Liraglutide in Overweight Patients with Type 1 Diabetes

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Complete Research Protocol (HRP-503)

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Sections that do not apply:

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PROTOCOL TITLE:

Include the full protocol title.

Response: Liraglutide in Overweight Patients with Type 1 Diabetes

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VERSION:

Include the version date or number.

Response: 10/2/2018

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response: Juvenile Diabetes Research Foundation

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response: Diabetes Endocrinology Center of WNY

Location: 1000 Youngs Road, Suite 105, Williamsville NY 14221

Address: 1000 Youngs Road, Suite 105, Williamsville NY 14221

Department: Diabetes Endocrinology & Metabolism

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research.

Response: To study the effects of liraglutide (a drug used to treat type 2 diabetes) on glucose (sugar) control over the 26 week study period when used in addition to insulin. The use of Liraglutide in Type 1 Diabetes is investigational

1.2 Describe the purpose, specific aims, or objectives.

Response:
Aim 1.1: To compare the mean HbA1c, fasting glucose, weekly glucose, the standard deviation of weekly blood glucose concentrations as recorded by continuous glucose monitoring, fructosamine and the dose of insulin required prior to and following 26 weeks of treatment with liraglutide.
Aim 1.2: To compare the postprandial glucose concentrations following a test meal before and after 26 weeks of treatment with liraglutide.
Aim 2.1: To compare the basal and postprandial glucagon and C-peptide concentrations following a test meal before and after 26 weeks of treatment with liraglutide.
Aim 3.1: To compare ROS generation, TBARS, intranuclear NFκB binding in MNC, the expression of TLR-4,TNFα, IkBα, MMP-9, SOCS-3, PKCβII, PTP-1B, GSK-3β, IKKβ, JNK-1, IRβ and pIRβ in MNC and adipose tissue and plasma concentrations of CRP, MCP-1, PAI-1, TNFα, RANTES, free fatty acids (FFA) prior to and following: a) a single injection of liraglutide 1.2mg at first study visit; b) treatment with liraglutide for 26 weeks.
Aim 3.2: To compare the changes in NFκB binding and the expression of TLR-4, TNFα, IkBα, SOCS-3, PTP-1B, PKCβII, IKKβ and JNK-1 in MNC following a standard meal challenge prior to and after 26 weeks of treatment with liraglutide..
Aim 4.1: To assess subcutaneous fat mass, hepatic fat content and visceral fat mass by MRI of abdomen and DEXA before and 26 weeks after treatment with liraglutide.
Aim 4.2: To assess change in waist circumference, blood pressure, triglycerides, HDL cholesterol and incidence of metabolic syndrome after treatment with liraglutide
Aim 5.1: To compare the gastric emptying as measured by acetaminophen absorption before and 26 weeks after treatment with daily subcutaneous liraglutide injection.

Aim 6.1: To compare the blood pressure using a 24 hour blood pressure monitor before and 26 weeks after treatment with liraglutide.
Aim 6.2: To compare endothelial function by measuring flow mediated dilatation (FMD) in brachial artery before and 26 weeks after treatment with liraglutide.

Aim 7.1: To compare the quality of life questionnaire scores and depression questionnaire scores before and 26 weeks after treatment with liraglutide

1.3 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response:

Hypothesis 1: Treatment with Liraglutide in overweight or obese patients with type 1 diabetes decreases fasting, postprandial and the overall mean glucose concentrations while decreasing the dose of insulin required.

Hypothesis 2: Treatment with Liraglutide decreases basal and postprandial glucagon concentrations and increases basal and postprandial C-peptide concentrations.
Hypothesis 3.Treatment with liraglutide suppresses indices of oxidative and inflammatory stress including the mediators of insulin resistance, in peripheral blood mononuclear cells (MNC), plasma and adipose tissue.
Hypothesis 4: Treatment with liraglutide reduces abdominal adiposity, hepatic and visceral fat mass and improves features of metabolic syndrome.
Hypothesis 5: Treatment with Liraglutide in obese patients with type 1 diabetes delays gastric emptying.
Hypothesis 6: Treatment with Liraglutide in obese patients with type 1 diabetes improves blood pressure and endothelial function.
Hypothesis 7: Treatment with Liraglutide in obese patients with type 1 diabetes improves quality of life and depression as measured by questionnaires.

2.0 Scientific Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.

NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should **not** be a date.

Response: **Primary endpoint:** Change from baseline in HbA1c at 26 weeks as compared to placebo. **Secondary endpoints**: Change from baseline as compared to placebo in a)fasting and postprandial blood sugars, mean weekly glucose concentrations, standard deviation of weekly blood sugars and fructosamine; b)fasting and postprandial glucagon and C-peptide concentrations; c)insulin doses; d)indices of oxidative and inflammatory stress in MNC, plasma and adipose tissue; e)oxidative and inflammatory stress in plasma

and MNC following meal challenge; f)subcutaneous fat mass, hepatic fat content and visceral fat mass; g)waist circumference, blood pressure, triglycerides, HDL cholesterol and incidence of metabolic syndrome; h)gastric emptying; i) 24 hour blood pressure; j) flow mediated dilatation in brachial artery, k) SF-36 score; l) depression (PHQ) score.

3.0 Background

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response: The treatment of type 1 diabetes is based on insulin replacement since the auto-immune destruction of β-cells leads to a near total loss of endogenous insulin reserve. The evolution of therapy in type 1 diabetes since the discovery of insulin in 1921 by Banting and Best has largely been based on modifications of insulin preparations or modifications of the insulin molecule (insulin analogs) to allow variable bio-availability(1, 2). Different ways of delivering insulin and monitoring glucose through subcutaneous insulin infusion pumps and continuous glucose monitoring systems have also been devised. Inspite of these advances, the control of glucose homeostasis in subjects with type 1 diabetes continues to be challenging since exogenous insulin cannot compensate totally for changing requirements and is still not precise either in terms of the dose or the bio-availability of the insulin injected (3, 4). Furthermore, in the near total absence of endogenous insulin secretion, the physiological post prandial inhibition of glucagon secretion by the α-cell is probably deficient in all type 1 diabetics, which may also contribute to the variability and unpredictability of glucose control with exogenous insulin alone(5). The concomitant use of metformin or pramlintide helps in some patients but the results are far from consistent and, therefore, these agents have not made an impact on the treatment of this condition(6). Thus, there is a need for therapies beyond insulin that can further improve glycemic control and reduce fluctuations in glucose in these subjects.

A recent trial of liraglutide, a glucagon like peptide (GLP)-1 analogue with a 24 hour duration of action, in 13 patients with type 1 diabetes led to a remarkable reduction in the excursions of blood glucose, both highs and lows, following meals and through the 24 hours within the first 2 days of treatment in all 13 subjects (7)(see preliminary data section). The mean glucose concentrations fell significantly from 136 to 111 mg/dl and the mean HbA1c fell significantly from 6.45 to 6.1% in 8 subjects who continued liraglutide for 24 weeks. The SD of glucose readings fell from 52 to 28. Remarkably, the requirement of insulin fell from 51 units to 28 units daily. The treatment also led to a reduction in appetite and to weight loss even during the short period of treatment for 9 weeks. The patients felt remarkably better and secure in terms of the 'predictability and stability' of glycemic and appetite control (7). The improvement in glycemia with the reduction in insulin requirements within days of starting treatment with liraglutide could be an evidence of insulin sensitization and /or endogenous insulinogenesis. Since C-peptide concentrations did not alter following the short term administration of liraglutide, it is likely that the suppression of glucagon may have contributed to this effect. It is also possible that the improvement in glucose homeostasis could partly have been due to a decrease in carbohydrate intake and reduced rate of gastric emptying, both of which are known actions of GLP-1 analogues (8, 9).

A recent study has shown that GLP-1 infusion suppresses basal and arginine induced glucagon secretion in subjects with type 1 diabetes(10). GLP-1 infusion also completely prevents the rise in post-prandial glucose or glucagon concentrations in these patients(11). A study by Rother et al on the effect of exenatide after a meal also showed a trend towards a reduction in the increase of glucagon after a meal for the first 45 min although there was no significant overall effect(12). In view of the 24 hour duration of action of liraglutide, it is possible that it may exert a protracted suppressive effect on glucagon and thus, decrease post prandial increases in glucagon concentrations which in turn would reduce post prandial excursions of glucose. The importance of glucagon in inducing hyperglycemia is further strengthened by the observation that glucagon receptor knockout mice do not develop diabetes inspite of complete β cell destruction by streptozotocin(13). Fasting as well as postprandial blood sugar concentrations were normal in these animals.

Our recent observations, mentioned above and described in greater detail below, could provide a potentially potent and significant advance in the treatment of type 1 diabetes if our investigations demonstrate that the use of liraglutide, a GLP-1 agonist, not only reduces glycemia but it reduces the magnitude of excursions of glucose even in stable, well controlled type 1 diabetics. This study will be the first randomized controlled prospective double blind study investigating the effect of liraglutide in such patients. If this drug is shown to be consistently effective, it will provide a major advance in the treatment of hyperglycemia and unpredictable alterations in glucose concentrations in type 1 diabetes, a disease that is newly diagnosed in 15000 children per year in the US and currently affects 3 million Americans(14).

Innovation rationale, and significance

1. This will be the first prospectively randomized controlled study to investigate the effect of liraglutide on glycemic levels and variability in overweight and obese type 1 diabetes treated with insulin alone. Liraglutide is the preferred agent for this study since its pharmacokinetics and pharmacodynamics ensure a duration of action of 24 hours. Hitherto, the treatment of type 1 diabetes is based on insulin replacement with novel analogs with appropriate pharmacodynamic profiles or with unique insulin delivery systems. The concomitant use of metformin or pramlintide helps in some patients but the benefits are far from consistent and, therefore, these agents have not made an impact on the treatment of this condition(6).
2. This will be the first study to investigate the role of glucagon and the potential basal and postprandial suppression of glucagon by liraglutide in the pathogenesis and control of glycemia in type 1 diabetics. This is particularly important since in the absence of insulin secretion from the β–cell, there is no paracrine inhibition of glucagon secretion by the α–cell. GLP-1 analogs are known to suppress glucagon(5).
3. With the use of CGM, this study will determine the rapidity of response by liraglutide, which in our preliminary study was observed within the first two days such that we advised patients to reduce their insulin doses by 25% in advance.
4. This will be the first study to attempt to reduce body weight and other features of the metabolic syndrome, while improving glycemic control with addition of a single therapeutic agent in overweight and obese patients with type 1 diabetes. This is particularly relevant since insulin induces weight gain and 40-50% of type 1 diabetics in the US have the metabolic syndrome(14). Liraglutide and the only other licensed drug in this class, exenatide, have been shown not only to reduce body weight but also

to reduce systolic blood pressure plasma triglyceride and CRP concentrations in subjects with type 2 diabetes(8; 9; 15; 16; 18).

5. Finally, it will allow us to assess whether liraglutide can activate the dormant β–cells which are known to survive in type 1 diabetics for a long time (19). An analysis in a subset of the study patients with detectable C-peptide will be carried out separately. This will assess the effect of liraglutide in preserving β–cells and the effect of residual β-cell function on the action of liraglutide

Liraglutide treatment in patients with type 1 diabetes

As mentioned above, the treatment of 14 type 1 diabetes patients; age (38.5 years), duration of diabetes (20±4 yrs), weight (66±6kg), HbA1c% (6.5±0.5%), C-peptide (< 0.10nmol/l), basal insulin dose of 24±6 units/day, bolus insulin dose of 22±4 units/day with liraglutide in addition to insulin resulted in significant reduction in fasting and mean blood glucose concentrations, insulin doses by 45%, HbA1c levels even at 24 weeks, and a reduction in appetite and caloric intake with weight loss. In addition, there was a reduction in the excursions of blood glucose concentrations, i.e., the standard deviations of blood glucose concentrations were markedly reduced. The changes were observed within 48h and improved marginally thereafter with fine tuning of insulin doses and a further reduction in these doses. The comparison of changes observed early (1 week) vs late (9 weeks) are evident in **tables 1 and 2.**These observations are noteworthy in that they were made in patients who had been well controlled, were meticulous, even obsessive, and were on CSII and CGM. They had all tried hard to improve their diabetic control by adjusting insulin doses but had not succeeded because of the induction of hypoglycemia. To establish this fact, the patients recorded their glucose concentrations for at least two weeks during which optimal control was attempted and no significant change was observed (data not shown). While our initial plan was to assess the effect with one week treatment, 7 patients wanted to continue with Liraglutide and were able to get insurance coverage for this treatment. This study was conducted to improve glycemic control in the clinic and not as a randomized or placebo controlled trial. In view of the significant effects that were observed **(Figure 1**), we now want to conduct a prospective randomized placebo controlled trial to investigate and confirm these effects of Liraglutide in subjects with type 1 diabetes.

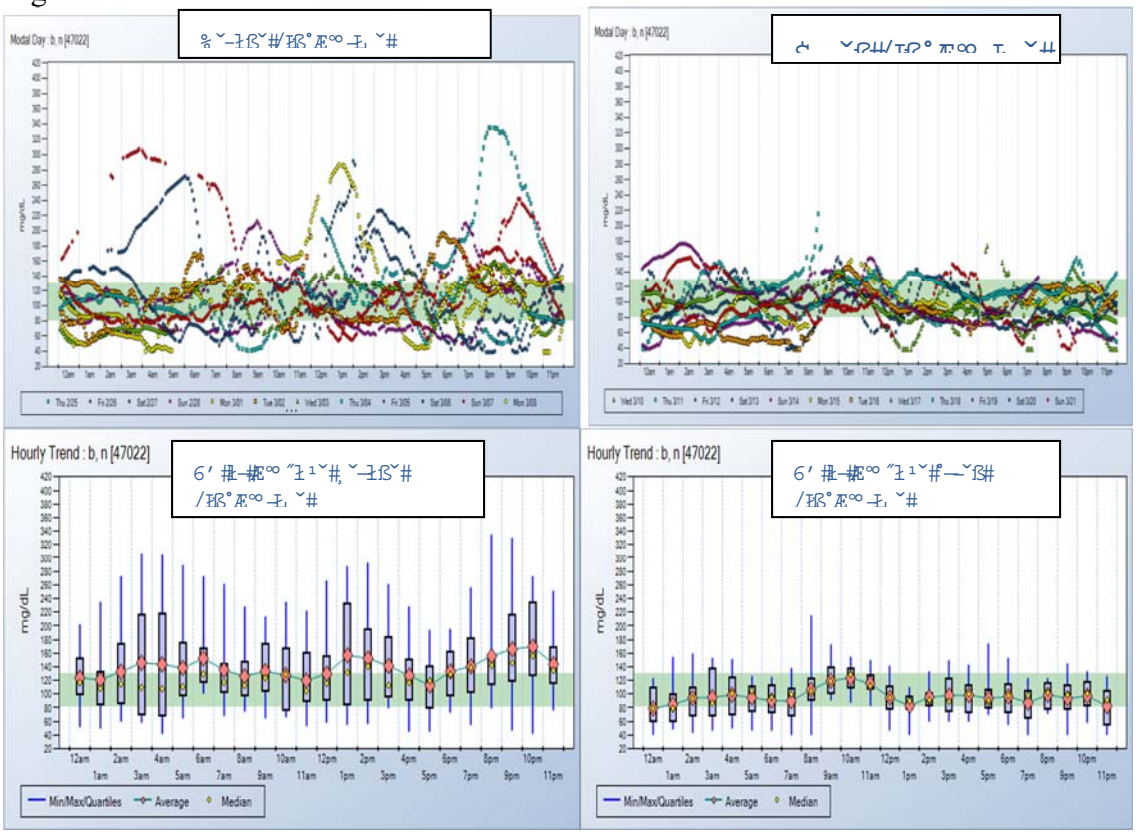
Table 1) Effects of Liraglutide after treatment for one week (n=14)

Table 1	Before treatment	On Liraglutide	P value
Weight(kg)	66 ± 6	65± 5	0.22
insulin dose (basal)	24 ± 6 U/d	16 ± 6 U/d	<0.01
insulin dose (bolus)	22 ± 4 U/d	15 ± 4 U/d	<0.01
Mean Fasting Blood Glucose (mg/dl)	129±10	110±8	0.02
Weekly Mean Blood Glucose (mg/dl)	141±20	115±12	<0.01
Time spent in hypoglycemia <70 mg/dl(% time)	2.1±2	2.6±2	0.08
Time spent in hypoglycemia <40 mg/dl(% time)	0.12±0.2	0.16±0.3	0.09
Time spent in hyperglycemia > 150 mg/dl(% time)	28± 6	22± 5	0.03
Time spent in hyperglycemia >200 mg/dl(% time)	18± 5	9± 2	<0.01
Time spent in hyperglycemia >250 mg/dl(% time)	8± 2	1.5± 1	<0.01
Mean weekly SD (mg/dl)	56±10	26±6	<0.01

Table 2) Effects of Liraglutide after treatment for mean duration of 24 weeks (n=8)

Table 2	Before treatment	On Liraglutide	P value
Weight (kg)	68±5	64±4	0.02
HBA1c %	6.45±0.5	6.1±0.4	0.02
insulin dose (basal)	26 ± 7 U/d	13 ± 6 U/d	<0.01
insulin dose (bolus)	25 ± 4 U/d	15 ± 4 U/d	<0.01
Mean Fasting Blood Glucose (mg/dl)	125±10	107±8	0.02
Weekly Mean Blood Glucose (mg/dl)	136±20	111±12	<0.01
Time spent in hypoglycemia <70 mg/dl (% time)	2±2	2.4±2	0.10
Time spent in hypoglycemia <40 mg/dl (% time)	0.1±0.2	0.14±0.3	0.21
Time spent in hyperglycemia > 150 mg/dl(%	27± 6	20± 5	0.01
Time spent in hyperglycemia >200 mg/dl(%	17± 5	6± 2	<0.01
Time spent in hyperglycemia >250 mg/dl(%	7.5± 2	1±1	<0.01
Mean SD weekly (mg/dl)	52±10	28±6	0.01

Figure 1: Weekly continuous glucose monitoring record of one patient prior to and following 1 week of liraglutide. Note the glycemic variability (SD) and the frequency of glucose concentrations within the target range prior to and following liraglutide
Fig 1



3.2 Include complete citations or references.

Response:

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4.0 Study Design

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).

Response: This investigation will be a prospective, randomized, double blind, placebo controlled parallel design study conducted in patients with type 1 diabetes. The study will be conducted at Diabetes–Endocrinology Center of WNY, affiliated to the State University of New York at Buffalo.

84 overweight or obese patients with type 1 diabetes on treatment with either continuous subcutaneous insulin infusion (CSII; also known as insulin pump) or multiple (four or more) injections of insulin per day will be included in the study. They will be randomized into 2 groups of 42 patients each. The patients will be randomized to daily subcutaneous injections of placebo or liraglutide. In view of the possibility of hypoglycemia and the side effect of nausea all patients will be started on 0.6 mg of liraglutide per day. The dose will then be titrated up to 1.8 mg.

5.0 Local Number of Subjects

5.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response: 84

5.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response: 100-110. All screened and qualified patients will be enrolled and randomized up to 84 enrolled patients.

5.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: The Diabetes and Endocrinology Center of WNY is the largest Diabetes center in the WNY area, seeing between 60 and 100 type 1 diabetic patients every month. Therefore, majority of recruited patients are our clinic patients. We do recruit a few patients through advertisement and researchmatch.org. These sources will suffice to recruit the needed number to subjects.

6.0 Inclusion and Exclusion Criteria

6.1 Describe the criteria that define who will be **included** in your final study sample.

NOTE: This may be done in bullet point fashion.

Response:

1) Type 1 Diabetes on continuous subcutaneous insulin infusion (CSII; also known as insulin pump) or multiple (four or more) injections of insulin per day.
2) Using a continuous glucose monitoring device (CGM) or regularly measuring their blood sugars four times daily.
3) HbA1c of less than 10.0%.
4) Well versed with carbohydrate counting**.**
5) Age 18-80 years
6) BMI≥ 25 kg/m^2
7) Age at diagnosis of type 1 diabetes should be <30 years.
8) Evidence of auto-immunity to beta cells (GAD-65 and islet cell antibody screen)

6.2 Describe the criteria that define who will be **excluded** from your final study sample.

NOTE: This may be done in bullet point fashion.

Response: 1)Type 1 diabetes for less than 6 months;
2)Coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery or coronary angioplasty) in the previous four weeks;
3)Hepatic disease (transaminase > 3 times normal) or cirrhosis;
4)Renal impairment (serum eGFR <30ml/min/1.73m^2);
5)HIV or Hepatitis B or C positive status;
6)Participation in any other concurrent clinical trial;
7)Any other life-threatening, non-cardiac disease;
8)Use of an investigational agent or therapeutic regimen within 30 days of study.
9) history of pancreatitis
10) pregnancy
11) inability to give informed consent
12) history of gastroparesis

13)history of medullary thyroid carcinoma or MEN 2 syndrome.
15) Use of any agent other than insulin for treatment of diabetes (metformin, pramlintide or thiazolidinediones;
16) painful gallstones;
17) alcoholism;
18) hypertriglyceridemia (>500 mg/dl)
19) History of pancreatitis

6.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response: None of the below populations will be enrolled

☐ Adults unable to consent

☐ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

6.4 Indicate whether you will include non-English speaking individuals in your study. **Provide justification if you will exclude non-English speaking individuals.**

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may **not** be routinely excluded from research as a matter of convenience.

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: We have no non-English speaking patients in this population. We have patients that English is a second language, but they are able to read, write and understand it. This population is less than 10% of the total population.

7.0 Vulnerable Populations

If the research involves special populations that are considered vulnerable, **describe the safeguards included to protect their rights and welfare.**

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

7.1 For research that involves **pregnant women,** safeguards include:
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response: We will not be using subjects from vulnerable populations

☒ **N/A**: This research does not involve pregnant women.

7.2 For research that involves **neonates of uncertain viability or non-viable neonates,** safeguards include:
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

7.3 For research that involves **prisoners**, safeguards include:
NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☒ **N/A:** This research does not involve prisoners.

7.4 For research that involves **persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")**, safeguards include:
NOTE CHECKLIST: Children (HRP-416)

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

7.5 For research that involves **cognitively impaired adults**, safeguards include:
NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. **Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.**

Response: No specific populations or vulnerable groups will be targeted. All subjects enrolled in this study will be of legal adult consenting age with the ability to speak, read and interrupt the English language. Patients will have the ability to speak with the research team regarding any questions or concern they have before signing the consent. Patients are made aware that this study is voluntary and they are able to stop participating at any time they feel uncomfortable. Patients are not

be pressured into participating and their clinic standard of care will remain the same if they participate or choose not to participate.

8.0 Eligibility Screening

8.1 Describe **screening procedures** for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.

Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).

Response: :

Prospective participants will be asked to read and understand the consent and any questions they may have regarding the protocol will be answered. If the subject wants to participate in the study, they will be asked to sign the informed consent form. The subject's medical history and current medications will be obtained as well as their blood pressure and vitals. A physical examination will also be done. Fasting labs before 10:00am include; CBC, CMP, HbA1c, lipid panel, C-peptide and GAD-6 and a urine pregnancy test. Blood samples of patients with negative GAD-65 antibodies will be screened for islet cell antibodies, if patient had evidence of auto- immunity to beta cells in the past, they will be retested during screening. Patients with no evidence of autoimmunity to beta cells will not be included in this trial. Patients meeting all the inclusion and exclusion criteria based on all screening tests will be enrolled in the study.

☐ **N/A:** There is no screening as part of this protocol.

9.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

9.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response: Participants will be identified by prescreening clinical charts, patient doctor interaction at the time of their visits, flyers advertisements and researchmatch.org. Diabetes Endocrinology Center of WNY Locations include:

1. 1020 Youngs Road, Williamsville NY 14221

2. 705 Maple Road, Williamsville NY 14221

3. 462 Grider Street, Buffalo NY 14215

The study clinical team will evaluate their clinic patients for possible participation in this study according to the inclusion and exclusion criteria at the Diabetes and

Endocrinology Center of WNY. Patients that may qualify for the study are referred to the research team for further eligibility evolution. Patients meeting the inclusion and exclusion criteria based on preliminary phone evaluation will be invited to participate in the study.

9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response: Patient charts will be screened according to the study inclusion and exclusion criteria by our trained clinical staff and physicians. If the patient qualifies and is of consenting age, the physicians will speak to them about their interests in participating in research. If the patient agrees, their information will be given to the research coordinator to be contacted for further evaluation. All personal information will be kept confidential and locked in the coordinator office.

9.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response: In addition to screening clinical charts, participations will be identified through; flyer advertisement and researchmatch.org

10.0 Procedures Involved

10.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response:
Screening Visit: Consent will be explained and signed. Fasting labs before 10:00am include; CBC, CMP, HbA1c, lipid panel, C-peptide and GAD-6 and a urine pregnancy test. Physician preformed physical and medical history, including; blood pressure, height and weight. Blood samples of patients with negative GAD-65 antibodies will be screened for islet cell antibodies, if patient had evidence of auto- immunity to beta cells in the past, they will be retested during screening. Patients with no evidence of autoimmunity to beta cells will not be included in this trial.
Study Visit day -14: After screening visit, qualifying patients will see a registered dietitian who will review their carbohydrate counting and diet and make an assessment of their calorie and carbohydrate intake. Then they will be seen by a CDE for instructions on

injection technique and CGM insertion. The patients will be blinded to CGM. Patients who have been using CGM prior to enrolling in the study can continue to use their CGM's (unblinded). All subjects will be advised to monitor their capillary blood glucose by fingerstick before and 2 hours after each meal and to wear their CGM constantly for a week. The subjects will also be asked to keep a diary of their food intake for a week to measure their calorie intake. Study subjects will not change the type of glucose meter during the trial. They will have their body composition measured by DEXA and MRI prior to the next visit. Smoking patients will be asked not to change their smoking habits during the study.

Study visit day -7: Meal challenge test: In order to assess the changes induced by liraglutide, a meal challenge will be carried out prior to and following liraglutide (week 0 and week 26): a 910 calorie high fat high carbohydrate meal will be given, as in several of our previous papers(20).Bolus dose will be given at 3-4 hours after the ingestion of the meal based on the blood sugar and correction factor for each individual subject as giving bolus insulin immediately before meal may confound the true effects of liraglutide. Acetaminophen (1000 mg for body weight <125lbs, 1250 mg for body weight 125-150 lbs, 1500 mg for body weight 151-175 lbs and 1750 mg for body weight >175 lbs) will be ingested at the beginning of the meal, and the blood levels of acetaminophen will be determined at intervals for assessment of the rate of gastric emptying. Liraglutide will be injected only at week 26 (45 min prior to the meal). Sequential blood samples will be obtained at 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 and 300 min. Samples at 15, 30, 45, 90, 150 and 210 min will be 5 ml while those at 0, 60, 120, 180, 240 and 300 min will be 30 ml (total volume=210 ml). Blood will be collected from an indwelling intravenous canula in a superficial forearm vein.

Study visit day -1: Subjects will come fasting for this visit. Records of blood glucose concentrations monitored by fingerstick and CGM for the previous 14 days will be obtained to assess their glycemic control prior to liraglutide treatment **(this will serve as the baseline assessment of mean blood glucose for the study)**. The subjects will have their 24 hour blood pressure measurements completed. Brachial reactivity will be assessed by measuring by flow mediated dilation (FMD). They will undergo a meal challenge test (described below) and a fat biopsy. 24 hr urine will be collected.

Study Visit day 0: Subjects will come fasting for this visit. Each subject will be given one injection of Liraglutide 1.2 mg or placebo. A fructosamine and blood samples will be collected at baseline. Blood samples will be collected after the baseline at 30, 60, 120, 180, 240 and 300 minutes after the injection. **(This is being done to evaluate the acute effect of a single injection of Liraglutide on oxidative stress and inflammatory mediators, before any adjustments of insulin dose or effect of Liraglutide on blood glucose and weight is evident)**. Subjects will be instructed by the study staff in the dosing and administration of the study medication. They will start Liraglutide injection at a dose of 0.6 mg per day or placebo injection on the following day. We will adjust the doses of basal and bolus insulin to eliminate low blood sugars(less than 70 mg/dl). At all subsequent visits insulin doses will be titrated to target blood sugars between 70-180 mg/dl at all times. Patients will return to the center after 7 days.

Study Visit week 1: Blood glucose concentrations will be reviewed. Insulin dose will be adjusted at the discretion of the study investigator to optimize blood sugar control as per

the targets mentioned above. Patients will be advised to increase the Liraglutide dose to 1.2 mg a day if they are able to tolerate the 0.6 mg dose. If they are experiencing mild nausea, subjects will continue with 0.6 mg daily for another 7 days. Those with severe nausea/vomiting will be dropped from the study. All other subjects will return in 7 days.

Study Visit week 2: Blood glucose concentrations will be reviewed. Insulin dose will be adjusted if needed. Subjects taking 0.6 mg dose and experiencing significant nausea will be dropped from the study. Subjects on 1.2 mg and experiencing significant nausea will decrease the dose to 0.6 mg and continue that dose for the duration of the study. Subjects on 1.2mg and experiencing mild nausea will continue on 1.2 mg for 2 more weeks. Subjects on Liraglutide 1.2mg daily without any gastro-intestinal side-effects will be asked to increase the dose to 1.8 mg daily. Study drug will be dispensed for additional 2 weeks.

Study Visit week 4: Subjects will be asked to bring in their used study pens and the pen that they are using so that study nurse can log in the amount of drug used. If needed, the dose will be increased. The goal in the first 4 weeks is to increase patient's liraglutide dose to maximum tolerated dose. Maximum dose of liraglutide will be 1.8 mg daily. Subjects experiencing mild nausea with 0.6 mg or 1.2 mg will continue at that dose in the study. Those with severe nausea/vomiting with 1.8mg will decrease their dose to 1.2 mg and continue that dose throughout the study. Blood glucose concentrations will be reviewed. Insulin dose will be adjusted if needed. CGM will be discontinued. Study drug will be dispensed to last till the next visit.

Study visit week 8: Subjects will be asked to bring in their used study pens and the pen that they are using so that study nurse can log in the amount of drug used. Blood glucose concentrations will be reviewed. Insulin dose will be adjusted if needed. Study drug will be dispensed to last till the next visit.

Study Visit week 12: Subjects will be asked to bring in their used study pens and the pen that they are using so that study nurse can log in the amount of drug used. Blood glucose concentrations will be reviewed and vascular activity will be performed. Insulin dose will be adjusted if needed. Fasting blood, research labs, HbA1c, fructosamine, lipid panel, urine pregnancy test and 24 hr urine will be collected. FMD and 24hr blood pressure will be studied. Study drug will be dispensed for additional 4 weeks.

Study Visit week 16 and 20: Subjects will be asked to bring in their used study pens and the pen that they are using so that study nurse can log in the amount of drug used. Blood glucose concentrations will be reviewed. Insulin dose will be adjusted if needed. Study drug will be dispensed for additional 4 weeks.

Study visit week 24: CGM will be inserted. They will have their body composition measured by DEXA and MRI prior to next visit.

Study Visit week 26: Subjects will come fasting for this visit. Research labs, CBC, CMP, Lipids, HbA1c and fructosamine will be collected. Records of blood glucose concentrations monitored by finger-stick and CGM for the previous 14 days will be obtained to assess their glycemic control. They will undergo meal challenge test (described above) and a fat biopsy. 24 hr urine will be collected. FMD and 24hr blood pressure will be performed. After this visit, subjects will be discharged from the study.

Blood samples (collected in protease and DPP-IV inhibitors) will be appropriately processed and assayed for glucose, C-peptide, glucagon, GLP-1 and gastric inhibitory peptide (GIP) which is also called gastric insulinotropic peptide, Reactive oxygen species (ROS) generation, Thiobarbituric acid reducing substances (TBARS), urinary isoprostane,

intranuclear nuclear factor kappa B (NFkB) binding, the expression and concentration of Toll like receptor-4 (TLR-4), tumor necrosis factor alpha (TNFα), Inhibitor kappa B (IkBα), Matrix metalloproteinase 9 (MMP-9), Suppressor of cytokine signaling-3 (SOCS-3), Protein kinase C (PKCβII), Phosphotyrosine phosphatase -1B (PTP-1B), Glycogen synthase kinase 3 beta (GSK-3β), Inhibitor kappa kinase (IKKβ), C-jun amino terminal kinase (JNK-1) and amount of Insulin receptor (IR-β) and p-IRβ in MNC and plasma concentrations of C-reactive protein (CRP), Monocyte chemoattractant protein -1 (MCP-1), Plasminogen activator inhibitor -1 (PAI-1), TNFα and Regulated upon activation Normal T cell Expressed and Secreted (RANTES). Adipose tissue samples will be processed and analyzed for intranuclear NFkB binding, the expression and concentration of TLR-4,TNFα, IkBα, MMP-9, SOCS-3, PKCβII, PTP-1B, GSK-3β, IKKβ, JNK-1 and amount of IR-β and p-IRβ.

Clinical and Laboratory Procedures

1. **Plasma glucose, glucagon, C-peptide, GLP-1, GIP and FFA measurements:** Glucose levels will be measured in plasma by YSI 2300 STAT Plus glucose analyzer (Yellow Springs, Ohio) (CV 2% for both intra and inter-assay). Free fatty acid levels will be measured by a colorimetric assay (Wako, Richmond, VA). CBC and comprehensive metabolic panel will be measured using well established assays by the clinical laboratory. C-peptide will be measured with Ultrasensitive ELISA kit (LOD is 2.5 pg/ml with 3.8% and 5.8% intra and inter-assay CVs) (Mercodia, NC). GLP-1 (8% and 7% CVs), GIP (2-6% and 3-8% CVs) and glucagon (<5% and <10% CVs) will be measured from samples collected in protease and DPP-IV inhibitors by ELISA kits form Millipore.
2. **Fat aspiration procedure:** Adipocytes will be harvested from the subjects by methods previously described in literature (21; 22). Subcutaneous fat tissue aspiration will be performed on abdomen at a 10 cm distance from umbilicus. The subjects will not have taken aspirin or NSAIDS in the last 72 hours. If that is the case, then the procedure will not be done. The skin will first be prepared with povidone-iodine (Betadine) and alcohol. A sterile drape will be placed around the appropriate area. 3 cc of 1% lidocaine will then be administered subcutaneously. After adequate anesthesia has been achieved, approximately 20-50cc of 0.5% lidocaine will be injected in the adipose tissue. Dose of lidocaine will not exceed 4.5mg/kg body weight. Aspiration of fat tissue will then be performed with a 3-holed canula (Tulip Instrumentation, length: 15cm, diameter: 2.1mm) fixed to a 10mL syringe. More than one attempt at aspiration can be done at the same site during the procedure to get adequate sample. After getting adequate fat tissue (500mg-3g), the puncture site will be pressed for at least ten minutes before the patient rises up from supine position (to minimize bruising). The study subjects will then be discharged home. The adipose tissue will be centrifuged to remove blood and fluid contaminants. The upper adipose tissue will be collected into a separate sterile tube, washed twice with cold sterile Phosphate Buffered Saline (PBS) and centrifuged to remove the PBS. The adipose tissue sample will be weighed and approximately 500 mg transferred to a separate tube for analysis. Total RNA, nuclear extracts and total cell lysates will be prepared from the adipose tissue.
3. **MRI and DEXA**: Multislice MRI of abdomen will be obtained(23). Abdominal subcutaneous adipose tissue, hepatic fat and intra-abdominal adipose tissue (adipose

tissue in the intra-abdominal cavity delineated at the innermost aspect of the abdominal and oblique muscle walls surrounding the cavity and the anterior aspect of the vertebral body. MRI images will be analyzed in a blinded fashion using customized software (24).MRI measurements will be expressed as volume in cm^3. All measurements will be done at one center, by the same machine and using the same software. The coefficient of variation of MRI measured abdominal subcutaneous fat is 1-2% and of visceral fat is 3-6%(25; 26). DEXA will used to measure lean body mass. Adipose tissue mass will be calculated by subtracting lean body mass from total body mass. Adipose tissue mass will be expressed as kilograms. All measurements will be done at one center and by the same machine using the same software. The within-center variability over time in measurement by DEXA of lean mass is 0.9% and of fat mass is 1.2% (27).

4. **24 Hr Blood Pressure monitoring**: Ambulo 2400 24-hour Ambulatory Blood Pressure Monitoring (ABPM) system from Tiba Medical will be used.
5. **Brachial flow-mediated dilatation (FMD)**: FMD is the capacity of blood vessels to respond to an increase in flow, or more precisely shear stress, by dilating. Endothelium-derived nitric oxide is a principal mediator of FMD. A 7.5 – 10 MHz broadband multi-frequency linear array transducer will be used to acquire images. The subject is positioned supine with the arm in a comfortable position for imaging the brachial artery. To create a flow stimulus, a blood pressure cuff is placed on the forearm. After acquiring a baseline rest image, arterial occlusion is created by cuff inflation to suprasystolic pressure. To occlude arterial inflow for a standardized length of time, the cuff is inflated to at least 50 mm Hg above systolic pressure. The resultant ischemia triggers dilatation of downstream resistance vessels via autoregulatory mechanisms. Following 5 minutes of occlusion, the cuff is deflated. This results in reactive hyperemia (a brief high-flow state) in the brachial artery to accommodate the dilated resistance vessels. The shear stress that results causes dilatation of the brachial artery. The recording of the arterial image is done continuously from 30 seconds before to 2 minutes following cuff deflation(28). This procedure has been utilized in several studies carried out in our unit, including the first studies describing abnormalities in African Americans(29), brachial reactivity improvements related to reversal of oxidative stress in the obese and type 2 diabetics following troglitazone(30) and gender differences in brachial reactivity and the effect of hormone replacement therapy (HRT) in post-menopausal women(31).
6. **Questionnaires:** The 36-item short form health survey version 2(SF-36, RAND corporation, Santa Monica, CA) will be used to measure quality of life. Depression will be assessed by the Patient Health Questionnaire (PHQ) Depression Measure (Pfizer Inc, New York, NY).(32; 33)
7. **MNC isolation:** Blood samples will be collected in Na-EDTA as an anticoagulant. Three and a half mL of anticoagulated blood sample are carefully layered over 3.5 mL of PMN medium (Cedarlane Laboratories, Hornby, ON). Samples are centrifuged and at the end of the centrifugation, two bands separate out at the top of the RBC pellet. The top band consists of MNC, while the bottom consists of PMN. The MNC band is harvested and washed twice with Hank's balanced salt solution (HBSS). This method provides yields greater than 95% pure PMN and MNC suspensions.

8. **NFκB DNA binding activity:** Nuclear NFκB DNA binding activity is measured by EMSA. Nuclear extract is prepared from MNC and adipose tissue by high salt extraction as described by Andrews et al (34). The specificity of the bands is confirmed by supershifting these bands with specific antibodies against Rel-A (p65) and p50 (Santa Cruz Biotechnology, CA) and by competition with cold oligonucleotides. DNA binding activity of NFκB will be adjusted to Oct-1 DNA binding activity to correct for any variable.
9. **Plasma concentrations of inflammatory mediators:** Concentrations of TNFα (CV: 5.3% Intra and 8.1% inter-assay, LD: 0.1pg/ml), MMP-9 (CV: 2.2% Intra and 7.1% inter-assay, LD: 0.156ng/ml), MCP-1 (CV: 5.7% Intra and 5.2% inter-assay, LD: 1.7pg/ml) and RANTES (CV: 3.2% Intra and 8.8% inter-assay, LD: 2.0pg/ml) are measured in plasma using ELISA kits (R&D Systems, MN). CRP concentrations (CV: 3.5% Intra and 5% inter-assay, LD: 0.35ng/ml) will be measured using an ELISA kit from Alpha Diagnostics International Inc. (San Antonio, TX)
10. **ROS generation measurement by chemiluminescence:** Five hundred µL of MNC (2×10^5 cells) are delivered into a Chronolog LumiAggregometer cuvette. Luminol is then added, followed by 1.0 µL of 10 mM formylmethionyl leucinyl phenylalanine (fMLP). Our method **(CV intra= <6% and intra= <9%),** developed independently is similar to that published by Tosi and Hamedani (35).
11. **15-isoprostane F_{2t}** (also known as 8-epi-PGF2α or 8-iso-PGF2α) in urine samples will be measured by an ELISA kit from Oxford Biomedical Research (Oxford, MI).
12. 7%$56 **will be measured using the a commercial kit (CVs, intra=6.4% and inter= 8.6%) from Zeptometrix (Buffalo, NY)**
13. **Quantification of TLR-4, IκBα, TNFα, MMP-9, SOCS-3, PKC-β II, IR-β, PTP-1B, GSK-3β IKKβ and JNK-1 mRNA, IRβ and pIRβ in MNC by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR):** Total RNA is isolated from MNC and adipose tissue using commercially available RNAqueous®-4PCR Kit (Ambion, Austin,TX) The quality and quantity of the isolated RNA is determined before using the RNA. Real Time RT-PCR is performed using Cepheid Smart Cycler (Sunnyvale, CA) in which 2 µL cDNA, 10 µL Sybergreen Master mix (Qiagen, CA) along with 0.5 µL of 20 µM gene specific primers (Life Technologies, MD) are used. The specificity and the size of the PCR products are tested by adding a melt curve at the end of the amplifications and by running it on a 2% agarose gel. All values are normalized to 18S expression.
14. **Western blotting of TLR-4, IκBα, IKKβ, IR-β, p-IR-β, JNK-1, SOCS-3, PKC-β II, GSK-3β and PTP-1B:** MNC and adipose tissue total cell lysates will be prepared lysis buffer. Sixty µg of total cell lysate are boiled in SDS buffer and proteins separated by SDS-PAGE and then transferred to PVDF membrane. Polyclonal or monoclonal antibodies against, TLR-4,IκBα, IKKβ, IR-β, p-IR-β, JNK-1, SOCS-3, PKC-β II, GSK-3β and PTP-1B are used and the membranes are developed using super signal, chemiluminescence reagent (Pierce Chemical, IL). Densitometry is performed using molecular analyst software (Biorad, CA) and all values are corrected for loading with actin.

10.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response: The following data will be collected during the conduct of the study based on the study design and protocol: HbA1c, fructosamine, average glucose, percent time spent in different glycemic thresholds, standard deviations which represent the variability in blood glucose, total insulin doses (basal dose, bolus dose and total daily dose), changes in carbohydrate intake and helpings; adverse events(including the most common side effects of nausea and vomiting which is often transient occurring at the time of initiation of liraglutide and at the time of escalation of the dose and the rare occurrence of pancreatitis, thyroid c-cell tumors and other patient reported adverse events which may occur anytime) and blood pressure. The principal investigator Paresh Dandona, MD, PhD and co-investigators Husam Ghanim, PhD and Antione Makdissi, MD will review the data every 3 months to assess the safety of the participants. Furthermore they will also assess other risks including the physical, psychological, social, legal and economic harm to these patients. The investigators listed above will carefully watch for any invasion of privacy and breach of confidentiality. The principal investigator will be sharing the results of safety analysis of the study with the sponsor (JDRF) and to the IRB. The study groups will remain blinded. If there are any safety concerns then co-investigator Husam Ghanim, PhD who is not directly involved with the patients and or in insulin titrations of the study participants will unblind the study groups on the discretion of principal investigator and the team will assess potential harm to the patients and inform the IRB and sponsor of this potential harm. The corrective actions will then be taken and research subjects will be withdrawn from the study if risks outweigh the benefits. The IRB will be kept well-informed at all times. During each patient visit, evolution of glucose levels (CGM) will be conducted to reduce the risk of hypoglycemia or hyperglycemia. After recruitment and completion of half of the target number of patients i.e. 42 patients, interim analysis will be performed to determine an overwhelming harms or benefits with one treatment option compared to another.

10.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response: Source documents will be used to collect patient information. Patients CGM, dietary intake, BP, weight are monitored every visit to ensure safety. CGM graphs will be evaluated every visit.

10.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: electronic medical records and research files.

10.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be

shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.

Response: Individual participant lab results will be disclosed to the participant upon their request. If the participant requests documentation be shared with another physician, physician office or hospital the participant must come to the research center to collect said documentation or the documentation can be mailed to their given home address.

10.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.

Response: Not Applicable. Study results will not be shared with the subjects. However, unidentifiable study results could be published in the form of a manuscript or abstract and will be reported to JDRF and to clinicaltrilas.gov.

11.0 Study Timelines

11.1 Describe the anticipated duration needed to enroll all study subjects.

Response: 48 months

11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response: After the screening visit, subjects who meet the inclusion and exclusion criteria, will be assigned a number and randomized to receive subcutaneous injection daily of either Liraglutide (42 subjects) or placebo (42 subjects) for 26 weeks. Total participation period will be 28 weeks including 2 weeks run in period before starting drug intervention.

11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response: 60 months

12.0 Setting

12.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response: Research will be conducted at the Diabetes Endocrinology Research Center of WNY, located at 1000 Youngs Road, Suite 105, Williamsville NY 14221 and at the CTRC located in 875 Ellicott St. Buffalo NY14203. The Diabetes Research Center has facilities and exam rooms available for insulin pump download, CGM device download, meal and infusion studies and presence of

study coordinator and registered nurse for data collection and blood work at all times. One of the investigators will be available at all times to address patients' related issues. CTRC location is a fully equipped laboratory with equipment include ultra-low freezers for sample storage, centrifuges, microscopes for sample preparation, infusion pumps, ELISA, PCR and immunoblotting instrumentation.

12.2 For research conducted outside of UB and its affiliates, describe:

- Site-specific regulations or customs affecting the research
- Local scientific and ethical review structure

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response:

☒ **N/A:** This study is not conducted outside of UB or its affiliates.

13.0 Community-Based Participatory Research

13.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response:

☒ **N/A:** This study does not utilize CBPR.

13.2 Describe the composition and involvement of a community advisory board.

Response:

☒ **N/A:** This study does not have a community advisory board.

14.0 Resources and Qualifications

14.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually

require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response: All study personnel are educated, trained, and licensed as required for their delegated role in this study. All study personnel have also received the required university training and will be trained by the PI before the study starts.

Describe other resources available to conduct the research.

14.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response: The principal investigator supervises the research project and weekly research meetings are conducted to discuss the recruitment rate, resolve and discuss issues related to the conduct, safety, analysis of the study and related publications. PI is expected to spend 5% of his academic time on this research. The co-investigators and study coordinator provide coverage to the research related activity for 365 days a year.

14.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response: Available medical literature will be provided as deemed appropriate or requested by patient through UB libraries, Pubmed, Google scholar as all the investigators have access to medical literature through listed resources above

The patient will also have access to physician (Investigators and Co-Investigators) who will be available to address any adverse effects or other questions during the course of the study who will be available to address any adverse effects or other questions during the course of the study

14.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: Education through training, meetings, conferences and discussions.

15.0 Other Approvals

15.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response:

☒ **N/A:** This study does not require any other approvals.

16.0 Provisions to Protect the Privacy Interests of Subjects

16.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response: Our clinical providers involved in the study will identify potential patients for recruitment from the Diabetes-Endocrinology Center of WNY Clinics according to the inclusions and exclusion criteria and through advertisements. Patient who qualify will be asked in private during their one on one consultation time with the physician if they wish to participate in the research study. If the patient agrees, the research coordinator will contact them for a telephone screening privately. The patients who call for potential participation in the study due to advertisement flyers will be screened over the phone with the research coordinator, using our telephone screening form.

When the patient is being seen at our clinics for the first time they sign the "Consent to use and disclosure of protected health information" form which clearly states that their protected health information (PHI) can be used for review in preparation for possible research.

If the patient passes the telephone screening, they will be asked to make an appointment to review and sign the consent. Patient will do this in a private, screen off area of the research department and will be allowed to discuss the consent in detail with the research coordinator and or study doctor. Patient will be no notified that it is completely voluntary to participate in the research study and can withdraw at any time.

We will not be accessing any medical information of the patients for whom the services are not provided by our clinic providers.

16.2 Indicate how the research team is permitted to access any sources of information about the subjects.

NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question **does apply** to records reviews.

Response: Consent of the subject and partial HIPAA waiver.

17.0 Data Management and Analysis

17.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response: The focus of the proposed research is to evaluate the effect of liraglutide on mean HbA1c% over the period of 26 weeks of treatment. The similarities between the study groups, baseline values for subject's demographics and study endpoints will be compared using appropriate parametric tests. Transformations of the data in order to meet statistical assumptions may be considered. The **primary endpoint** of the study is to detect

a difference in HbA1c after 26 weeks of treatment with Liraglutide or placebo. The statistical analysis will be carried out using analysis of covariance (ANCOVA) and tested at the 0.05 level. Change in weight will be a covariate. The results will be computed as mean ± SD. Analysis will be carried out on the basis of intention to treat (with last observation carried forward).

The secondary end points based on glycemic changes will include the difference from baseline in mean weekly glucose concentrations, standard deviations of the mean weekly glucose concentrations, HbA1c, fructosamine, the duration of time spent in hyperglycemia (>150mg/dl, > 200mg/dl, > 250mg/dl) and hypoglycemia (< 70mg/dl, < 40mg/dl), insulin dosage. A reduction in the AUC following the meal will constitute another secondary end point. Between groups comparisons of the magnitude of change from baseline will also be made for these glycemia related secondary endpoints using student's t-test. Comparisons for these and the primary endpoints will also be made using the paired t-test or Wilcoxson's test for paired data within each group.

The other secondary end-points of the study will be change from baseline after 26 weeks of treatment in the fasting and postprandial blood sugars, glucagon and C-peptide concentrations, indices of oxidative and inflammatory stress in MNC, plasma and adipose tissue; subcutaneous fat mass, hepatic fat content and visceral fat mass; features of metabolic syndrome; gastric emptying, blood pressure, vascular analysis, patient reported nausea, quality of life and depression scores. Between groups comparisons will be made using students t-test or ANCOVA (adjustment will be done for baseline differences). Within group comparisons for these endpoints will be made using paired t-test or Wilcoxon's test or ANCOVA.

17.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response: There are no prior randomized controlled trials that have examined the effect of Liraglutide on HbA1c in subjects with type 1 diabetes. In our observational study (preliminary data), we found a decrease in HbA1c of 0.35% after 6 months of liraglutide in patients with type 1 diabetes who had a mean HbA1c of 6.45±0.5%. In our proposed study, we will include patients with HbA1c up to 8.5%. Thus we expect a greater difference in HbA1c among the two groups at the end of the study. Conservatively estimating a difference in HbA1c of 0.35% between the two groups, a sample size of 32 patients per treatment group should provide 80% power to detect a significant difference ($\alpha = 0.05$), provided the standard deviation of the residuals is not greater than 0.5. Thus 64 subjects will be needed for the study. To account for a dropout rate of 30%, we will recruit 84 subjects into the study.

17.3 Describe any procedures that will be used for quality control of collected data.

Response: Three investigators and research nurse will double check the accuracy of collected data. All laboratory testing will be standardized using references and standards.

18.0 Confidentiality

A. Confidentiality of Study Data#

Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.

18.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.

Response: All patients' data records will be stored on password protected computers and or in locked cabinets within the research department. The research unit is locked after 5pm daily and all day on weekends. Identifiable patient information along with randomization information for each patient will be stored in locked cabinets in an locked archive room. This will only be accessible by study coordinator and the PI. Electronic data will be stored on password protected computers as coded data based on randomization number eg R-12 without any patients identifiable information attached. These electronic files will only be accessible by authorized study personnel.

18.2 A. How long will the data be stored?

Response: Data and specimens storage has no expiration date and will be stored for a minimum of 7 years. The researchers may continue to rely on this for future use in research study

18.3 A. Who will have access to the data?

Response: Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens

18.4 A. Who is responsible for receipt or transmission of the data?

Response: Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens and can handle transfer of data and samples

18.5 A. How will the data be transported?

Response: All data are stored at one location and is not transported unless it is being archived. At that point files will be transferred to Iron Mountain for storage and archiving. Samples that are transported will be done so using dry ice in a properly labeled Styrofoam container by the laboratory technician.

B. Confidentiality of Study Specimens

Describe the local procedures for maintenance of confidentiality of **study specimens**.

☐ **N/A:** No specimens will be collected or analyzed in this research. (Skip to Section 19.0)

18.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response: The specimens will be stored in the CRC laboratory located at 1000 Youngs Road, Suite 105, Williamsville NY 14221 and at the CTRC located in 875 Ellicott St. Buffalo NY14203. Samples will be stored in a locked -80^{o} C freezers. Ultimately, all specimens will be transported to CTRC location for banking. Specimens will be labeled as a coded sample, using the patient's randomization number (e.g. R-12), visit time and number and sample type. Specimens will not be stored with any patient identifiable information which is kept in locked cabinets in the CRC at Youngs Rd.

18.7 B. How long will the specimens be stored?

Response: Data and specimens storage has no expiration date and will be stored for a minimum of 7 years. The researchers may continue to rely on this for future use in research study

18.8 B. Who will have access to the specimens?

Response: Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens.

18.9 B. Who is responsible for receipt or transmission of the specimens?

Response: Those physicians, nurses, and laboratory staff that are on all documentation for the study will have access to the data and specimens and can handle transfer of data and samples

18.10 B. How will the specimens be transported?

Response: All data are stored at one location and is not transported unless it is being archived. At that point files will be transferred to Iron Mountain for storage and archiving. Samples that are transported will be done so using dry ice in a properly labeled Styrofoam container by the laboratory technician

19.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments

that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

19.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: The principal investigator Paresh Dandona, MD, PhD and co-investigators Husam Ghanim, PhD and Antione Makdissi, MD will review the data every 3 months to assess the safety of the participants. Furthermore they will also assess other risks including the physical, psychological, social, legal and economic harm to these patients. The investigators listed above will carefully watch for any invasion of privacy and breach of confidentiality. The principal investigator will be sharing the results of safety analysis of the study with the sponsor (JDRF) and to the IRB. The study groups will remain blinded. If there are any safety concerns then co-investigator Husam Ghanim, PhD who is not directly involved with the patients and or in insulin titrations of the study participants will unblind the study groups on the discretion of principal investigator and the team will assess potential harm to the patients and inform the IRB and sponsor of this potential harm. The corrective actions will then be taken and research subjects will be withdrawn from the study if risks outweigh the benefits. The IRB will be kept well-informed at all times. During each patient visit, evolution of glucose levels (CGM) will be conducted to reduce the risk of hypoglycemia or hyperglycemia. After recruitment and completion of half of the target number of patients i.e. 42 patients, interim analysis will be performed to determine an overwhelming harms or benefits with one treatment option compared to another.

19.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: Patients CGM, dietary intake, BP, weight are monitored every visit to ensure safety. CGM graphs will be evaluated every visit to reduce risk of hypoglycemia or hyperglycemia. Other adverse events (including the most common side effects of nausea and vomiting, injection site allergic reaction and the rare occurrence of pancreatitis, thyroid c-cell tumors and other patient reported adverse events) will be collected.

19.3 Describe any safety endpoints.

Response: Frequency and severity of hypoglycemia.

19.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: The safety information will be collected at the time of the participants visit, and or during telephone calls with the participant

19.5 Describe the frequency of safety data collection.

Response: The data collection will be done at all study visits which will be at intervals of either one or two weeks depending on the number of study visit. The patients, however, will be asked to report any adverse event or safety related information via phone as soon as it occurs and it will be reviewed the same day.

19.6 Describe who will review the safety data.

Response: The principal investigator Paresh Dandona, MD, PhD and co-investigators, Antione Makdissi, MD and Husam Ghanim, PhD will review the data at the completion of all visits by each subject and every 3 months to assess the safety and any potential risks to the participants. Furthermore they will also assess other risks including the physical, psychological, social, legal and economic harm to these patients. The investigators listed above will carefully watch for any invasion of privacy and breach of confidentiality. The principal investigator will be sharing the results of safety analysis of the study with the sponsor (JDRF) and with the IRB. The study groups will remain blinded. If there are any safety concerns then co-investigator Husam Ghanim, PhD who is not directly involved with the study participants will unblind the study groups on the discretion of principal investigator and the team will assess potential harm to the patients and inform the IRB and sponsor of this potential harm. The corrective actions will then be taken and research subjects will be withdrawn from the study if risks outweigh the benefits. The IRB will be kept well-informed at all times.

19.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: Safety data will be reviewed every 3 months. Study endpoint data will be reviewed once after half of the recruited patients have completed the study and then at the end of the study

19.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: The statistical analysis will be carried out using student t-test, Chi-square and Wilcoxson's test for paired data

19.9 Describe any conditions that trigger an immediate suspension of the research.

Response:

1- New information about the safety of the used drug (Victoza) – liraglutide
2- Sponsor suspension of the funds.
3- Significant high incidence of SAE and events leading to withdrawal of subjects determined based on the continuous review by the investigators.

20.0 Withdrawal of Subjects

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

20.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.

Response: Pregnancy, DKA, severe and frequent hypoglycemia and drug intolerability (severe nausea and/or vomiting) developing any of the exclusionary condition listed in the inclusion and exclusion criteria.

The principal investigator of the study can remove a participant from the research study without their approval if for any reason he/she feels is appropriate, including: severe side effect, injury or medical condition which may place the patient at risk of further complications if patient continues to participate, failure to take the medication as instructed, failure to keep your scheduled appointments, cancellation of the study by the sponsor, or other administrative reasons.

Participation in this research study is voluntary. Subjects have the right to refuse to participate or to withdraw from participation at any time for any reason. Refusal to participate or withdrawal from the study will involve no penalty or loss of entitled benefits, nor affect the subjects ongoing medical care

20.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: If a subject withdraws from the research, the data collected to that point will be used toward the research finding. If applicable the subject will have to bring back any unused research drug and or device. If necessary, they will be asked to complete an end of study visit for their safety.

20.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: If a subject withdraws from the research, the data collected to that point will be used toward the research finding. Patients are allowed to withdraw from some procedures while continuing to participate in the study (take study medication). Efficacy and safety data will continue to be collected for the parts of study that patients agree to participate in.

21.0 Risks to Subjects

21.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response:

Subjects who experience severe nausea or vomiting after starting liraglutide will discontinue the study. Those with mild or moderate nausea will continue for at least one more week. If they continue to experience significant nausea (defined as interfering with normal activities), they will discontinue the study.

Subjects who develop pancreatitis will be withdrawn from the study.

Subjects who develop a new thyroid tumor during the study will be withdrawn. Patients will be informed that they should let study investigators know if they develop any swelling in the neck.

For the entire duration of the study, the patients will maintain a diary to record any hypoglycemia and other untoward side effects like nausea, changes in appetite and other experiences. Patients will be instructed to call the Diabetes Center to speak to a study investigator directly in case of any problem or untoward side effects. They will be specifically asked to call if they have hypoglycemia (blood sugar <70 mg/dl) or hyperglycemia (blood sugar >250 mg/dl) on more than one occasion. The target blood glucose during the study will be between 70-180mg/dl at all times, without increasing the incidence of blood glucose < 70mg/dl.

The following Information from the boxed warning in the package insert regarding the risk of thyroid c-cell tumors will be discussed in details with all participating subjects:

"Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors."

In addition, the following FDA text regarding the risk of developing fibrosarcomas will be discussed with all participating subjects

“In a 2-year repeat subcutaneous dose carcinogenicity study of liraglutide injected once a day in CD-1 mice, a treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10 times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL)”.

21.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response: For the entire duration of the study, the patients will maintain a diary to record any hypoglycemia and other untoward side effects like nausea, changes in appetite and other experiences. Patients will be instructed to call the Diabetes Center to speak to a study investigator directly in case of any problem or untoward side effects. They will be specifically asked to call if they have hypoglycemia

(blood sugar <70 mg/dl) or hyperglycemia (blood sugar >250 mg/dl) on more than one occasion. Insulin doses will be titrated to target blood sugars between 70-180 mg/dl at all times without increasing the incidence of blood glucose < 70mg/dl. The following Information from the boxed warning in the package insert regarding the risk of thyroid c-cell tumors will be discussed in details with all participating subjects.

21.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.

Response: Any adverse effects of Liraglutide that are not currently known or those unique to their use in Type 1 diabetes may be some of the unforeseeable risks.

21.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: Not applicable, we will not be enrolling pregnant participants or who may become pregnant or with in child baring years without signing the consent stating they will use at least two forms of birth control. If a participant becomes pregnant they will be withdrawn from the study immediately

21.5 If applicable, describe risks to others who are not subjects.

Response: Not applicable, there is no risk to others not participating in this study

22.0 Potential Benefits to Subjects

22.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

NOTE: Compensation **cannot** be stated as a benefit.

Response: There are no potential benefits individual participants will experience

23.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

23.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.

Response: Routinely, Buffalo General Hospital, Erie County Medical Center, and/or the University at Buffalo, State University of New York, its agents, or its employees do not compensate for or provide free medical care for human subjects/participants in the event that any injury results from participation in a human research project. In the unlikely event that they become ill or injured as a direct result of participating in this study, they may receive medical care, that will be covered by study.

23.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.

Response: No contract injury language available.

24.0 Economic Burden to Subjects

24.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response: All research expenses will be covered. Participants will not be subjected to any out of pocket cost.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

25.0 Compensation for Participation

25.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response:
700.00 after completion of all study visits and procedures:-

- $50 for study visit day 1,
- $50 for each fat biopsy,
- $50 for each meal challenge,
- $50 for each 24 hour blood pressure monitoring
- $25 for blood draw (week 12)
- $15 for each urine sample
- $15 per visit (for visits 1, 2, 4, 8, 16, 20 and 24)
- $15 for each DEXA scan
- $25 for each MRI
- $15 for each brachial reactivity study

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

26.0 Consent Process

26.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.

☒ **Yes** (If yes, Provide responses to each question in this Section)
☐ **No** (If no, Skip to Section 27.0)

26.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response: All participants will come to the research department to be consented. Participants will be placed in a private, screened off area and or room where they can review the consent. Participant questions and or concerns will be address with a member of the study team or research doctor if applicable. The research coordinator will discuss in length the participants requests for privacy of their PHI.

26.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: participants will be made aware that participating in research is completely voluntary, and they may withdraw at any time with no consequence to their routine clinic care. If the patients requires time to decide and or discuss partaking in a research study, the subject will be given said time.

26.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: The research coordinator and study team are available to answer any question or concerns with the patient during the duration of the research trial. At each study visit, the patient is asked a series of questions to ensure they are on task with the study visits and feel comfortable. Upon departing from their study visit, the patients are told of their next visit and given detail instruction for their next visit. If study is revised or amendment or new information becomes available about drug safety that may affect patients participation, the patient may be re-consented to ensure patient ongoing consent,

26.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- The role of the individuals listed in the application who are involved in the consent process
- The time that will be devoted to the consent discussion
- Steps that will be taken to minimize the possibility of coercion or undue influence
- Steps that will be taken to ensure the subjects' understanding

Response:

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

☒# **N/A:** This study will not enroll Non-English speaking subjects. (Skip to Section 26.8)

26.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.

Response:

26.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response:

Cognitively Impaired Adults

☒ **N/A**: This study will not enroll cognitively impaired adults. (Skip to Section 26.9)

26.8 Describe the process to determine whether an individual is capable of consent.

Response:

Adults Unable to Consent

☒ **N/A**: This study will not enroll adults unable to consent. (Skip to Section 26.13)

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10) **and, where possible, assent of the individual should also be solicited** (Sections 26.11 and 26.12).

26.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

26.10 **For research conducted outside of New York State**, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response:

26.11 Describe the process for **assent of the adults**:

- Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.

Response:

- If assent will not be obtained from some or all subjects, provide an explanation of why not.

Response:

26.12 Describe whether **assent of the adult** subjects will be documented and the process to document assent.

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☒ **N/A**: This study will not enroll subjects who are not yet adults. (Skip to Section 27.0)

26.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under**

the age of 18 years). For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response:

26.14 **For research conducted outside of New York State**, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response:

26.15 Describe whether parental permission will be obtained from:

Response: N/A

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

26.16 Describe whether permission will be obtained from individuals **other than parents**, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.

Response:

26.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.

Response:

26.18 When assent of children is obtained, describe how it will be documented.

Response:

27.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ **N/A:** A waiver or alteration of consent is not being requested.

27.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

27.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

28.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 29.0)

28.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response:

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

29.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

29.1 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as:

- All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.
- All required approvals have been obtained at each site (including approval by the site's IRB of record).
- All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites will safeguard data as required by local information security policies.
- All local site investigators conduct the study appropriately.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Response:

29.2 Describe the method for communicating to engaged participating sites:

- Problems
- Interim results
- Study closure

Response:

29.3 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response:

29.4 If this is a multicenter study for which UB will serve as the IRB of record, and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.

Response:

30.0 Banking Data or Specimens for Future Use

☐ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

30.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the

data/specimens will be accessed, and who will have access to the data/specimens.

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

Response: The study electronic data will be stored in a locked closet and password protected computers located in our research locations in Youngs Rd and CTRC. Data is backed up by university on daily bases. Specimens will be stored in -80 freezer at our CTRC research laboratory at 875 Ellicott St. 14203 for at least 7 years. Samples and electronic data will be labeled as a coded sample, using the patient randomization number (e.g. R12) and visit time and date. Electronic data and specimens will not be identifiable.

The research staff (study personnel including coordinator) only will be authorized to access data and or specimens

30.2 List the data to be stored or associated with each specimen.

Response: Patient ID number, study visit information and date of collection will be stored with specimen. Other data stored will include record files of all patients participating in the study, including data collection sheets, lab results, CGM and insulin pump data.

30.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: The copy of the individual patient data collected during the study period will be provided to these individual patients who can choose to hand carry it to their respective physicians and a copy will be faxed to their respective clinical providers upon verbal request from the patient. The data provided will include the insulin pump or CGM data or any of the lab results obtained during the study period. The results of the completed study will be made available to the patients if requested through published manuscript.

31.0 Drugs or Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

31.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.

Response:

Investigational product	Dosage form and strength	Approval status	Manufacturer

Liraglutide 1.2mg-1.8mg	Pen Injection	Approved for type 2 diabetes	Novo Nordisk
Matching placebo for Liraglutide 1.2 mg-1.8mg	Pen Injection	N/A	Novo Nordisk

31.2 Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: Drugs will be stored in a locked cabinet and temperature controlled refrigerator at 4C at the research facility of the Diabetes and Endocrinology Center of WNY.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

31.3 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: IND holder: Dr Paresh Dandona. FDA has issued IND exempt and this is on file with IRB

31.4 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	**IND Studies**	**IDE studies**	**Abbreviated IDE studies**
21 CFR 11	**X**	**X**	
21 CFR 54	**X**	**X**	
21 CFR 210	**X**		
21 CFR 211	**X**		
21 CFR 312	**X**		
21 CFR 812		**X**	**X**
21 CFR 820		**X**	

Response: All FDA sponsor requirements have been reviewed and will be followed during the study procedures.

32.0 Humanitarian Use Devices

☒ **N/A:** This study does not involve humanitarian use devices. This does not apply.

32.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response:

32.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: