PROTOCOL TITLE:

Include the full protocol title.

Response: **Liraglutide in Type 1 Diabetes**

PRINCIPAL INVESTIGATOR:

Response:

Principal Investigator:	**Paresh Dandona, MBBS, PhD**
Co- Investigators:	**Husam Ghanim, PhD**
	Antoine Makdissi, MD

Paresh Dandona, M.B.B.S., Ph.D., F.R.C.P, F.A.C.P, F.A.C.C, FACE,

SUNY Distinguished Professor,
Director, Diabetes-Endocrinology Center of Western NY

Chief of Endocrinology, Diabetes, Endocrinology and Metabolism, SUNY at Buffalo

1000 Youngs Road, Suite 105, Williamsville NY 14221

Telephone: (716) 535-1850

Fax: 716-639-1200

E-mail: pdandona@kaleidahealth.org

VERSION:

Include the version date or number.

Response: 10/04/2018

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: National Institutes of Health (NIH)

Complete Research Protocol (HRP-503)

Table of Contents

Template Instructions

Sections that do not apply:

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
    - *If an N/A checkbox is present, select the appropriate justification from the list.*
    - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
    - *For research where the only study procedures are records/chart review: Sections 19, 20, 22, 23, 24, 25, 31, and 32 do not apply.*
    - *For exempt research: Sections 31 and 32 do not apply.*

Studies with multiple participant groups:

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

  Response:

  Intervention Group:

  Control Group:

Formatting:

- *Do not remove template instructions or section headings when they do not apply to your study.*

If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.

Amendments:

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

PROTOCOL TITLE:

Include the full protocol title.

Response: **Liraglutide in Type 1 Diabetes**

PRINCIPAL INVESTIGATOR:

Response:

Principal Investigator:	**Paresh Dandona, MBBS, PhD**
Co- Investigators:	**Husam Ghanim, PhD**
	Antoine Makdissi, MD

Paresh Dandona, M.B.B.S., Ph.D., F.R.C.P, F.A.C.P, F.A.C.C, FACE,

SUNY Distinguished Professor,
Director, Diabetes-Endocrinology Center of Western NY

Chief of Endocrinology, Diabetes, Endocrinology and Metabolism, SUNY at Buffalo

1000 Youngs Road, Suite 105, Williamsville NY 14221

Telephone: (716) 535-1850

Fax: 716-639-1200

E-mail: pdandona@kaleidahealth.org

VERSION:

Include the version date or number.

Response: 10/04/2018

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: National Institutes of Health (NIH)

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 Research Center of WNY

Location: 1000 Youngs Road

Suite 105

Williamsville NY 14221

Department: Diabetes Endocrinology

1.0 Objectives

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

Response:

Specific Aims:

The control of glucose homeostasis in subjects with type 1 diabetes is fragile since exogenous insulin cannot compensate for changing requirements and is not precise either in terms of the dose or the bio-availability of the insulin injected. Furthermore, in the near total absence of insulin secretion, the physiological post prandial inhibition of glucagon secretion by the α-cell is also probably deficient in all patients with type 1 diabetes. Thus, there is a need for therapies beyond insulin that can further improve glycemic control and reduce fluctuations in glucose in these subjects. We have recently shown that Liraglutide, a glucagon like peptide (GLP)-1 analogue with duration of action of 24 hours, when added to insulin in subjects with **well controlled type 1 diabetes** reduces mean and standard deviation of blood glucose, HbA1c and insulin requirements. Since C-peptide concentrations did not alter following Liraglutide, it is likely that the suppression of glucagon may have contributed to this effect. The glucose lowering effects of GLP-1 agonists are well established in subjects with type 2 diabetes, however, these have not been studied prospectively in subjects with type 1 diabetes. We have, therefore, designed this study to investigate the **central hypothesis** that in patients with type 1 diabetes, Liraglutide has a glucose lowering effect. A major secondary objective of this study is to elucidate the mechanisms responsible for its glucose lowering effects and those involved in reducing the insulin dose. The **specific aims** of this proposal are:

Hypothesis 1: Treatment with Liraglutide in patients with type 1 diabetes decreases HbA1c, fasting, postprandial and the overall mean glucose concentrations while decreasing the dose of insulin required.

Aim 1.1: To compare the HbA1c, mean fasting, glucose, mean weekly glucose, standard deviation of weekly blood glucose concentrations as recorded by continuous glucose monitoring and the dose of insulin required prior to and following 52 weeks of treatment with liraglutide daily.

Aim 1.2: To compare the postprandial glucose concentrations following a test meal before and after 52 weeks of treatment with liraglutide daily.

Hypothesis 2: Treatment with Liraglutide in patients with type 1 diabetes decreases basal and postprandial glucagon concentrations and increases basal and postprandial C-peptide concentrations.

Aim 2.1: To compare the basal and postprandial glucagon and C-peptide concentrations following a test meal before and after 52 weeks of treatment with liraglutide daily.

Hypothesis 3: Treatment with Liraglutide in patients with type 1 diabetes delays gastric emptying.
Aim 3.1: To compare the gastric emptying as measured by acetaminophen absorption before and after treatment with liraglutide.

Hypothesis 4: Treatment with Liraglutide in patients with type 1 diabetes improves treatment satisfaction and quality of life.
Aim 4.1: To assess treatment satisfaction and estimate preference weighted treatment satisfaction score using components of a previously validated Diabetes specific Quality of Life Scale (DSQOLS).

Aim4.2: To assess quality of life with validated instruments including DSQOLS and Problem Areas in Diabetes Survey (PAID).

1.2 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 patients with type 1 diabetes decreases HbA1c, fasting, postprandial and the overall mean glucose concentrations while decreasing the dose of insulin required.

Hypothesis 2: Treatment with Liraglutide in patients with type 1 diabetes decreases basal and postprandial glucagon concentrations and increases basal and postprandial C-peptide concentrations.

Hypothesis 3: Treatment with Liraglutide in patients with type 1 diabetes delays gastric emptying.

Hypothesis 4: Treatment with Liraglutide in patients with type 1 diabetes improves treatment satisfaction and quality of life.

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:

The focus of the proposed research is to evaluate the effect of liraglutide on mean weekly glucose concentrations over the period of 52 weeks of treatment. The **primary endpoint** of the study is to detect a difference in HbA1c after 26 weeks of treatment with Liraglutide or placebo.

The **secondary end** points based on glycemic changes will include the difference between the two groups in standard deviations of the mean weekly glucose concentrations, mean fasting and weekly blood glucose concentrations, HbA1c, the duration of time spent in hyperglycemia (>150mg/dl, >

200mg/dl, > 250mg/dl) and insulin dosage. A reduction in the area under curve following the meal will constitute another secondary end point. The other secondary end-points of the study will be the difference between the two groups at 52 weeks following meal challenge in the 1)C-peptide, glucagon, GLP-1 and GIP concentrations, 2) Area under curve of glucose concentrations following meal challenge, and 3) gastric emptying. Between group comparisons of the magnitude of change from baseline will also be made for these glycemia related secondary endpoints. The statistical analysis will be carried out using ANCOVA and tested at the 0.05 level. The relation between change in postprandial sugars, glucagon, GLP-1, GIP-1 and gastric emptying will be studied by regression analysis to evaluate the relative contribution of each of these parameters to the improvement in post-prandial blood sugars. Change in the quality of life with validated instruments including DSQOLS and Problem Areas in Diabetes Survey (PAID) will also constitute secondary endpoint.

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).

Patients with type 1 diabetes can be overwhelmed with burdens of the illness and complications. They can also be equally frustrated by hypoglycemic reactions or glucose fluctuation with treatment regimen. These burdens and frustrations accompanied with worries have significant adverse impact on patient's quality of life. Emotional distress and poor quality of life further correlate with poor adherence to treatment regimen and poor glycemic control. Patient- assessed psychosocial distress and quality of life become important measures in evaluation of new treatment regimen in type 1 diabetes patients.
The diabetes specific quality of life scale (DSQOLS) was developed to measure quality of life of type 1 diabetes patients. It consists of a preference-weighted treatment satisfaction measure and six homogeneous subscales assessing quality of life in the following domains: social relations, leisure time flexibility, physical complaints, worries about future, diet restrictions, and daily hassles. The original DSQOLS was validated in a cross sectional study to assess quality of diabetes care in a representative community level sample of patients with type 1diabetes. The questionnaire took about 10-20 min to complete. All six subscales had high degrees of internal consistency with homogeneity coefficients (Cronbach's α) exceeding 0.7. The validity of the subscales was justified by statistical correlations with the already validated positive well-being scale. Subsequent studies using this questionnaire demonstrated evidence of sufficient discriminant validity of the questionnaire to distinguish between different treatment regimen and evidence of responsiveness to treatments.
The problem areas in Diabetes survey (PAID) questionnaire is a 20-item scale, single factor measure of diabetes related psychosocial distress including frustration, fear, worry, depressed mood, guilt, denial, and desperation. It was validated with key psychometric attributes, including reliability, validity, and responsiveness. These psychometric tests indicate that the PAID questionnaire possesses high internal reliability with Cronbach's α of 0.95. It was significantly associated with other relevant psychosocial measures of distress. It was strongly correlated with clinical variables including regimen adherence, diabetic complications, and glycemic control. It

was also linked to long term glycemic control at over 1 year. It is sensitive to change with diabetes treatment interventions with effect size ranged from 0.32 to 0.64.

This study will evaluate the impact of liraglutide as additional treatment in type 1 diabetes patients on their quality of life and treatment satisfaction. The quality of life will be assessed comprehensively with the DSQOLS and PAID instruments. Each of these instruments consisting of either one or several subscales is psychometrically valid in investigating varied areas of quality of life. Concurrent use of these instruments will allow assessment of a broad range of domains in diabetic patient's life. The treatment satisfaction will be assessed with preference-weighted treatment satisfaction measure components of the DSQOLS

3.2 Include complete citations or references.

Response:

1. Bliss, M. 2005. Resurrections in Toronto: the emergence of insulin. *Horm Res* 64 Suppl 2:98-102.
2. Hahr, A.J., and Molitch, M.E. 2008. Optimizing insulin therapy in patients with type 1 and type 2 diabetes mellitus: optimal dosing and timing in the outpatient setting. *Am J Ther* 15:543-550.
3. Pickup, J.C., and Renard, E. 2008. Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. *Diabetes Care* 31 Suppl 2:S140-145.
4. Bolli, G.B., Kerr, D., Thomas, R., Torlone, E., Sola-Gazagnes, A., Vitacolonna, E., Selam, J.L., and Home, P.D. 2009. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. *Diabetes Care* 32:1170-1176.
5. Unger, R.H., and Orci, L. 2010. Paracrinology of islets and the paracrinopathy of diabetes. *Proc Natl Acad Sci U S A* 107:16009-16012.
6. Lebovitz, H.E. 2010. Adjunct therapy for type 1 diabetes mellitus. *Nat Rev Endocrinol* 6:326-334.
7. Varanasi, A., Bellini, N., Rawal, D., Vora, M., Makdissi, A., Dhindsa, S., Chaudhuri, A., and Dandona, P. 2011. Liraglutide as additional treatment for type 1 diabetes. *Eur J Endocrinol* 165:77-84.
8. Montanya, E., and Sesti, G. 2009. A review of efficacy and safety data regarding the use of liraglutide, a once-daily human glucagon-like peptide 1 analogue, in the treatment of type 2 diabetes mellitus. *Clin Ther* 31:2472-2488.
9. Buse, J.B., Klonoff, D.C., Nielsen, L.L., Guan, X., Bowlus, C.L., Holcombe, J.H., Maggs, D.G., and Wintle, M.E. 2007. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. *Clin Ther* 29:139-153.
10. Kielgast, U., Asmar, M., Madsbad, S., and Holst, J.J. 2010. Effect of glucagon-like peptide-1 on alpha- and beta-cell function in C-peptide-negative type 1 diabetic patients. *J Clin Endocrinol Metab* 95:2492-2496.
11. Kielgast, U., Holst, J.J., and Madsbad, S. Antidiabetic Actions of Endogenous and Exogenous GLP-1 in Type 1 Diabetic Patients With and Without Residual {beta}-Cell Function. *Diabetes* 60:1599-1607.
12. Rother, K.I., Spain, L.M., Wesley, R.A., Digon, B.J., 3rd, Baron, A., Chen, K., Nelson, P., Dosch, H.M., Palmer, J.P., Brooks-Worrell, B., et al. 2009. Effects of exenatide alone and in combination with daclizumab on beta-cell function in long-standing type 1 diabetes. *Diabetes Care* 32:2251-2257.

13. Lee, Y., Wang, M.Y., Du, X.Q., Charron, M.J., and Unger, R.H. 2011. Glucagon receptor knockout prevents insulin-deficient type 1 diabetes in mice. *Diabetes* 60:391-397.
14. 2010. Fact sheets.
15. Meier, J.J., Bhushan, A., Butler, A.E., Rizza, R.A., and Butler, P.C. 2005. Sustained beta cell apoptosis in patients with long-standing type 1 diabetes: indirect evidence for islet regeneration? *Diabetologia* 48:2221-2228.
16. Aljada, A., Mohanty, P., Ghanim, H., Abdo, T., Tripathy, D., Chaudhuri, A., and Dandona, P. 2004. Increase in intranuclear nuclear factor kappaB and decrease in inhibitor kappaB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect. *Am J Clin Nutr* 79:682-690.

Study Design

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

Response: Ninety six 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 48 patients each. The patients will be randomized to placebo or 1.8 mg liraglutide daily. 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 1.2 mg and then to 1.8 mg over a period of 4-5 weeks depending upon the tolerability. Subjects will be recruited from our own clinic patients. Subjects randomized to placebo will receive liraglutide from week 26 onwards (and will be referred as Group B) and dose will be titrated to 1.8 mg as stated above. Subjects randomized to liraglutide since the beginning (and will be referred as Group A) will continue to receive the maximum tolerable dose for rest of the study period.

4.0 Local Number of Subjects

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

Response: 96

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

Response: NA

4.3 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, therefore, majority of recruited patients are our clinic patients.

We do recruit a few patients through advertisement. Both these sources suffice to recruit the needed number to recruit

5.0 Inclusion and Exclusion Criteria

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

NOTE: This may be done in bullet point fashion.

Response:

INCLUSION CRITERIA:

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) Regularly measuring blood sugars four times daily. 3) HbA1c of less than 10%. 4) Well versed with carbohydrate counting**.** 5) Age 30-75 years. 6) BMI 20-40 kg/m^2

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

NOTE: This may be done in bullet point fashion.

Response:

EXCLUSION CRITERIA:

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.

5.3 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:

- ☐ Adults unable to consent
- ☐ Individuals who are not yet adults (infants, children, teenagers)
- ☐ Pregnant women
- ☐ Prisoners

*5.4 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.

6.0 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.

*6.1 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.

*6.2 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.

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

Response:

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

*6.4 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").

*6.5 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.

*6.6 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: 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.

7.0 Eligibility Screening

*7.1 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: The study team will evaluate their clinical patients for possible involvement in this study according to the inclusion and exclusion criteria at the Diabetes and Endocrinology Center of WNY.

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

8.0 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.

8.1 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, and patient doctor interaction at the time of their visit at the 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

8.2 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 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.

8.3 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.

9.0 Procedures Involved

*9.1 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:

Each patient will have completed the following procedures prior to participating in the study.

1) Informed consent.
2) Physical Exam;
3) Medical History; .
4) Lipid Panel
5) Fructosamine
6) C Pep tide and GAD-65 (*Blood samples of patients with negative GAD-65 antibodies will be screened for islet cell antibodies, if patient had evidence of auto- immunity to bata cells in the past, they will be retested during screening. Patients with no evidence of autoimmunity to bata cells will not be included in this trial.)*
7) Baseline lab draw to measure CBC, comprehensive metabolic panel, HbA1c and urine pregnancy test. All labs will be drawn in the fasting state in the morning before 10am.

Randomization Method: After the screening visit, subjects who meet the inclusion and exclusion criteria, will be assigned a number by a computerized random number generation program (Microsoft office – Excel) and randomized to receive subcutaneous injection daily of either Liraglutide (48 subjects) or placebo (48 subjects) for 26 weeks. The subjects and the study coordinators will be blinded to the treatment. The Liraglutide/placebo will be administered via a pen kit (obtained from Novo Nordisk Pharmaceuticals). At 26 weeks both groups will be unblinded; the placebo group will be crossed over to receive liraglutide for remaining 26 weeks and will be labeled as Group B while the group randomized to liraglutide will continue to receive the maximum tolerable dose for another 26 weeks.

Subjects will now enter a pre-study phase for one month. During this phase a blinded CGM will be used for active insulin titration to control the blood sugars. This will minimize the effect of insulin titration on glucose control during the study, thus allowing us to evaluate the effect of liraglutide on glycemia with minimal bias. They will be randomized but will not start treatment till study intervention visit on day 0.

Pre-study visit day -30: Subjects 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 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 throughout the study in an unblinded fashion. 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. The subjects will also be asked to keep a diary of their food intake for a week to measure their calorie intake. Subjects who are on

an insulin pump will be asked to always put their carbohydrate intake in the bolus wizard throughout the study. Subjects who are not on an insulin pump will keep a record of their carbohydrate intake and insulin boluses for the next 2 months.

Pre-study visit day -20: CGM and finger-stick blood glucose concentrations will be reviewed. Careful adjustments will be made to insulin doses by the study investigator on the basis of the glucose data obtained from the patients. The target blood glucose will be preprandial 80-120mg/dl and 2h postprandial < 140mg/dl, without increasing the incidence of blood glucose < 70mg/dl.

Pre-study visit day -10: CGM and finger-stick blood glucose concentrations will be reviewed. Insulin dose will be adjusted by the study investigator to optimize glucose control to above mentioned targets. Subjects will be asked to collect 24 hour urine for one day, just before next visit.

For the entire duration of the study, the patients will maintain a diary to record any hypoglycemia and other untoward side effects. 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.

Study visit day 0:-
Subjects will come fasting for this visit, a **fresh fructosimine blood sample will draw and** 24 hour urine sample would be collected. Patients will be administered a urine pregnancy test before starting study drug. Records of blood glucose concentrations monitored by fingerstick and CGM for the previous 10 days will be obtained to assess their glycemic control prior to liraglutide treatment. They will undergo a meal challenge test (described below).
They will see a CDE for instructions of injection technique for liraglutide. Subjects will then be advised to start on Liraglutide injection at a dose of 0.6 mg per day or placebo injection on the following day. If their HbA1c is <7.0%, subjects will decrease the doses of basal and pre-prandial insulin boluses by 25%. If their HbA1c is >7.5%, they will continue on their current doses of basal and preprandial insulin doses. Those with HbA1c of 7.0-7.5% will decrease their doses by 10%. This reduction is based on our experience (see preliminary data). The investigators will be blinded to the study treatment. Patients will return to the center after 10 days.

Study visit day 10:-
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 on day 1 visit. 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 10 days. Those with severe nausea/vomiting will be dropped from the study. All other subjects will return in 10 days.

Study visit day 20:-
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. 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 10 more days. Subjects on Liraglutide 1.2mg daily without any gastro-intestinal side-effects will be asked to increase the dose to 1.8 mg daily. Subjects will return to the research centre in 10 days.

Study visit day 30:-
Records of blood glucose concentrations of the last 10 days will be collected. Insulin dose will be adjusted at the discretion of the study investigator to optimize blood sugar control as per the targets mentioned above. If needed, the dose will be increased. The goal in the first month 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. Subjects experiencing severe nausea with Liraglutide 1.2mg daily will be dropped from the study. CGM will be discontinued.

Study visits on weeks 8, 12, 16 and 20:-
Records of blood glucose concentrations since the last visit will be collected. Insulin dose will be adjusted at the discretion of the study investigator to optimize blood sugar control. A fasting blood sample will be collected at week 12 to measure HbA1c and research labs, Fructosamine and urinary pregnancy test performed.

Study visit week 24
Records of blood glucose concentrations since the last visit will be collected. Insulin dose will be adjusted at the discretion of the study investigator to optimize blood sugar control. CGM will be inserted. Subjects would be asked to collect urine for 24 hours one day before next visit. Subjects will be asked to keep a food diary to calculate their calorie intake for one week prior to the next visit.

Study Visit Week 26:
You will come fasting for this visit. A fasting blood sample will be collected to measure HbA1c, CBC, CMP, Fructosamine, Lipid panel and research labs and urinary pregnancy test performed. Food diary and 24 hour urine sample would be collected. Records of blood glucose concentrations (finger-stick & CGM) since the last visit will be collected. You will be asked to complete two questionnaires namely DSQOLS (Diabetes specific Quality of Life Scale) and PAID (problem areas in Diabetes survey). Patients receiving placebo will now receive liraglutide for remaining 26 weeks from next day starting with 0.6 mg. Insulin dose will be adjusted by the study investigator based on blood sugars for the group on liraglutide since Day 0 (Group A) and for cross-over group (Group B).

Study Visit Week 27:
Only Group B will come for this visit. Liraglutide dose will be increased to 1.2 mg (if 0.6 mg is tolerated) or else you will continue 0.6 mg for additional week. Records of blood glucose concentrations since the last visit will be collected. Insulin dose will be adjusted by the study investigator to keep blood sugar levels in target range (as mentioned above).
If you experience mild nausea you would be continued on 0.6 mg dose for 10 more days.
If you experience severe nausea or vomiting you will NOT continue further in study.

Study visit week 28:
Group B will increase the liraglutide dose to 1.2 mg or 1.8 mg if dose at Week 27 is well tolerated or else they will stay on the same dose. Records of blood glucose concentrations monitored by finger-stick and CGM from previous visits for both groups will be obtained

and insulin dose will be adjusted accordingly to keep blood sugars in target range (as mentioned above). CGM will be discontinued in Group A who are not using it for clinical care while Group B will continue it for another one week.

Study Visit Week 29:
Only Group B will come for this visit. CGM will be discontinued. Liraglutide dose will be increased to 1.8mg if you are tolerating and still on 1.2 mg. You will continue the maximum tolerable dose for the rest of the study period. Subjects experiencing mild nausea with 0.6 mg or 1.2 mg or 1.8 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 those on 1.2 mg will decrease it to 0.6 mg and will continue that dose throughout the study. Records of blood glucose concentrations monitored by finger-stick and CGM from previous visits for both groups will be obtained and insulin dose will be adjusted accordingly to keep blood sugars in target range (as mentioned above).

Study visit week 32, 36, 40 and 44
Records of blood glucose concentrations since the last visit will be collected. Insulin dose will be adjusted at the discretion of the study investigator to optimize blood sugar control. A fasting blood sample will be collected at week 40 to measure HbA1c and research labs, Fructosamine and patients will be administered a urine pregnancy test before starting study drug

Study visit week 48:
Records of blood glucose concentrations since the last visit will be collected. Insulin dose will be adjusted at the discretion of the study investigator to optimize blood sugar control. CGM will be inserted. Subjects would be asked to collect 24 hour urine for one day, before next visit. Subjects will be asked to keep a food diary to calculate their calorie intake for one week prior to the next visit.

Study visit week 52:
Subjects will come fasting for this visit. A fasting blood sample will be collected to measure HbA1c, CBC, CMP, Lipid Panel, fructosamin and research labs for inflammatory mediators. Patients will be administered a urine pregnancy test. Records of blood glucose concentrations monitored by fingerstick and CGM for the previous 28 days will be obtained to assess their glycemic control. 24 hour urine sample would be collected. Subjects will undergo meal challenge test (described below).

Meal challenge test:-
In order to assess the changes induced by liraglutide, a meal challenge will be carried out prior to and following liraglutide (day 0 and week 52): a 910 Calorie High fat High carbohydrate meal will be given, as in several of our previous papers(16).
Acetaminophen (1000 mg for body weight <125 lbs, 1250mg for weight 125-150 lbs, 1500 mg for 151-175 lbs and 1750 mg for 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 on week 52 (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). A fresh fructosimine blood sample and 24 hour urine will be collected. Blood will be collected from an indwelling intravenous canula in a superficial forearm vein. The total amount of blood drawn for the meal challenge will be 15 tablespoons (230 ml).

Table-3) Flow Chart of Study Procedures

VISIT	History and Physical exam	CMP /CBC	HbA1c/ Pregnancy test	Research blood	Meal test	CGM insertion or Collection	CDE	Vitals and Blood pressure	Collect 24 hr urine/Quality of life questionnaire	collect fingerstick/ CGM data, adjust insulin
Screening	**X**	**X**	**X**					**X**		
Day -30						**X(Insert)**	**X**	**X**		
Day -20, -10								**X**		**X**
Day 0			**X**	**X**	**X**			**X**	**X**	**X**
day 10, 20, 30						**X Collect (Day 30)**		**X**		**X**
Week 12			**X**	**X**				**X**	**X**	**X**
Week 8, 16, 20								**X**		**X**
Week 24						**X(Insert)**		**X**		**X**
Week 26		**X**	**X**	**X**				**X**	**X**	**X**
Week 27(Cross-over group only)								**X**		**X**
Week 28						**X(collect) (Group A)**		**X**		**X**
Week 29(Cross-over group only)						**X(Collect Group B)**		**X**		**X**
Week 32, 36								**X**		**X**
Week 40			**X**	**X**				**X**		**X**
Week 44								**X**		**X**
Week 48						**X**		**X**		**X**
Week 52	**X**	**X**	**X**	**X**	**X**	**X (Collect)**		**X**	**X**	**X**
VISIT	History and Physical exam	CMP /CBC	HbA1c/ Pregnancy test	Research blood	Meal test	CGM insertion or Collection	CDE	Vitals and Blood pressure	Collect 24 hr urine/Quality of life questionnaire	collect fingerstick/ CGM data, adjust insulin
Screening	**X**	**X**	**X**					**X**		
Day -30						**X(Insert)**	**X**	**X**		
Day -20, -10								**X**		**X**
Day 0			**X**	**X**	**X**			**X**	**X**	**X**
day 10, 20, 30						**X Collect (Day 30)**		**X**		**X**
Week 12			**X**	**X**				**X**	**X**	**X**

Week 8, 16, 20								X		X
Week 24						X(Insert)		X		X
Week 26		X	X	X				X	X	X
Week 27(Cross-over group only)								X		X
Week 28						X(collect) (Group A)		X		X
Week 29(Cross-over group only)						X(Collect Group B)		X		X
Week 32, 36								X		X
Week 40			X	X				X		X
Week 44								X		X
Week 48						X		X		X
Week 52	X	X	X	X	X	X (Collect)		X	X	X

9.2 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: During meal challenge (Visit 1 and final visit), blood samples will be appropriately processed and assayed for glucose, insulin, c-peptide, glucagon, GLP-1 and gastric inhibitory peptide (GIP; also called gastric insulinotropic peptide) and DPP-IV.

1) **Plasma glucose, insulin, glucagon, C-peptide, GLP-1 and GIP measurements:** Insulin and C-peptide levels will be determined using an ELISA kits from Diagnostic Systems Laboratories Inc. (Webster, TX). Glucose levels will be measured in plasma by YSI 2300 STAT Plus glucose analyzer (Yellow Springs, Ohio). CBC and comprehensive metabolic panel will be measured using well established assays by the clinical laboratory. GLP-1, GIP (Millipore, Billerica, MA) and glucagon (Wako Chemicals USA, Inc, Richmond, VA) will be measured by ELISA. Samples will be collected in tubes containing protease and DPP-IV inhibitors (Millipore, Billerica, MA) to insure stability of the measured peptides
2) **Serum Acetaminophen** concentrations during meal challenge study will be measured by clinical laboratory (Quest diagnostics) by colorimetry. The time to peak acetaminophen concentrations and the area under curve (0-180 minutes) will be calculated.

9.3 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. The CGM or insulin pump will be used to collect glucose and insulin data. Food diary will be use to collect food intake.

9.4 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.

*9.5 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.

*9.6 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, study results could be published in the form of a manuscript or abstract.

10.0 Study Timelines

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

Response:72 months

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

Response: 52 Weeks

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

Response: 7/2018

11.0 Setting

11.1 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. 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. Equipment include ultra-low freezers for sample storage, centrifuges, microscopes for sample preparation, infusion pumps, ELISA, PCR and immunoblotting instrumentation. CTRC location is a fully equipped laboratory

11.2 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.

12.0 Community-Based Participatory Research

12.1 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.

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

Response:

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

13.0 Resources and Qualifications

*13.1 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.

13.2 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.

13.3 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

13.4 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 meetings, conferences and discussions

14.0 Other Approvals

14.1 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: NA

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

15.0 Provisions to Protect the Privacy Interests of Subjects

15.1 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 and through advertisements. The patients who call for potential participation in the study will be screened over the phone 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.

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

15.2 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 HIPAA waiver.

16.0 Data Management and Analysis

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

Response:

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)

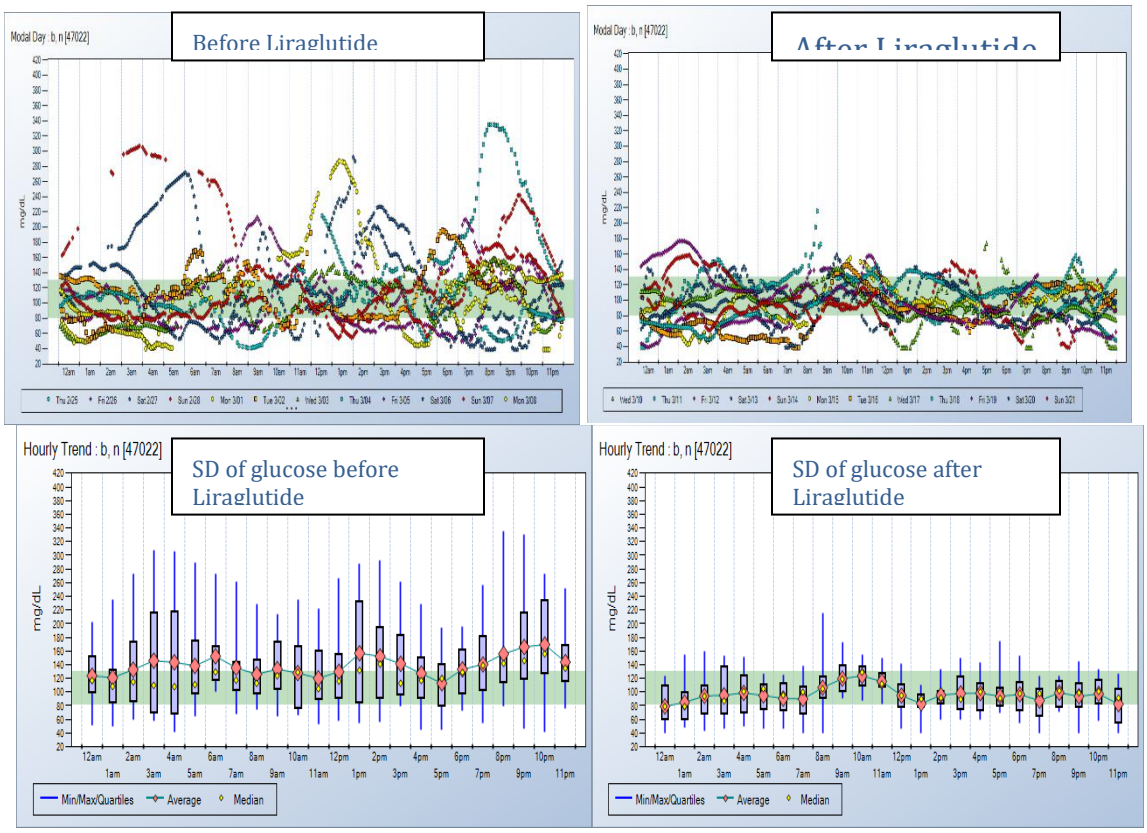
Table 2	Before treatment	On Liraglutide	P value
Weight(kg)	66 ± 6	65± 5	0.22
insulin dose (basal)	24 ± 6 U/d	16 ± 6 U/d	<0.01
insulin dose (bolus)	22 ± 4 U/d	15 ± 4 U/d	<0.01
Mean Fasting Blood Glucose (mg/dl)	129±10	110±8	0.02
Weekly Mean Blood Glucose (mg/dl)	141±20	115±12	<0.01
Time spent in hypoglycemia <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 3	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 (%	2±2	2.4±2	0.10
Time spent in hypoglycemia <40 mg/dl (%	0.1±0.2	0.14±0.3	0.21
Time spent in hyperglycemia > 150	27± 6	20± 5	0.01
Time spent in hyperglycemia >200	17± 5	6± 2	<0.01
Time spent in hyperglycemia >250	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



16.2 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

- This will be the first prospectively randomized and controlled study to investigate the effect of liraglutide on glycemic levels and variability in 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).
- 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).
- With the use of continuous glucose monitoring device (CGM), this study will determine the rapidity and consistency of the response to liraglutide. In our preliminary study, this response was observed within the first two days such that we advised patients to reduce their insulin doses by 20% in advance.
- 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(15).

16.3 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:

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

Response: Data will not be imputed to replace missing data and only observed data will used to run the mixed model for repeated measurement (MMRM) analysis

17.0 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**.*

*17.1 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.

17.2 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

17.3 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

17.4 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

17.5 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)*

17.6 A. 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.T

17.7 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

17.8 C. 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

17.9 D. 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

17.10 E. 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

18.0 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.

18.1 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 Antoine Makdissi, MD will review the data every 3 months to assess the safety and potential benefits to the participant. 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 (AZ) 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 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

18.2 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*

18.3 Describe any safety endpoints.

Response:

Adverse Events Definitions and Reporting:

Adverse event (AE)*: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research*

Serious adverse event (SAE)*: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria: 1) results in death;*

2) is life-threatening (places the subject at immediate risk of death from the event as it occurred); 3) requires inpatient hospitalization or prolongation of existing hospitalization; 4) results in a persistent or significant disability/incapacity; 5) results in a congenital anomaly/birth defect; or any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

Adverse drug reaction (AR):

*All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. An adverse reaction will become a serious drug reaction (**SAR)** only if it meets the requirements as defined in the above definition. The term suspected unexpected serious adverse reaction (**SUSAR)** defined as follows:*

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (package insert/summary of product characteristics for an approved product)

All serious adverse reactions (SARs) or suspected unexpected adverse drug reaction (SUSARs) will be reported to the IEC/IRB or within day 15 from the Investigator becoming aware of such adverse events, whichever comes first.

Non-serious events/problems that impacted on the rights and welfare of the subjects will be reported as they occur or at the time of knowledge or notification.

The following table represents the time frames for reporting serious events at the State University of New York at Buffalo:

TIMEFRAMES FOR REPORTING ON-SITE "SERIOUS" EVENTS/PROBLEMS (SEPs)	
Type of Report	**When to Report**

Deaths - except when death is the endpoint of the study	**Within 24-hours** of knowledge or notification
Life-threatening (i.e., events/problems that place the subject at immediate risk of death from the event as it occurred)	**Within 72-hours** of knowledge or notification
Required hospitalization or prolongation of existing hospitalization	**Within 72-hours** of knowledge or notification
Resulted in persistent or significant disability or incapacity	**Within 72-hours** of knowledge or notification
Resulted in congenital anomaly or birth defect	**Within 72-hours** of knowledge or notification
Based on appropriate clinical judgment, the event required or may require medical or surgical intervention to: • prevent a life-threatening event/problem (the subject is at immediate risk of death from the event as it occurred) • Required hospitalization or prolongation of existing hospitalization • Resulted in persistent or significant disability or incapacity • Resulted in congenital anomaly or birth defect	**Within 72-hours** of knowledge or notification
Deviation, in an emergency situation, from the approved investigational plan initiated in order **to protect the life** or physical well-being of a subject	**Within 5 days** of the emergency
Deviation, in an emergency situation, from the approved investigational plan initiated in order **to eliminate an apparent hazard to a participant**	**Within 5 days** of the emergency
Increased Risk of Harm to subjects or others than was previously known or recognized (whether or not actual harm has occurred). Risks may be physical, psychological, economic, or social: *Examples:* • *Theft or loss of stored research data* • *A subject complaint indicates unexpected risks* • *Unexpected subject withdrawal poses increased risks to the subject or others* • *Incarceration of an enrolled subject, in a study not approved for participation of prisoners, where ceasing all study involvements or interventions with the now-incarcerated prisoner-subject may increase risks to his/her health or safety.*	**Within 10 working days** of knowledge or notification
Breach of Confidentiality that caused harm or places subjects or others at **increased risk of harm** (physical, psychological, economic, or social harm (even if actual harm has not occurred).	**Within 10 working days** of knowledge or notification
Significant impact on the integrity of the research data *Examples:* • *Unplanned destruction of study records*	**Within 10 working days** of knowledge or notification

• *Withdrawal of subject(s) impacts data integrity or causes inability to complete the study*	
Unanticipated Adverse Device Effects Any serious adverse effect on health or safety of any life-threatening problem or death caused by, or associated with, an FDA regulated device, if that effect problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.	**Within 10 working days** of knowledge or notification
Any event/problem that would cause the sponsor to modify the investigator's brochure, informed consent document or would prompt other action by the IRB to assure protection of subjects.	**Within 10 working days** of knowledge or notification.
Any other "Serious" Event/Problem not described above	**Within 10 working days** of knowledge or notification

18.4 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.

18.5 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

18.6 Describe who will review the safety data.

Response: The Safety data will be reviewed by the principle and sub investigators along with the research coordinator.

18.7 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.

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

Response: The statistical analysis will be carried out using the paired t-test or Wilcoxson's test for paired data

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

Response: If the risks of the treatment outweigh the benefits

19.0 Withdrawal of Subjects

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

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

Response: Pregnancy and other conditions included in the exclusion criteria

19.2 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: 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 you at risk of further complications if you continue 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.

If any of the subjects become pregnant during the period of study, they will need to withdraw from the study.

19.3 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. 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.

20.0 Risks to Subjects

20.1 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: **Hypoglycemia:** To minimize the risk of hypoglycemia, we are reducing the dose of insulin when initiating the study intervention. Subjects will be advised to call if they have more than one blood glucose < 70 mg/dl. For uncontrolled blood glucose, subjects will be advised to

call if they have more than one blood glucose above 250 mg/dl. Patients will monitor their blood sugars by fingerstick and or continuous glucose monitoring system diligently as part of the study protocol. Blood sugars will be reviewed on a regular basis by the study investigators and insulin dose will be adjusted to prevent hypoglycemia.

2. **Nausea and vomiting:** Mild to moderate nausea occurs in 8-30% of subjects, and vomiting occurs in 5%. Patients will be told that this is the commonest side-effect of liraglutide. The incidence of nausea decreases after the first week of the drug. Patients will be advised to call the study coordinator if they have persistent or intolerable nausea.

3. **Pancreatitis:** There have been reports of pancreatitis associated with Liraglutide, however, a cause and effect relationship has not been established and the prevalence seems to be consistent with what is expected in subjects with diabetes. The consent form includes this description: "In studies, there were more cases of pancreatitis among patients treated with liraglutide. Inflammation of the pancreas (pancreatitis) may be severe and lead to death. Certain medical conditions make you more likely to get pancreatitis. Therefore before taking liraglutide, tell your healthcare provider or us if you have had pancreatitis, stones in your gallbladder (gallstones), a history of alcoholism, or high blood triglyceride levels. Stop taking liraglutide and call your healthcare provider or us right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. These may be symptoms of pancreatitis."
Subjects who have abdominal pain will be asked to stop the drug immediately and blood test will be done to rule out pancreatitis. If pancreatitis is confirmed, subjects will be discontinued from the study. We will exclude patient with a prior history of pancreatitis from the study.

4. **Medullary thyroid cancer:** In rats and mice at a dose 8 to 45 times that used in humans, Liraglutide administration was associated with an increase in C- cell tumors. According to FDA, the human relevance of the animal data is not clear and Liraglutide is contraindicated in subject with medullary carcinoma of thyroid or the MEN 2 syndrome. The consent form includes this description: "In animal studies, liraglutide caused rats and mice to develop thyroid tumors, some of which were cancerous. It is not known whether liraglutide causes thyroid tumors or a type of thyroid cancer called medullary thyroid cancer (MTC) in humans. MTC may lead to death. Do not use liraglutide if you or any of your family members have a history of MTC or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumors in more than one gland in their body. You should tell your healthcare provider or us if you get a lump or swelling in your neck, hoarseness, difficulty swallowing, or shortness of breath while you are taking Liraglutide because these may be symptoms of thyroid cancer."
Physical examination at the beginning and the end of the study will include thyroid palpation. Any new thyroid nodules will be promptly investigated with an ultrasound and calcitonin concentrations, and biopsy if clinically indicated.

5. **Hypersensitivity:** Liraglutide may also be associated with allergic and hypersensitivity reactions. Patients will be made aware of this. Subjects will be advised to stop the drug if they have a hypersensitivity reaction.
All pregnancies in trial subjects occurring during the use of Novo Nordisk Products will be promptly reported to Novo Nordisk within the same timeframes outlined above for reporting SARs.
Records of all participants in this study will be kept confidential so far as permitted by law. However, the subject's doctor and the Institutional Review Board (IRB) will be able to inspect and have access to confidential information that identifies subjects by name. Any publication of the data will not identify the subjects.

Subject participation in this research study is voluntary. They have the right to refuse to participate or to withdraw from participation at any time for any reason. His refusal to participate or his withdrawal from the study will involve no penalty.
All of the key personnel on this project have completed a training program in the protection of human research subjects.
The conduct of the study will be in compliance with the ethical responsibility standards (The Declaration of Helsinki and ICH-GCP).
The conduct of the study will be in compliance with all the requirements of Health Sciences Institutional Review Board (HSIRB) of the State University of New York at Buffalo.

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

Response: NA

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

Response: NA: There is could always be an unforeseeable risk or adverse advent during a study procedure.

20.4 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 be enrolling pregnant participants who are within child baring years sign the consent stating they will use two forms of birth control. If a participant becomes pregnant they will be withdrawn from the study immediately.

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

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

21.0 Potential Benefits to Subjects

21.1 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 an individual participants will experience.

22.0 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.

22.1 ***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, but it will not be free of charge even if the injury is a direct result of their participation.

22.2 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: NA

23.0 Economic Burden to Subjects

23.1 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 expensed 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.

24.0 Compensation for Participation

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

Response:

To help defray the costs of your participation, you will be receiving compensation after the completion of the study and after returning all the DEXCOM (Continuous Glucose Monitoring) Supplies in working condition. If any of these supplies are damaged in any matter, you will not

receive any of your payment. You will receive following based on assigned group, which will be identified at 6-month time point in study. Group A: $545.00 after completion of the study: $15 per visit (for days -30,-20,-10, 10, 20, 30; and weeks 8, 16, 20, 24, 28,32, 36, 44, 48), $75 for each meal challenge, $25 for each blood draw (weeks 12, 26 and 40), $25 for each urine sample (Day 0, week 26 and week 52).

Group B: up to $575.00 after completion of the study: $15 per visit (for days -30,-20,-10, 10, 20, 30; and weeks 8, 16, 20, 24, 27,28, 29,32, 36, 44, 48), $75 for each meal challenge, $25 for each blood draw (weeks 12, 26 and 40), $25 for each urine sample (Day 0, week 26 and week 52)

Parking for entire study duration: $20.00 if paid by the patient.

☐ **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.

25.0 Consent Process

25.1 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)*

25.2 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 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.

25.3 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.

25.4 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.

25.5 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)*

25.6 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:

25.7 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)

25.8 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).*

25.9 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)."

25.10 ***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:

*25.11 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: All subjects will be required to assent for participation in the study. The assent will be documented on the IRB approved consent form

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

Response: All subjects will be required to assent for participation in the study. The assent will be documented on the IRB approved consent form

*25.12 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: The study involves certain procedures like counting carbohydrates with each meal, and insulin administration which can only be performed by individuals with a good degree of cognition. As such, individuals with cognitive decline preventing them to have a decision making capacity will automatically be excluded from the study.

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)*

*25.13 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: Participants age will be verified using their date of birth on electronic medical records, and their drivers license or state issued ID upon arrival for the consenting process.

25.14 ***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: Not applicable,

All research activities are performed within New York State.

25.15 Describe whether parental permission will be obtained from:

Response:

☐ 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)."

25.16 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: Not applicable.

25.17 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: Not applicable

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

Response: Not applicable

26.0 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.

26.1 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:

26.2 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:

27.0 Process to Document Consent

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

27.1 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).

28.0 Multi-Site Research (Multisite/Multicenter Only)

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

*28.1 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:

28.2 Describe the method for communicating to engaged participating sites:

- *Problems*
- *Interim results*
- *Study closure*

Response:

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

Response:

28.4 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:

29.0 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.

*29.1 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

29.2 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. The data stored will include record files of all patients participating in the study, including data collection sheets, lab results, CGM and insulin pump data.

29.3 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.

30.0 Drugs or Devices

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

30.1 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: **Drugs used:** *Liraglutide (Victoza) or placebo*
Device: continuous glucose monitoring device (CGM), this study will determine the rapidity and consistency of the response to liraglutide.

30.2 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:

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

Response:

NA

30.4 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

31.0 Humanitarian Use Devices

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

31.1 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:

31.2 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: