG will be measured before each meal using bedside point-of-care meters and at bedtime (9 pm) daily. BG may also be measured if patient experiences symptoms of hypoglycemia, to assure correction of hypoglycemia, and if requested by a physician.

Appendix 2. Insulin Titration protocol

Basal insulin:

Fasting BG 101-140 mg/dL: continue dose the same

Fasting hyperglycemia (BG 141-180 mg/dL): increase dose by 10%

Fasting hyperglycemia (BG >180): increase dose by 20%.

Fasting BG 70-100 mg/dL: decrease insulin glargine dose by 10%

If patient develops fasting hypoglycemia (BG 60-69 mg/dL), decrease insulin glargine dose by 20%

If patient develops fasting hypoglycemia (BG 40-59 mg/dL), decrease insulin glargine dose by 30%

If patient develops severe fasting hypoglycemia (BG <40 mg/dL) decrease insulin glargine dose by 40%

Correction insulin

Insulin sensitivity factor will be recalculated daily whenever there is a change in insulin dose.

Prandial insulin:

Adjust based on BG levels obtained pre-lunch, presupper, and at bedtime as below for hyperglycemia:

If 2 or more BG levels are 170-190 mg/dL without hypoglycemia, increase dose by 10%

If 2 or more BG levels are 191-230 mg/dL without hypoglycemia, increase dose by 20%

If 2 or more BG levels are 231-250 mg/dL without hypoglycemia, increase dose by 30%

If 2 or more BG levels are >250 mg/dL at separate times of a single day, study team to stop study titration algorithm, recalculate TDD and adjust insulin based on clinical judgement. If any BG 70-100 mg/dL, decrease dose by 20%

If any BG 60-69 mg/dL, decrease dose by 30%

If any BG <60 mg/dL, decrease dose by 50%

Appendix 3. Prescreening form

1. Primary language: English ____ Spanish ____ Other_____ cannot determine ____
2. Located on non-intensive care unit: _____ (Y/N)
3. Age 21-80: _____ (Y/N)
4. Patient pregnant/breastfeed: _____ (Y/N/unknown)
5. Serum creatinine ≥ 2 mg/dL: _____ (Y/N)
6. History type 2 diabetes prior to admission: _____ (Y/N)
7. Outpatient medications:
    a. HbA1c of ≥8% on ≥1 oral or injectable agent: _____ (Y/N)
    b. Insulin: _____ (Y/N)
    c. 2 oral agents: _____ (Y/N)
    d. Insulin dose >1 unit/kg/day: _____ (Y/N)
8. Discharge planned within 48 hours: _____ (Y/N)
9. BMI <45: _____ (Y/N)
10. History of type 1 diabetes or LADA (late-onset autoimmune diabetes): _____ (Y/N)
11. History of gastroparesis or cirrhosis: _____ (Y/N)
12. Currently on glucocorticoids OR plan for treatment with glucocorticoids within the next 72 hours.(prednisone, dexamethasone, methylprednisolone, hydrocortisone): _____ (Y/N)
13. Admission diagnosis of diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, solid organ transplantation, or coronary artery bypass surgery: _____ (Y/N)
14. Receiving tube feeds or total parenteral nutrition: _____ (Y/N)
15. Expected to be NPO for >24 hours: _____ (Y/N)
16. Receiving > 1 gram of acetaminophen or hydroxyurea in the hospital: _____ (Y/N)
17. Using insulin pump or continuous glucose monitoring device in the hospital: _____ (Y/N)
18. Currently incarcerated: _____ (Y/N)
19. Allergy to insulin: _____ (Y/N)
20. Tested positive for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) OR there is an ongoing clinical suspicion for COVID-19 infection in spite of a negative test: _____(Y/N)

Appendix 4. Patient Reported Outcome (PRO) Questionnaire

Instructions:

A Patient Reported Outcome (PRO) questionnaire is being included in this trial to obtain information about the acceptability of wearing a continuous glucose monitoring device while in the hospital.

When should the PRO questionnaire be administered?
At completion of the study. It takes approximately 5 minutes.

Before giving the PRO questionnaire to the subject
Fill in the header on each page

Giving the PRO questionnaire to the subject
-Explain that the questionnaire assesses the subject's perception of wearing a continuous glucose monitoring device in the hospital
-Explain that the subject should answer the questions him-/herself, without assistance from family, friends or medical staff
-Encourage the subject to answer every question to the best of his/her ability
-Ask the subject to select only one answer for each question
-Ask the subject to refrain from writing any extraneous comments in the questionnaire
-Explain to the subject that the completed questionnaire will be reviewed for any written comments that may suggest issues with wearing the continuous glucose monitoring device

Completion of the PRO questionnaire
-Ensure that a staff member is accessible if questions arises
-If interpretive questions arise, ask the subject to read the question again and answer based on what he/she thinks the question means
-if the subject accidentally marks an incorrect response, ask him/her to strike it out with a single line and mark the correct response instead

After completion of the PRO questionnaire
-Collect the completed questionnaire from the subject
-Review them for potential adverse events and document the review on the designated signature sheet
-File the completed questionnaires in the trial file.

Questionnaire:

Trial ID: Subject number: _____ Date: (DD/MMM/YYY):_____

Dear Study Participant,

Please complete the questions on the following pages. The study staff will review your answers to see if you have reported any adverse effects with wearing the continuous glucose monitoring device, and how satisfied you are with wearing it. Any adverse events will be reported. Otherwise, your responses remain confidential. They will be compiled with the responses from the other study participants and treated anonymously. The data will be used to better understand the experience of wearing a glucose monitoring device in the hospital.

- Please select only one answer
- Please answer every question, even if you think they are similar to each other
- Please choose the response that most closely represents how you feel, even if none of the options match exactly
- If you are not sure how to answer a question, please select an answer based on what you think the question means
- There are no “right” or “wrong” answers
- When you have finished, please hand in the completed forms to the study staff

If you have questions, please ask the study staff.

Thank you for your time. Your opinion is highly appreciated.

Trial ID: Subject number: _____ Date: (DD/MMM/YYY):_____

Continuous Glucose Monitoring Patient Experience Measure

The following questions are about your experience with the continuous glucose monitoring device, referred to as "sensor" in the questions. There are no right or wrong answers. Please choose only one response for each question.

	Not at all easy	Somewhat easy	Very easy
1. When the sensor was applied, how easy or difficult was this?	☐	☐	☐

	None	Mild	Moderate	Severe
2. When the sensor was applied, how much discomfort did you notice?	☐	☐	☐	☐
3. After you had been wearing the sensor for several hours, how much discomfort did you notice?	☐	☐	☐	☐

4. Did you experience any of the following problems wearing the sensor:

Sensor falling off? ☐ Yes ☐ No

Skin irritation at the site of the sensor? ☐ Yes ☐ No

If yes, how bothersome ☐ mild ☐ moderate ☐ severe

5. Based on your experience wearing the senor, would you prefer to use the sensor to measure your blood sugar instead of having a fingerstick checked while <u>in the hospital</u>? ☐ Yes ☐ No

6. Based on your experience wearing the senor, would you prefer to use the sensor to measure your blood sugar instead of having a fingerstick checked while <u>at home</u>? ☐ Yes ☐ No

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