PROTOCOL TITLE:

Include the full protocol title.

Response: **GLP-1 Receptor Agonist Therapy and Albuminuria in Patients with Type 2 Diabetes**

PRINCIPAL INVESTIGATOR:

Response:

Principal Investigator: **Paresh Dandona, MBBS, PhD**
Co- Investigators: **Husam Ghanim, PhD**
Manav Batra, MD

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

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VERSION:

Include the version date or number.

Response: 10/12/2018, V3

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.***

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VERSION:

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Response: 10/12/2018, V3

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: Astra Zeneca

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/ Address: *1000 Youngs Rd, Suite 105, Williamsville, NY 14221*
Department: Diabetes Endocrinology

1.0 Objectives

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

Response:

Aim 1.1: To compare changes in albuminuria levels (UACR) following 1-year treatment with exenatide-extended release (weekly exenatide) or placebo in T2DM with macro- and microalbuminuria.

Aim 1.2: To evaluate changes in creatinine, creatinine clearance, GFR and cystatin C following 1-year treatment with exenatide-extended release (weekly exenatide) or placebo in T2DM with macro- and microalbuminuria.

Aim 2.1: To evaluate the changes in TGFβ levels and in the expression of two major signal transducers of TGFβ signaling, SMAD3 and SMAD4 in MNC following 1-year treatment with exenatide-extended release or placebo in T2DM with macro- and microalbuminuria.

Aim 2.2: To investigate the changes in profibrotic genes such as type I and IV collagen, connective tissue growth factor (CTGF), PAI-1, TIMP-1 and 2 and fibronectin (fibronectin EDA) following 1-year treatment with exenatide-extended release or placebo in T2DM with macro- and microalbuminuria.

Aim 3.1: To evaluate the change in reactive oxygen species (ROS) generation and NADPH oxidase subunit ($p47^{phox}$) in MNC and urinary isoprostanes following 1-year treatment with exenatide-extended release or placebo in T2DM with macro- and microalbuminuria.

Aim 3.2: To investigate the changes in Nrf-2/keap-1 system activation and anti-oxidant response genes including NQO-1, GST-1P and HO-1 expression following 1-year treatment with exenatide-extended release or placebo in T2DM with macro- and microalbuminuria

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 weekly exenatide reduces the rate of progression and possibly reverses the rate of albuminuria in patients with type 2 diabetes (T2DM).
Hypothesis 2 (exploratory): Exenatide extended release treatment suppresses TGF-β1 activation in T2DM with micro and macroalbuminuria.

Hypothesis 3 (exploratory): Exenatide extended release treatment suppresses oxidative stress and induces anti-oxidant mediators in T2DM with micro and macroalbuminuria.

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:

This is a prospective study to evaluate effect of Exenatide extended release treatment for 1 year on albuminuria levels in T2DM patients with micro- and macroalbuminuria compared to placebo. The similarities in baseline values between the study groups will be compared using appropriate parametric tests. Transformations of the data on order to meet statistical assumptions may be considered. All statistical analysis will be carried out using SPSS software (SPSS Inc, Chicago, Illinois) based on intention to treat principle. Data will be presented as mean±standard error. The primary endpoint of the study is the change from baseline in albuminuria level at weeks 12, 26, 39 and 56 following Exenatide extended release and placebo treatments. Fasting samples collected at weeks 0, 12, 26, 39 and 56 will be used for this assessment with values at week 0 considered as baseline. Changes from baselines form both drugs arms will be compared to those from the placebo arms in both the micro and macroalbuminuria groups. The statistical analysis will be done using mixed model for repeated measurement (MMRM) analysis with assigned α value of 0.05. Our preliminary data on retrospective analysis of the difference in albuminuria following GLP-1RA treatment for 2.5 yrs in T2DM patients with micro and macroalbuminuria show regression of albuminuria (UACR) by approximately 55mg/mg and 500mg/g (about 50% reduction), respectively. Conservatively estimating a difference in the change from baseline in albuminuria after 1 year between the Exenatide extended release and placebo groups (across both albuminuria groups) of 60mg/g, with standard deviation of no more than 91mg/g, a sample size of 38 patients per group should provide adequate power ($\beta = 0.2$) to detect a significant difference ($\alpha = 0.05$). Aassuming a drop-out rate of 15% and 2:1 drug:placebo randomization ratio, 60 active and 30 control will be recruited for a total of 90 patients (rounded up). Patients will be enrolled based on a predetermined stratification according to the two albuminuria categories (micro and macro at 1:1 ratio) with 45 patients in each.

The secondary end points include the comparison of the changes in albuminuria based on baseline albuminuria category (micro or macro), creatinine clearance, Cystatin C, TGFβ, type I and IV collagen, CTGF, and fibronectin levels, the expression of SMAD3, SMAD4, NQO-1, GST-1P and HO-1, Nrf-2/keap-1 system activation between the Exenatide extended release and placebo groups and across albuminuria categories.

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:

Diabetic nephropathy is the leading cause of chronic kidney disease accounting for nearly 50% of all end-stage renal disease worldwide (1). Current therapies that aim to lower blood glucose are not effective in blocking renal damage, and cotreatment with renoprotective drugs often results in toxicity, limiting efficacy. Hence, there remains an urgent need to develop effective medicines to preserve normal renal function and to prevent or slow the progression of diabetic nephropathy.

Although diabetic nephropathy involves many renal cell types, mesangial activation by cytokines under hyperglycemic conditions plays an important role in the progression of diabetic nephropathy (2). The cytokine transforming growth factor-β1 (TGF-β1) is central to the profibrotic switch and activation of mesangial cell hypertrophy and matrix production and is upregulated in diabetic nephropathy (3). Previous interventions at the level of TGF-β1 ameliorated several pathological symptoms of diabetic nephropathy (4), indicating reduction of hypertrophy and extracellular matrix (ECM) accumulation in the kidney may be a viable therapeutic avenue.

The transcription factor NFE2-related factor 2 (Nrf2) is an emerging therapeutic target for several diseases Nrf2 regulates expression of numerous genes through antioxidant response elements in their promoters to neutralize free radicals and accelerate removal of environmental toxins (5). Using streptozotocin (STZ)-induced diabetic models, a protective role of Nrf2 against renal damage through mediation of free radicals was demonstrated (6). This may be also associated with the suppression of TGFβ related genes including fibronectin, collagen IV and thrombospondin-1 (TSP-1), which too are known to contribute to the pathogenesis of diabetic nephropathy. In addition, recent work has shown that heparanase, the enzyme which destroys heparan sulfate, an important integral part of the glomerular basement membrane, may also contribute to the pathogenesis of diabetic nephropathy (7).

Treatment of type 2 diabetes with GLP-1 receptor agonists over the past decade has revealed a number of important attributes of this drug class besides their ability to improve glycemic control through increased insulinogenesis, decreased glucagon secretion, slowing of gastric emptying and the suppression of appetite and carbohydrate intake (8-10). We reported for the first time that exenatide, the first marketed drug in this class, induced a significant reduction in systolic blood pressure and plasma CRP concentrations. The latter observation was indicative of an anti-inflammatory effect. The systolic blood pressure lowering effect of exenatide, liraglutide and other drugs in this class has now been confirmed by other studies, including our own, in both type 2 and type 1 diabetes. In addition, the reduction in CRP concentrations has been followed by studies demonstrating

a rapid and comprehensive ROS suppressive and anti-inflammatory action of exenatide at the cellular and molecular level. Since hypertension and oxidative and inflammatory stress are major factors in the pathogenesis of diabetic nephropathy, we wondered whether exenatide and other drugs in this class could prevent or reverse albuminuria. This suspicion was strengthened further by the observation that exenatide suppresses the plasma concentrations of TGFβ and also suppresses TGFβ signal transduction by reducing the expression of SMAD3 and SMAD4. In addition, exenatide also enhances the expression of key anti-oxidant enzymes, NQO-1, GST-1P and HO-1, modulated by anti-oxidant response elements (ARE) which, in turn, are regulated by the Nrf-2/Keap-1 system. The action of this system has now been shown to be protective to the kidney in mouse models of experimental diabetes (11).

On the basis of the above, we hypothesized that exenatide and other drugs in this class reverse albuminuria. Data from a retrospective analysis on patients with type 2 diabetes from our center clearly show that treatment with GLP-1 receptor agonists (mainly exenatide and liraglutide) is associated with reductions in the magnitude of albuminuria in the entire group. In addition, there was a significant reversal of macroalbuminuria to micro- and normoalbuminuria and that of microalbuminuria to normoalbuminuria. In contrast, no such changes were observed in patients treated with other anti-diabetic drugs in spite of similar glycemic and blood pressure control.

Clearly, therefore, a prospectively randomized study needs to be set up to determine whether GLP-1RAs reduce the progression of albuminuria or reverse albuminuria. If indeed, this is shown to be true, we shall have an anti-diabetic drug class which for the first time will have an effect on the development of microangiopathy in addition to its role as an anti-hyperglycemic agent. In this proposal, we intend to investigate the hypothesis that treatment of with weekly exenatide reduces the rate of progression of albuminuria in patients with type 2 diabetes.

Preliminary data:

1- ***Effect of GLP-1 RA on evolution of albuminuria in type 2 diabetes: A retrospective study.***

Among 466 patients with type 2 diabetes, 70.6 % (n=329) had normoalbuminuria, 24 % (n=112) had microalbuminuria and 5.1 % (n=24) had macroalbuminuria. Over a mean 3 year follow up, there was a reduction in UACR in the entire group by 21.1±328 mg/g from a mean of 85.8±374 mg/g to 65.1±225 mg/g. In group A, UACR fell by 37±193 mg/g (from 87±250 mg/g to 49.8±147 mg/g, $p<0.0001$), while in group B, UACR increased by 6±454mg/g (from 81.1±500 mg/g to 87±302 mg/g, $p<0.05$) ($p<0.001$ between groups).
Since there was a significant difference in the reduction of HbA1c between groups A and B, we carried out a secondary analysis on UACR differences to adjust for the fall in HbA1c. UACR changes from baselines were first log transformed and difference between groups were tested with ANCOVA with changes in HbA1c used as a covariate. HbA1c adjusted log change in UACR in group A was -0.09±0.49 and in group B was 0.08±0.056 ($p=0.007$, ANCOVA).

In the entire cohort (n=466), those with baseline normoalbuminuria (n=329), 88.7 % (n=292) remained normal, 10% (n=33) developed microalbuminuria and 1.2% (n=4) developed macroalbuminuria. Among those with baseline microalbuminuria (n = 112), 47.3% (n = 53) regressed to normal, 47.3 % (n =53) remained microalbuminuric, while 5.3 % (n=6) progressed to macroalbuminuria. Among those with baseline macroalbuminuria (n=24), 4% regressed to normal, and 50% regressed to microalbuminuria while 46 % remained macroalbuminuric.

The GLP-1RA users (group A; n =275) were followed up for a mean of 2.3 years.

(a) Among those who had normoalbuminuria at baseline (n=183), 171 (93.4%) remained normal, 10 developed microalbuminuria (5.4%) and 2 developed macroalbuminuria (1%) as depicted in Figure 1. The mean UACR changed from 9.4±7.1 mg/g to 18.1±17.2 mg/g. The mean creatinine concentration changed from 0.98±0.38 mg/dl to 1±0.34 mg/dl. The eGFR decreased by 5.1±18.4 ml/min from 95.7±31.3 ml/min to 90.7±30.2 ml/min. The mean HbA1c decreased by 0.7±1.7 % from 7.9±1.7% to 7.2±1.4%.

(b) Amongst 76 patients who had baseline microalbuminuria, 44 patients (57.8%) normalized while 32 (42.1%) remained microalbuminuric during follow up. No patient developed macroalbuminuria. The mean UACR fell by 57.7±64.5 mg/g from 103.5±68.8 mg/g to 45.8±48.7 mg/g, a decrease of 42±74%. The mean creatinine changed from 1.04±0.34 to 1.15±0.42 mg/dl. The mean eGFR decreased by 8.6±18 from 90.2±36.9 ml/min (Table 2).Even in those who remained microalbuminuric, 22 had a reduction in UACR of 71.1±54 mg/g from 155.4±74 mg/g to 84.3±55 mg/g. The mean HbA1c decreased by 0.8±2.2% from 8.4±2% to 7.6±2% in this group. The 10 patients who had no reduction in UACR had a significant increase in HbA1c from 9.2±1.2 % to 9.7±2.7 %.

(c) Among the 15 patients who had macroalbuminuria at baseline, 1 normalized (6.6%), 8 became microalbuminuric (53.3%), and 6 remained macroalbuminuric (40%). The mean UACR fell by 500±606 mg/g from 936±579 mg/g to 436±398 mg/g, a decrease of 40±57%. The mean creatinine increased from 1.37±0.6 mg/dl to 1.47±0.6 mg/dl. The e GFR decreased from 76.5±36.5 ml/min to 70.1±34.6 ml/min. The mean HbA1c decreased by1±1.2% from 8.4±1.8% to 7.4±1.6%.

The GLP-1RA non-users (group B; n=191), were followed up for a mean period of 3.6 years.

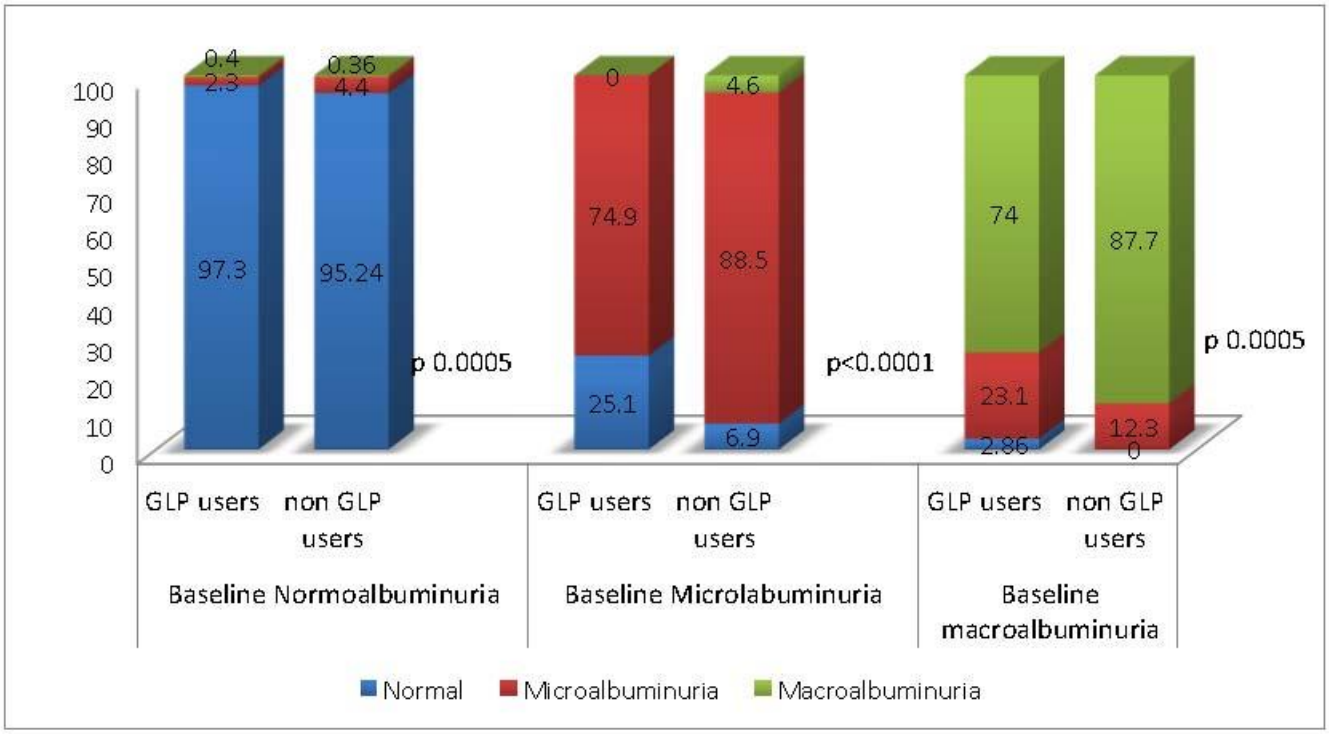
a) 146 patients had normo-albuminuria at baseline. Of these, 121 (82.8%) remained normal, 23 (15.7%) developed microalbuminuria and 2 developed macroalbuminuria (1.3%). The mean UACR increased by 20.6±81 mg/g from 8.1±6.9 mg/g to 28.7±82.4 mg/g. The mean creatinine remained stable from 1±0.36 mg/dl to 1.04±0.39 mg/dl. The eGFR decreased from 89.1±27.9 ml/min to 87.4±29.5 ml/min. The mean HbA1c decreased by 0.4±1.8% from 7.5±1.7% to 7.1±1.4%.

b) 36 patients had microalbuminuria at baseline. Of these, 9 normalized (25%), 21 remained microalbuminuric (58.3%) and 6 developed macroalbuminuria (16.6%). The mean UACR increased by 60±201 mg/g from 85±48 mg/g to 145±199 mg/g, an increase of 105±311%. The mean creatinine changed from 1.06±0.39 mg/dl to 1.2±0.46 mg/dl. The eGFR decreased by 12.1±15.8 ml/min from 85.3±31.3 ml/min to 73.2±26.7 ml/min. The mean HbA1c decreased by 0.5±1.6% from 7.8±2.1% to 7.3±1.8%.

c) 9 patients had baseline macroalbuminuria. Of these, none normalized, 4 became microalbuminuric (44.4%), 5 remained macroalbuminuric (55.5%). The mean UACR

fell by 453±2085 mg/g from 1248±2075 mg/g to 795±1111 mg/g, a decrease of 11±98%. The mean creatinine increased from 1.15±0.5 mg/dl to 1.6±0.59 mg/dl. The mean eGFR decreased by 30.3±23.3 ml/min from 88.5±47.9 ml/min to 58.2±37.5 ml/min. The mean HbA1c decreased by 1.5±3.3% from 9.2±2.9 % to 7.7±1.5%.

Figure 1 below compares the evolution of albuminuria per annum between groups A and B.



2- Effect of exenatide on Nrf-2/keap-1 system, expression of anti-oxidant enzymes and TGFb-1 in MNC. Twenty four obese type 2 diabetics taking insulin were randomized to receive either exenatide 10µg twice daily or placebo twice daily for 12 weeks. Fasting blood samples were obtained at baseline and 3, 6 and 12 weeks later. Exenatide treatment suppressed Keap-1 protein by 21±8% and increased the mRNA expression of NQO-1, GST-1P and HO-1 by 51±15%, 42±10% and 39±10%, with an increase in NQO-1 protein by 25±10% ($p<0.05$) in MNC. Exenatide also suppressed plasma TGFβ1 concentrations by 20±7% and SMAD-3 expression in MNC by 28±8% (Figure 2, $p<0.05$).

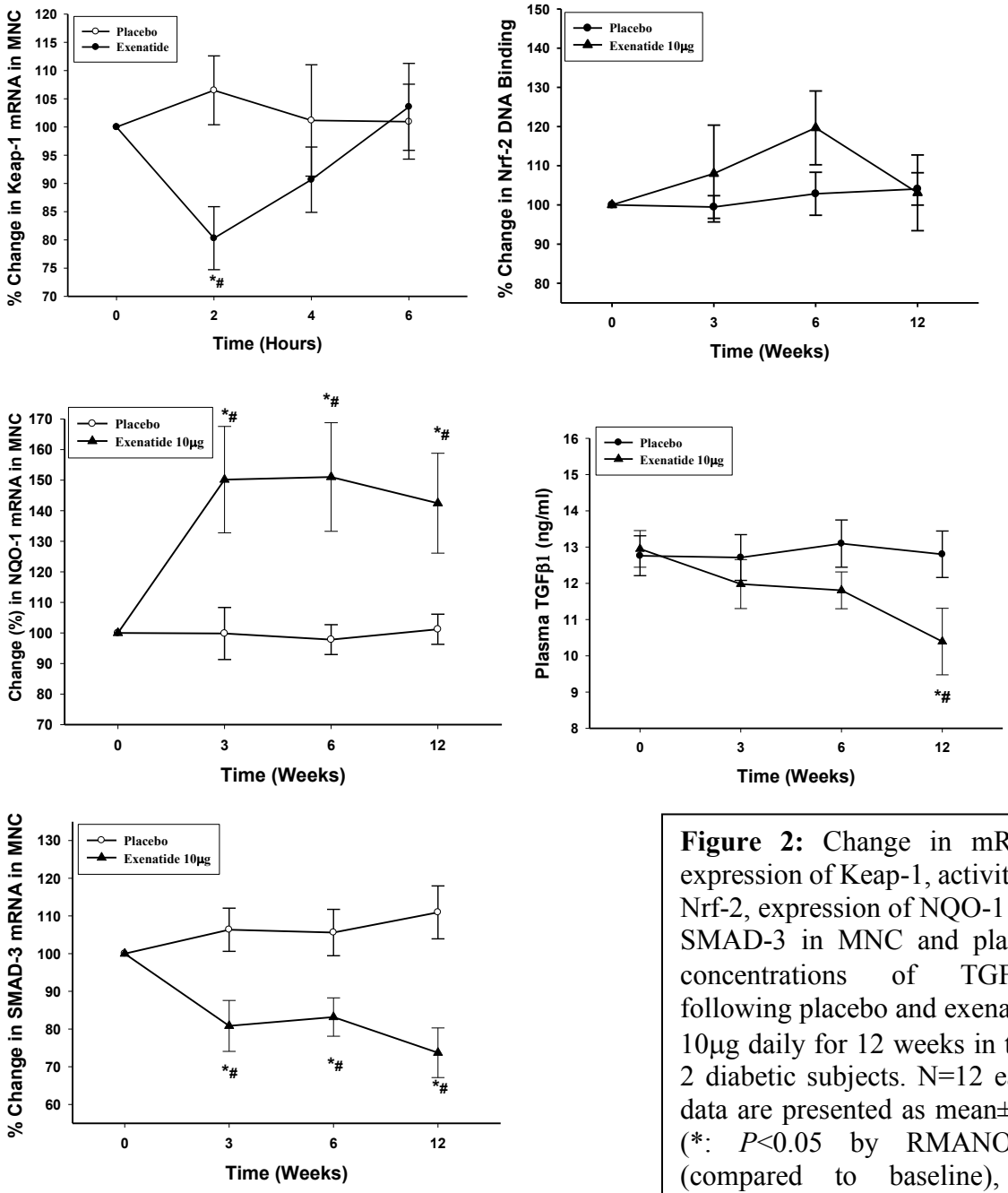


Figure 2: Change in mRNA expression of Keap-1, activity of Nrf-2, expression of NQO-1 and SMAD-3 in MNC and plasma concentrations of TGF-β1 following placebo and exenatide 10μg daily for 12 weeks in type 2 diabetic subjects. N=12 each, data are presented as mean±SE. (*: $P<0.05$ by RMANOVA (compared to baseline), #: $P<0.05$ by Two-way RMANOVA compared to control groups.

3.2 Include complete citations or references.

Response:

1. Dronavalli S, Duka I, and Bakris GL. The pathogenesis of diabetic nephropathy. *Nat Clin Pract Endocrinol Metab.* 2008;4(8):444-52.
2. Kanwar YS, Sun L, Xie P, Liu FY, and Chen S. A glimpse of various pathogenetic mechanisms of diabetic nephropathy. *Annu Rev Pathol.* 2011;6(395-423.
3. Shankland SJ, Scholey JW, Ly H, and Thai K. Expression of transforming growth factor-beta 1 during diabetic renal hypertrophy. *Kidney Int.* 1994;46(2):430-42.
4. Sharma K, Jin Y, Guo J, and Ziyadeh FN. Neutralization of TGF-beta by anti-TGF-beta antibody attenuates kidney hypertrophy and the enhanced extracellular matrix gene expression in STZ-induced diabetic mice. *Diabetes.* 1996;45(4):522-30.
5. Osburn WO, and Kensler TW. Nrf2 signaling: an adaptive response pathway for protection against environmental toxic insults. *Mutat Res.* 2008;659(1-2):31-9.
6. Jiang T, Huang Z, Lin Y, Zhang Z, Fang D, and Zhang DD. The protective role of Nrf2 in streptozotocin-induced diabetic nephropathy. *Diabetes.* 2010;59(4):850-60.
7. Assady S, Alter J, Axelman E, Zohar Y, Sabo E, Litvak M, Kaplan M, Ilan N, Vlodavsky I, and Abassi Z. Nephroprotective effect of heparanase in experimental nephrotic syndrome. *PLoS One.* 2015;10(3):e0119610.
8. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, and Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care.* 2004;27(11):2628-35.
9. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, and Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care.* 2005;28(5):1092-100.
10. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, and Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care.* 2005;28(5):1083-91.
11. Zheng H, Whitman SA, Wu W, Wondrak GT, Wong PK, Fang D, and Zhang DD. Therapeutic Potential of Nrf2 Activators in Streptozotocin-Induced Diabetic Nephropathy. *Diabetes.* 2011;60(11):3055-66.

4.0 Study Design

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

Response:

This is a single center, prospective, double blind, randomized, placebo –controlled in a parallel design study. The study will be conducted at the Diabetes – Endocrinology Center of Western New York under the direction of Dr. Paresh Dandona, M.D, Dr Manav Batra, MD and Dr Husam Ghanim, PhD.

Ninety (90) T2DM patients with micro- or macroalbuminuria (45 each) will be enrolled and randomized into 2 groups to receive placebo or exenatide-extended release treatments for 1 year. The study groups and treatment arms of this study are:

1. T2DM with Microalbuminuria: 30 patients on Exenatide extended release and 15 patients on placebo for 1 year
2. T2DM with Macroalbuminuria: 30 patients on Exenatide extended release and 15 patients on placebo for 1 year

5.0 Local Number of Subjects

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

Response: 90

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

Response: All screened and qualified patients will be enrolled and randomized

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

Response: The Diabetes and Endocrinology Center of WNY is the largest Diabetes center in the WNY area, seeing between 100 to 120 type 2 diabetes patients every week. Therefore, majority of recruited patients are our Kaleida Health and UBMD clinic patients. We will also recruit patients through advertisement, Buffalo Research Registry and researchmatch.org. These sources will suffice to recruit the needed number to subjects.

6.0 Inclusion and Exclusion Criteria

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

6.2 sample.

NOTE: This may be done in bullet point fashion.

Response:

Inclusion Criteria

- Type 2 Diabetes for at least 1 year.
- Microalbuminuria for at least 6 months (UACR: 30-300 mg/g)
- Macroalbuminuria for at least 6 months (UACR: >300 mg/g)
- HbA1c of ≤10%
- Ages 18-65 years (inclusive of ages 18 and 65)
- On ARBs/ACEi for at >3months

*6.3 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

- Use of GLP-1 Receptor agonists or SGLT-2 inhibitors therapy in the last 3 months
- History or risk for pancreatitis (e.g., history of gallstones, alcohol abuse, and hypertriglyceridemia)
- Coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery or coronary angioplasty) in the previous 3 months
- Hepatic disease: Severe hepatic insufficiency and/or significant abnormal liver function defined as:
    1. Aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >3x ULN
    2. Total bilirubin >2.0 mg/dL (34.2 μmol/L)
    3. Positive serologic evidence of current infectious liver disease including Hepatitis B viral antibody IGM, Hepatitis B surface antigen and Hepatitis C virus antibody
    4. Liver function tests more than 3 times the upper limit of normal
- *Renal impairment (serum eGFR <30 ml/min)*
- HIV
- Inability to give informed consent
- History of gastroparesis
- History of medullary thyroid carcinoma or MEN 2 syndrome
- Alcoholism
- Hypertriglyceridemia (>500 mg/dl).
- Any other life-threatening, non-cardiac disease
- Uncontrolled hypertension (BP > 160/100 mm of Hg)
- Congestive Heart Failure class III or IV
- Use of an investigational agent or therapeutic regimen within 30 days of study
- Participation in any other concurrent clinical trial
- Pregnant or breastfeeding patients or females of childbearing age not on 2 forms of acceptable contraceptives.

6.4 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: NA

☐ Adults unable to consent

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

☐ Pregnant women

☐ Prisoners

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

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

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

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

7.0 Vulnerable Populations

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

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

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

Response: We will not be using subjects from vulnerable populations

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

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

Response:

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

7.3 For research that involves ***prisoners****, safeguards include:*

NOTE CHECKLIST: Prisoners (HRP-415)

Response:

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

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

Response:

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

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

Response:

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

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

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

8.0 Eligibility Screening

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

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

Response:

After obtaining all necessary approval to conduct the study, study coordinator or investigators will conduct a prescreening phone conversation with referred or interested patients. Patients will then be schedule for a screening visit. Prospective participants will be asked to read and understand the consent and any questions they may have regarding the study will be answered. If the subject wants to participate in the study, they will be asked to sign the informed consent form. The subject's medical history and current medications will be obtained as well as their blood pressure and vitals. Females of childbearing age will be tested for pregnancy and

asked to sign a commitment form to be on 2 forms of acceptable contraceptives for duration of study. A physical examination will also be done. Blood samples will be taken in order to evaluate HbA1c, CBC, CMP and liver and kidney functions and pregnancy status. Patients meeting all the inclusion and exclusion criteria based on all screening tests will be enrolled in the study.

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

9.0 Recruitment Methods

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

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

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

Response: Potential participants will be identified by prescreening clinical charts, patient doctor interaction at the time of their visits. In addition patients will be recruited through advertisements , Buffalo Research Registry and researchmatch.org. Diabetes Endocrinology Center of WNY Locations include:

1. 1020 Youngs Road, Williamsville NY 14221
2. 705 Maple Road, Williamsville NY 14221
3. 462 Grider Street, Buffalo NY 14215

The study clinical team will evaluate their clinic patients for possible participation in this study according to the inclusion and exclusion criteria at the Diabetes and Endocrinology Center of WNY. Patients that may qualify are asked during their clinic visits if they are interested in participating in research. Patients that agree will be referred to the research team for further eligibility evolution. If these patients meeting the inclusion and exclusion criteria based on preliminary phone evaluation will be scheduled for a screening visit.

Facebook and Craigslist will be used for recruitment. The approved advertisement will be posted on the main advertising board at Erie County Medical Center. A generic flyer will be utilized also for recruiting.

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

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

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

subjects recruited from advertisement will call the research team for more information regarding participating in research. All personal information will be kept confidential and locked in the coordinator office.

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

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

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

Response: In addition to screening clinical charts, participations will be identified through; advertisement, Buffalo Research Registry, researchmatch.org, craigslist.com, and facebook

10.0 Procedures Involved

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

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

Response:

Visit 1 (week 0):
Qualifying subjects will be asked to come for the visit in a fasting state (10-12 hr fasting), vitals will be done and safety labs for CBC, CMP, HbA1C, kidney function tests will be drawn and 24hr urine will be collected. Blood samples (30ml) will be collected for research endpoints. Training on administrating study drug and information about side effects and how to report any adverse events will be discussed with patients. One of the treatment arms will be administered to the patient (placebo or Exenatide extended release in a randomized fashion) and enough drug supply for 13+2 weeks will be dispensed. Other diabetes medications will be reviewed and any standard of care adjustments will be made. A 24hr urine collection container will be dispensed and patients will be instructed to come back after 13 weeks.

Visits 2, 3 and 4 (Weeks 13, 26 and 39):
Patients will come to this visit in the fasting state. Physical exam (only on visit 3) and vitals will be performed, safety labs for CBC, CMP, HbA1c, kidney function tests will be drawn and 24hr urine collected. Blood samples (30ml) will be collected for research endpoints. Other diabetes medications will be reviewed and any standard of care adjustments will be made. Study medication use compliance will be assessed and drug supply for 13+2 weeks will be dispensed. A 24hr urine collection container will be dispensed and patients will be instructed to come back after 13 weeks.

Visit 5 (Week 52): Patients will come to this visit in the fasting state. Physical exam and vitals will be performed, safety labs for CBC, CMP, HbA1c, kidney function tests will be drawn and 24hr urine collected. Blood samples (30ml) will be collected for research endpoints. Other diabetes medications will be reviewed and any standard of care adjustments will be made. Patient will be discharged from the study after the final safety phone call at week 56.

Phone call will also be made at weeks 2, 8, 18, 34 and 46 weeks to inforce compliance and to ensure safety. Patients will also be instructed to call if they develop unexpected symptoms.

LABORATORY PROCEDURES

1. **MNC isolation:** Blood samples (30-40ml) is collected in Na-EDTA and carefully layered on Lympholyte medium (Cedarlane Laboratories, Hornby, ON) according to manufacturer's instructions. Samples are centrifuged and two bands separate out at the top of the RBC pellet. The MNC band was harvested and washed twice with Hank's balanced salt solution (HBSS). This method provides yields greater than 95% MNC preparation.
2. **ROS generation measurement by chemiluminescence:** Five hundred μL of MNC (2 x 10^5 cells) are delivered into a Chronolog LumiAggregometer cuvette. Luminol is then added, followed by 1.0 μL of 10 mM formylmethionyl leucinyl phenylalanine (fMLP). Chemiluminescence is recorded for 15 minutes. In this assay system, the release of superoxide radical as measured by chemiluminescence, has been shown to be linearly correlated with that measured by the ferricytochrome C method. The interassay coefficient of variation of this assay is 8 %. We have further established that the biological variation in reactive oxygen species generation in normal subjects is approximately 6 % for readings obtained 1 to 2 weeks apart. Similarly, the variation in reactive oxygen species generation in the obese over a period of 1 to 2 weeks is less than 8 %.
3. **Quantification of $p47^{phox}$, Keap-1, NQO-1, GST-1P, HO-1 and SMADs 2-4 expression:** The mRNA expression is measured in MNC by RT-PCR: Total RNA was isolated using commercially available RNAqueous®-4PCR Kit (Ambion, Austin, TX). One μg of total RNA is reverse transcribed using Advantage RT-for-PCR Kit (Clontech, CA). Real Time RT-PCR was performed using Stratagene Mx3000P QPCR System (La Jolla, CA), Sybergreen master mix (Qiagen, CA) and gene specific primers (Life Technologies, MD). All values were normalized to the expression of a group of housekeeping genes including actin, ubiquitin C and cyclophilin A.
4. **Western blotting:** MNC total cell lysates are prepared and proteins separated by SDS-PAGE and then transferred to PVDF membrane. Polyclonal or monoclonal antibodies against $p47^{phox}$, Keap-1, Nrf-2, SMADs and NQO-1 (Abcam, Cambridge, MA) and actin (Santa Cruz Biotechnology, CA) will be used. Densitometry is performed using molecular analyst software (Biorad, CA) and all values are corrected for loading with actin.

5. **Nrf-2 DNA binding:** Nuclear Nrf-2 DNA binding activity will be measured by EMSA. Nuclear extract is prepared from freshly tissues by NE-PER® Nuclear Extraction kit (Pierce Biotechnology, Rockford, IL). The specificity of the bands is confirmed by supershifting these bands with specific antibodies against Nrf-2 (Santa Cruz Biotechnology, CA) and by competition with cold oligonucleotides. DNA binding activity of Nrf-2 will be adjusted to Oct-1 DNA binding activity to correct for technical variables.
6. **Plasma measurements:** Glucose levels are measured in plasma by YSI 2300 STAT Plus glucose analyzer (Yellow Springs, Ohio). ELISA kits will be used to measure insulin (Millipore, MA), TGF-b1, CTGF, TIMPs, PAI-1 (R&D Systems), type I and IV collagen and fibronectin (fibronectin EDA). HbA1c, serum creatinine and cystatin C will measured by standard assays by Quest Diagnostic Labs.
7. **Urinary measurements:** Albuminuria, creatinine, creatinine clearance, GFR will measured from 24hr urine collection by standard assays by Quest Diagnostic Labs.
8. **15-isoprostane $_{F2t}$** (also known as 8-epi-PGF2α or 8-iso-PGF2α) in urine samples will be measured by an ELISA kit from Oxford Biomedical Research (Oxford, MI).

10.2 Describe what data will be collected.

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

Response:

The study investigations include evaluation of the effects of 1-year treatment with Exenatide extended release or placebo on progression of albuminuria and related kidney function measures in T2DM patients with established micro- or macroalbuminuria. Qualified patients will come fasting to the research center. Review of study procedures and vitals will be performed. Basal blood and 24-urine samples will be obtained. Patients will be randomized (in 2:1 ratio) to receive either Exenatide extended release or placebo for 1 year. Plasma and mononuclear cell (MNC) fractions will be prepared from the blood samples. Additional fasting blood and 24hr urine samples will be collected every 13±2 weeks (3, 6, 9 and 12 months) for a total of 5 study visits. Measurements of albuminuria, creatinine, creatinine clearance, GFR, isoprostanes and cystatin C following 1-year treatment with Exenatide extended release or placebo will be done on all urine samples collected before and at 3, 6, 9 and 12 months following treatment with Exenatide extended release or placebo. HbA1c, CBC, CMP, TGFβ, type I and IV collagen, CTGF, PAI-1, TIMP-1 and 2 and fibronectin EDA levels will be measured in all plasma samples collected while the expression of SMAD3, SMAD4, NQO-1, GST-1P and HO-1, Nrf-2/keap-1 system activation, $p47^{phox}$ levels and ROS generation will be done in all MNC samples collected before and at 13, 26, 39 and 62 weeks following treatment with Exenatide extended release or placebo.

Visit #	Screening	1	2	3	4	5
Weeks #	<-4	0	13±2	26±2	39±2	52±2
Medical History	X					
Physical exam	X			X		X

CBC/CMP/kidney function	X	X	X	X	X	X
Vitals and BP	X	X	X	X	X	X
Pregnancy test	X		X	X	X	X
HbA1c	X	X	X	X	X	X
MNC endpoints		X	X	X	X	X
Plasma mediators endpoints		X	X	X	X	X
Urinary endpoints		X	X	X	X	X
Other diabetes medications review and adjustments		X	X	X	X	X

10.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).
Include copies of these documents with your submission.

Response: Source documents will be used to collect patient information. Food and glucose measurement diaries will be also reviewed for medication adjustment.

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

Response: electronic medical records and research files.

*10.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

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

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

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

11.0 Study Timelines

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

Response: Enrollment of 90 patients should be completed within 10 months at a rate of 9 patients/month.

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

Response: 52 Weeks

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

Response: Approximately 30 Months

12.0 Setting

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

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

Response: Research will be conducted at the Diabetes Endocrinology Research Center of WNY, located at 1000 Youngs Rd, Suite 105, Williamsville, NY 14221 and at the CTRC located in 875 Ellicott St. Buffalo NY14203.The Diabetes Research Center has facilities and exam rooms available for insulin pump download, CGM device download, meal and infusion studies and presence of study coordinator and registered nurse for data collection and blood work at all times. One of the investigators will be available at all times to address patients' related issues. CTRC location is a fully equipped laboratory with equipment include ultra-low freezers for sample storage, centrifuges, microscopes for sample preparation, infusion pumps, ELISA, PCR and immunoblotting instrumentation.

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

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

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

Response:

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

13.0 Community-Based Participatory Research

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

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

Response:

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

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

Response:

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

14.0 Resources and Qualifications

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

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

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

Describe other resources available to conduct the research.

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

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

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

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

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

Response: Available medical literature will be provided as deemed appropriate or requested by patient through UB libraries, PubMed, Google scholar as all the investigators have access to medical literature through listed resources above. The patient will also have access to physician (Investigators and Co-Investigators) who will be available to address any adverse effects or other questions during the course of the study and make the appropriate referrals.

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

Response: Education through training meetings, conferences and discussions. Training records will be kept by study coordinator and updated when following any amendments

15.0 Other Approvals

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

Response: NA

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

16.0 Provisions to Protect the Privacy Interests of Subjects

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

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

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

Response:

When the patient is being seen at our outpatient 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.

Our clinical providers involved in the study will identify potential patients for recruitment from the Diabetes-Endocrinology Center of WNY Clinics according to the inclusions and

exclusion criteria and through advertisements. Patient who may qualify will be asked in private during their one on one consultation time with the physician if they wish to participate in the research study. If the patient agrees, the research coordinator will contact them for a telephone screening interview privately. During phone conversation, no private information will be spoken loudly by study staff conducting the interview. The patients who call for potential participation in the study due to advertisement flyers will be screened over the phone with the research coordinator, using our telephone screening form. All records of this telephone interview will be kept in the study binder locked in the research unit.

If the patient passes the telephone screening, they will be asked to make an appointment to review the consent. Patient will do this in a private, screen off area of the research department and will be allowed to discuss the consent in detail with the research coordinator and or study doctor. Patient will be notified that it is completely voluntary to participate in the research study and can withdraw at any time.

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

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

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

Response: Consent of the subject and partial HIPAA waiver.

17.0 Data Management and Analysis

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

Response: **DATA ANALYSIS**

This is a prospective study to evaluate effect of Exenatide extended release treatment for 1 year on albuminuria levels in T2DM patients with micro- and macroalbuminuria compared to placebo. The similarities in baseline values between the study groups will be compared using appropriate parametric tests. Transformations of the data on order to meet statistical assumptions may be considered. All statistical analysis will be carried out using SPSS software (SPSS Inc, Chicago, Illinois) based on intention to treat principle. Data will be presented as mean±standard error. The primary endpoint of the study is the change from baseline in albuminuria level at weeks 12, 26, 39 and 56 following Exenatide extended release and placebo treatments. Fasting samples collected at weeks 0, 12, 26, 39 and 56 will be used for this assessment with values at week 0 considered as baseline. Changes from baselines form both drugs arms will be compared to those from the placebo arms in both the micro and macroalbuminuria groups. The statistical analysis will be done using mixed model for repeated measurement (MMRM) analysis with assigned α value of 0.05. Our preliminary data on retrospective analysis of the difference in albuminuria following GLP-1RA treatment for 2.5 yrs in T2DM patients with micro and macroalbuminuria show regression of albuminuria (UACR) by approximately 55mg/mg and 500mg/g (about 50% reduction), respectively.

The secondary end points include the comparison of the changes in albuminuria based on baseline albuminuria category (micro or macro), creatinine clearance, Cystatin C, TGFβ, type I and IV collagen, CTGF, and fibronectin levels, the expression of SMAD3, SMAD4, NQO-1, GST-1P and HO-1, Nrf-2/keap-1 system activation between the Exenatide extended release and placebo groups and across albuminuria categories

17.2 If applicable, provide a power analysis.

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

Response:. Conservatively estimating a difference in the change from baseline in albuminuria after 1 year between the Exenatide extended release and placebo groups (across both albuminuria groups) of 60mg/g, with standard deviation of no more than 91mg/g, a sample size of 38 patients per group should provide adequate power ($\beta = 0.2$) to detect a significant difference ($\alpha = 0.05$). Aassuming a drop-out rate of 15% and 2:1 drug: placebo randomization ratio, 60 active and 30 control will be recruited for a total of 90 patients (rounded up). Patients will be enrolled based on a predetermined stratification according to the two albuminuria categories (micro and macro at 1:1 ratio) with 45 patients in each.

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

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

18.0 Confidentiality

A. Confidentiality of Study Data

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

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

Response: All patients' data records will be stored on password protected computers and or in locked cabinets within the research department. The research unit is locked after 5pm daily and all day on weekends. Identifiable patient information along with randomization information for each patient will be stored in locked cabinets in an locked archive room. This will only be accessible by

study coordinator and the PI. Electronic data will be stored on password protected computers as coded data based on randomization number eg R-12 without any patients identifiable information attached. These electronic files will only be accessible by authorized study personnel.

18.2 A. How long will the data be stored?

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

18.3 A. Who will have access to the data?

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

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

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

18.5 A. How will the data be transported?

Response: All data are stored at one location and is not transported unless it is being archived. At that point files will be transferred to Iron Mountain for storage and archiving.

B. Confidentiality of Study Specimens

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

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

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

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

18.7 B. How long will the specimens be stored?

Response: 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 studies.

18.8 B. Who will have access to the specimens?

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

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

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

18.10 B. How will the specimens be transported?

Response: Fresh samples collected for screening and safety will be transported by Quest Diagnostics courier at ambient temperature and according to Quest Diagnostics instructions. Frozen samples that are transported will be done so using dry ice in a properly labeled Styrofoam container by the laboratory technician.

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

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

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

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

Response: The principal investigator Paresh Dandona, MD, PhD and co-investigators, Manav Batra, MD and Husam Ghanim, PhD will review the data at the completion of all visits off each subject and every 3 months to assess the safety and any potential risks or benefits to the participants. Furthermore they will also assess other risks including the physical, psychological, social, legal and economic harm to these patients. The investigators listed above will carefully watch for any invasion of privacy and breach of confidentiality. The principal investigator will be sharing the results of safety analysis of the study with AZ and with the IRB. The study groups will remain blinded. If there are any safety concerns then co-investigator Husam Ghanim, PhD who is not directly involved with the study participants will unblind the study groups on the discretion of principal investigator and tabulate and present unblinded data to the investigators for review. Based on review of the data presented, assessment of potential harm to the patients will be carried out to determine the best course of action. The IRB and sponsor will be informed of this potential harm along with the recommended course of action. Research subjects will be withdrawn from the study if risks are significant and/or

not manageable (see subject withdrawal section). The IRB will be kept well-informed at all times.

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

Response Safety data (vitals, CBC, CMP, urinary markers) will be collected at screening, during and at end of the study. Injection site reactions and hypoglycemia data will be monitored and collected at every visit. Physical examination will be performed at 26 and 52 weeks visits and safety assessments performed. Pregnancy results and contraceptive adherence plan (if applicable) will be reviewed at screening, 16 and 39 and 52 weeks.

19.3 Describe any safety endpoints.

Response: *N/A*.

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

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

19.5 Describe the frequency of safety data collection.

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

19.6 Describe who will review the safety data.

Response: The principal investigator Paresh Dandona, MD, PhD and co-investigators, Manav Batra, MD and Husam Ghanim, PhD will review the data at the completion of all visits by each subject and every 3 months to assess the safety and any potential risks to the participants.

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

Response: Every 3 months, Dr. Dandona, Dr. Batra and Dr. Ghanim will assess the safety and any potential risks to the participants. Safety data (vitals, CBC, CMP, urinary markers) will be collected at screening, during and at end of the study. Injection site reactions and hypoglycemia data will be monitored and collected at every visit. Physical examination will be performed at 26 and 52 weeks visits and safety assessments performed. Pregnancy (if applicable) will be tested at screening, 16 and 39 and 52 weeks. Oral anti-hyperglycemic agents and/or insulin dose titration will be done to avoid hypoglycemia. Phone calls will be made for safety and compliance follow-up at least 6 time during the study. The patients, however, will be instructed to report any adverse event or safety related information via phone as soon as it occurs. All safety data will be reviewed by the PI or sub-investigators within 1-2 days of collection.

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

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

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

Response:

1. New safety information becoming available concerning the safety of study drugs.
2. Termination of funding.
3. Withdrawal of study drug by FDA
4. Significant increase in risks (beyond expected risks) based in review of safety data.

20.0 Withdrawal of Subjects

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

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

Response: 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

i. Pregnancy
ii. Developing conditions included in the exclusion criteria
iii. Subjects decision to withdraw from the study
iv. Severe side effects specific to study drugs
v. Any medical condition that may place patient at risk of further complications
vi. failure to take the medication as instructed, failure to keep your scheduled appointments,
vii. cancellation of the study by the sponsor, or other administrative reasons.

20.2 Describe any procedures for orderly termination.

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

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

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

Response: If a subject withdraws from the research, the data collected to that point will be used toward the research finding. 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.

21.0 Risks to Subjects

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

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

Response:

All subjects will be referred to exenatide and extended release exenatide labeling safety information and discussions of the potential side effects and the different warning and precautions will take place at the time of signing the informed consent and prior to treatment.

Potential side effects of GLP-1 agonist include hypotension, nausea, vomiting and other GI side effects. Patients will be provided guidance on potential side effects and how to properly manage and report it. The potential benefits including improved glycemia, improved BP, potential renal protection, improved quality of life (QOL) will most probably overcome the potential side effects.

Exenatide extended release caused rats to develop tumors of the thyroid gland. Some of these tumors were cancer. It is not known if Exenatide extended release will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people. This will be discussed in details with all participating subjects. Exenatide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Injection-site reactions: Serious injection-site reactions, with or without bumps (nodules), have happened in some people who use exenatide extended release. Some of these injection-site reactions have required surgical intervention. Report any injection site reactions including nodules to study investigators.

Severe allergic reaction (anaphylaxis) to study drugs or placebo ingredients or other interventions may accrue in rare cases. Epinephrine is the primary treatment for anaphylaxis with no absolute contraindication to its use. Our site and staff are trained and equipped to assist patients with such reactions. Severe conditions that are not satisfactory managed in site will be transferred to the hospital emergency department for further assessment and help.

All subjects will be informed of the potential complication of administration a blood draw, which includes mild bruising at the site . This should resolve in few days

Breach of confidentiality is always a risk. However, to minimize this risk patient data will be coded using a unique identification number and the data will only accessible to the study personnel.

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

Response: 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. Pregnancy (if applicable) will be tested at screening, 16 and 39 and 52 weeks. Oral anti-hyperglycemic agents and/or insulin dose titration will be done to avoid hypoglycemia. Phone calls will be made for safety and compliance follow-up at least 6 time during the study. The patients, however, will be instructed to report any adverse event or safety related information via phone as soon as it occurs. All adverse events will be reviewed by the PI or sub-investigators within 24 hr of reporting and all safety data will reviewed every 3 months.

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

Response:

Any adverse effects of Exenatide not currently known or those unique to their use in Type 2 diabetes with diabetic kidney disease may be some of the unforeseeable risks.

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

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

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

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

22.0 Potential Benefits to Subjects

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

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

Response: *Exenatide LR is approved for treatment of Type 2 diabetes and has beneficial effects on glycemic control and weight. Subjects will also benefit from close monitoring of their renal disease..*

23.0 Compensation for Research-Related Injury

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

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

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

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

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

Response: *AstraZeneca shall reimburse the Institution for the direct, reasonable and necessary medical expenses incurred by the Institution for the treatment of any personal injury that is a direct result of adverse drug experiences to subjects resulting directly from any manufacturing defects in the Study Drug to which the Subjects would not have been exposed but for their participation in the Study if (i) the Institutional parties have complied with this Agreement, the Protocol and any written instructions of AstraZeneca concerning the Study Drug and (ii) all the requirements of informed consent have been complied with. AstraZeneca will not provide compensation for lost wages or for any other damages, expenses or losses, or for medical expenses that have been covered by a Subject's medical or other insurance.*

24.0 Economic Burden to Subjects

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

NOTE: Some examples include transportation or parking.

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

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

25.0 Compensation for Participation

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

Response:

Total compensation for this study will be up to $400.00 after the completion of all study visits. Each completed study visit will be paid at $80.00. There is a total of 5 study visits. This payment will be received in the form of a check to the study participant.

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

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

26.0 Consent Process

26.1 Indicate whether you will be obtaining consent.

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

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

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

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

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

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

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

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

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

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

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

Response:

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

Non-English Speaking Subjects

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

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

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

Response:

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

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

Response:

Cognitively Impaired Adults

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

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

Response:

Adults Unable to Consent

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

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

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

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

Response:

☐

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

Response:

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

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

Response:

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

Response:

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

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

Response:

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

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

*26.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

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

Response:

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

Response:

26.15 Describe whether parental permission will be obtained from:

Response: N/A

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

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

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

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

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

Response:

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

Response:

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

Response:

27.0 Waiver or Alteration of Consent Process

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

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

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

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

Response:

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

Response:

28.0 Process to Document Consent

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

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

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

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the

script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response:

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

29.0 Multi-Site Research (Multisite/Multicenter Only)

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

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

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

Response:

29.2 Describe the method for communicating to engaged participating sites:

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

Response:

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

Response:

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

Response:

30.0 Banking Data or Specimens for Future Use

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

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

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

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

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

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

Response: Patient ID number, study visit information and date of collection will be stored with specimen.

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

Response: The copy of the individual patient data collected during the study period will be provided to these individual patients who can choose to hand carry it to their respective physicians and a copy will be faxed to their respective clinical providers upon verbal request from the patient. The results of the completed study will be made available to the patients if requested through published manuscript. Specimens (unidentified) will be used by current study staff or future collaboration for other research projects with appropriate approvals.

31.0 Drugs or Devices

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

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

Response: **Drugs used:**

Description or Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Exenatide vials	2.0mg/vial, powder for injection	AstraZeneca
Matching Exenatide placebo vials	powder for injection	AstraZeneca

- Exenatide extended release vials 2.0 mg/vial and matching placebo will be provided in one month kits containing:
  - One carton containing 4 vials of active or placebo powder
  - One carton containing 4 prefilled syringes with diluent, 5 vial adaptors and 8 needles.

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

Response: Drugs will be stored in a locked cabinet and temperature controlled refrigerator at 4C at the research facility of the Diabetes and Endocrinology Center of WNY at 1000 Youngs Rd, Suite 105, Williamsville, NY 14221. The study drug will be dispensed and documented by the research nurse, Jeanne Hejna. Training on administrating study drug and information about side effects and how to report any adverse events will be discussed with patients

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

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

Response: IND will not be filed. Exenatide will be used according to indication.

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

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

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

32.0 Humanitarian Use Devices

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

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

Response:

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

Response: