Adding Liraglutide to High Dose Insulin: Breaking the Cycle
(A Randomized Double Blind Placebo-Controlled Trial Evaluating the Role of Liraglutide in Patients with Uncontrolled Type 2 Diabetes Mellitus on High Insulin Dose)

INVESTIGATOR-INITIATED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN)
U1111-1122-0457

Department of Internal Medicine – Division of Endocrinology and Diabetes
UT Southwestern Medical Center
5323 Harry Hines Blvd. Dallas, TX 75390-8857

Correspondence to:
Ildiko Lingvay, MD, MPH, MSCS
Assistant Professor
UT Southwestern Medical Center, Division of Endocrinology
5323 Harry Hines Blvd 75390-8857
214-648-2779
Ildiko.Lingvay@UTSouthwestern.edu
SPECIFIC OBJECTIVES:

Primary Objective:
To evaluate the glycemic effect of the addition of liraglutide 1.8 mg/day to a high-dose insulin regimen (>1.5 units/kg/day) in patients with uncontrolled (HbA1c >7.5%) type 2 diabetes mellitus.

Secondary Objectives:
1. To evaluate the effect of the addition of liraglutide to a high-dose insulin regimen on pancreatic steatosis as well as hepatic steatosis;
2. To explore the mechanisms of glycemic improvement by assessing weight, beta cell function, and fasting and postprandial glucagon values;
3. To evaluate other metabolic effects of the addition of liraglutide to a high-dose insulin regimen including weight, blood pressure, lipid profile, and liver function;
4. To quantify other patient-related outcomes including the change in the total daily insulin requirement, the number of daily injections, patient compliance, and quality of life after adding liraglutide to a high-dose insulin regimen;
5. To assess the safety of the addition of liraglutide to a high-dose insulin regimen in patients with uncontrolled type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Hypotheses:
The addition of liraglutide to high-dose insulin in patients with uncontrolled type 2 diabetes will:
1. Improve glycemic control as measured by HbA1c and percent patients who achieve ADA glycemic targets.
2. Improve pancreatic steatosis
3. Improve hepatic steatosis
4. Reduce fasting and postprandial glucagon levels
5. Improved beta-cell function
6. Cause weight loss
7. Improve metabolic and cardiovascular milieu including better lipid profile, blood pressure, and liver function tests
8. Decrease the total daily insulin dose and the number of daily insulin injections
9. Increase patient compliance with the prescribed treatment regimen
10. Enhance treatment satisfaction and quality of life
11. Be accomplished safely, with minimal and/or transient side effects.

Endpoints:
Primary Endpoint:
1. Change in HbA1c from baseline
Secondary Endpoints:
1. Pancreatic triglyceride content
2. Hepatic triglyceride content
3. Fasting and postprandial glucagon levels
4. Beta-cell function
5. Weight
6. Percent reaching ADA HbA1c goal of <7%
7. Total daily insulin dose
8. Number of injections per day
9. Systolic and diastolic blood pressure
10. Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
11. ALT and AST
12. Quality of Life
13. Treatment satisfaction
14. Compliance with treatment
15. Percent with any treatment related side effects except hypoglycemia
16. Rate of hypoglycemic events (overall and nocturnal)

**Study type:**
- Single Center (UT Southwestern Medical Center at Dallas, TX)
- Randomized
- Double Blind
- Placebo-Controlled
- Two treatment arms (treatment and control)
- Length of intervention: 24 weeks
- Efficacy & safety trial

After the initial screening all eligible patients will undergo a placebo-only run-in phase for 1-2 weeks, followed by randomization to either the study drug or placebo. Both groups will undergo weekly titration from the initial dose of 0.6 mg/day to the target dose of 1.8 mg/day. Evaluations will occur at randomization, 4-, 8-, 16-, and 24-weeks post-randomization.

A visual summary of the study design is provided below:
Study population:

Patients with uncontrolled type 2 diabetes treated with high dose insulin will be recruited from Parkland Memorial Hospital inpatient and outpatient services or by self-referral to the Clinical Diabetes Research Clinic at University of Texas Southwestern. Based on the sample calculations provided in the statistical section, 64 volunteers will have to complete the study (32 in each treatment arm). Anticipating a drop-out rate of approximately 20%, we plan to randomize 80 volunteers. We anticipate screening approximately 100 volunteers for this study, of which 80 will qualify and complete the run-in period.

Inclusion Criteria

1. Type 2 diabetes mellitus
2. Insulin dose of >1.5 units/kg/day (represents total daily insulin dose, regardless of formulation, regimen, number of daily shots)
3. HbA1c ≥ 7.5% and ≤ 11%
4. Age ≥ 18
5. Stable comorbidities (no medication changes or exacerbations in >3 months prior to enrolment)
6. Stable dose of all oral hypoglycemics for ≥ 3 months prior to enrollment
7. Ability to provide informed consent before any trial-related activities

Exclusion Criteria
1. Type 1 diabetes mellitus
2. Any contraindication to the MRI procedure (metallic implants, severe claustrophobia, pregnancy, unable to lie still on a hard table for the duration of the procedure, weight above 400 lb – limit of the MRI table, magnet’s inner circumference smaller than the largest body circumference)
3. History of any pancreatic disease as it might interfere with the pancreatic TG measurement (i.e. pancreatitis, tumors, cysts, type 1 diabetes, any pancreatic surgery)
4. Lipase >3x the upper limit of normal
5. Creatinine Clearance ≤ 30 ml/min—due to increased risk of hypoglycemia, and possible interference with the accurate measurement of HbA1c
6. Incretin therapy (any GLP-1 agonist or DPP-IV inhibitor)
7. Unstable or decompensated comorbidities (including but not limited to recent acute coronary or cerebrovascular accident, planned arterial revascularization, chronic heart failure NYHA class III-IV, end-stage liver disease, or malignant neoplasm with treatment in the last 5 years)
8. Personal or family history of medullary thyroid carcinoma or MEN-2 syndrome
9. Severe gastroparesis
10. Pregnancy, breast feeding, intention to become pregnant, or not using adequate contraceptive measures
11. Organ transplant recipient or waiting list candidate
12. Steroid use (current or potential use during the trial)
13. Known or suspected allergy to trial medication(s), excipients, or related products
14. Contraindications to study medications, worded specifically as stated in the product’s prescribing information
15. Non-English speaking volunteers since no interpreters are available and the safety of the volunteers could be jeopardized if adequate and reliable communication is not possible.

Randomization Criteria

1. Compliance with the test product during the run-in period will be assessed at visit 2 prior to randomization. Only patients with an estimated compliance of >50% during the run-in period will be randomized.
2. Successfully complete the baseline MR Spectroscopy procedure.

Withdrawal Criteria

1. The subject may withdraw consent at any time.
2. Severe drug-related side effects including (but not limited to) acute pancreatitis, severe nausea and/or vomiting, renal failure, diagnosis of medullary thyroid cancer.
3. Pregnancy or intention of becoming pregnant

Subject Replacement

Subjects who withdraw or become ineligible will not be replaced. A drop-out rate of 20% is estimated and already calculated in the recruitment plan.
Visit Procedures

A graphical review of the visit procedures and timing is presented below:

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<th>Visit Time</th>
<th>Screen 1-3 wks</th>
<th>V1 1-2 wks</th>
<th>V2 0</th>
<th>Phone 2A 3 days</th>
<th>Phone 2B 7 days</th>
<th>Phone 2C 14 days</th>
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Insulin Dose Titration:

At randomization we will reduce the total daily dose of insulin by 20% if the screening HbA1c is ≤ 8%. Administration of the reduced dose of insulin would commence on the day of introduction of study treatment (liraglutide or placebo). For subjects with screening HbA1c ≥ 8.0%, the total daily dose of insulin will be considered and established individually for each patient. Insulin will be down-titrated if needed (see guidelines below) at all three phone encounters (day 3, 7, and 14) as well as at 4-week visit. If no hypoglycaemia has occurred we will increase the insulin dose back up to baseline at one month post-randomization. We will not further increase (up-titrate) insulin during the first 8 weeks post randomization, unless required to control acute hyperglycaemia and prevent acute complications of diabetes. Starting with the 8 weeks visit the insulin dose can be up-titrated or down-titrated based on the parameters noted below and the investigator’s clinical judgement to ensure optimal glycemic control. All decisions about the insulin dose titration will be performed by an experienced medical doctor specializing in diabetes management based on reviewing blood glucose values and the entire clinical context of the patient.
Dietary Modifications:
Counseling regarding the type and amount of food consumed with strong encouragement to count carbohydrates and/or calories will be performed for all patients by the investigator at visits 1-5.

Lifestyle Modifications:
All patients will receive recommendations regarding type/amount/intensity of physical activity and be provided future goals at visit 1. Reinforcement of these objectives will take place at visits 2-5.

Assessments for Efficacy
1. HbA1c – measured at screening, randomization, visit 4 (2-months) and end of study (6 months). Samples are processed immediately and stored at 0-5°C. It will be analyzed within 24 hrs at the UT Southwestern Medical Centre Diabetes laboratory using an HPLC technique. The laboratory is accredited by the National Glycohemoglobin Standardization Program. HbA1c interassay coefficient of variability is ≤2%, and the intra-assay variability is ≤0.3%.
2. Beta-cell function - determined using the C-peptide area under the curve (AUC) following a mixed-meal challenge test. Results will be compared with baseline and between the treatment groups. The rate of change in beta-cell function will be measured as ΔC-peptide/ΔGlucose. Following an overnight fast (10 hrs), patients will arrive at the Diabetes Research Center at UT Southwestern and an IV catheter will be placed. Following the collection of a baseline sample (for insulin, c-peptide, glucose and all other efficacy variables), the patient will be instructed to ingest Chocolate Boost at a dose of 1g CHO/kg over 5 minutes. Blood will be collected at the following time-points starting with the first drink of the Boost: 15, 30, 60, 90, 120, 180, 240 minutes for measurement of c-peptide, glucagon, and glucose. All samples are processed immediately, alliqoted, and stored at -80°C until analysis.
3. Glucagon will be measured fasting and following the mixed-meal challenge test (see time-points above) by RAI at the Touchstone Diabetes Laboratory at UT Southwestern Medical Center, Dallas, TX.
4. Pancreatic and liver triglyceride content - will be done using a 1.5 Tesla clinical whole body MR system (Gyrosan Intera, Philips Medical Systems, North America). High-resolution images through the abdomen will be collected to locate the pancreas (and liver, respectively) with patients in supine position holding their breath at exhalation. Using three perpendicular images of the pancreas (or liver, respectively), a volume of 2cc (10*10*20 mm3) for spectroscopic testing is selected within the

<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
<th>Very likely to adjust</th>
<th>Consider Adjusting</th>
<th>Unlikely to adjust</th>
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<td>Preprandial</td>
<td>&lt;70</td>
<td>70-80</td>
<td>80-130</td>
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<td>&gt;160</td>
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<tr>
<td>Postprandial</td>
<td>&lt;80</td>
<td>80-100</td>
<td>100-140</td>
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<td>&gt;200</td>
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</table>
body of the pancreas (or 30x30x30 mm³ for the liver), avoiding any peri-visceral fat.

Spectroscopic data will be collected as patients breath freely with MR signal triggering at exhalation, using a cardiac synergy coil and PRESS sequence. Data processing will be done using the NUTS software.

5. **Weight** - will be measured at each visit using the same calibrated digital scale, while patients wearing no shoes and only light clothing.

6. **Total daily insulin dose** – will be calculated at each visit by summing all insulin shots of all types over a 24 hrs period. The average of the 3 most recent 24 hrs prior to each visit will be used.

7. **Number of daily injections** – will be counted at each visit, by adding all shots regardless of the type of insulin. The average of the 3 most recent 24 hrs prior to each visit will be used.

8. **Systolic and diastolic blood pressure** - will be measured in sitting position using an Amron digital manometer, on the right arm, after 5 minutes of rest.

9. **Lipid profile, liver function test, hemoglobin, amylase, and lipase** will be collected at screening and end of study in fasting state, processed immediately, stored at 0-5°C, picked up by the currier same day, and analyzed at Quest laboratories, Irving, Tx.

**Assessments for Safety**

All safety assessments are performed at each visit, in person or by phone. Any unanticipated or serious adverse events will be reported to the local IRB and sponsor in accordance with local guidelines.

1. **Hypoglycemia** – All plasma glucose values ≤ 70 mg/dL, as well as values > 70 mg/dL when hypoglycaemic symptoms have occurred, should be recorded by the subjects in the diaries. The recording should include:
   - date of hypoglycaemic episode
   - time of hypoglycaemic episode
   - time of last main meal prior to episode
   - whether the episode was symptomatic
   - whether the episode was in relation to exercise
   - whether seizure or coma developed (only in the CRF)
   - whether the subject was able to treat him/herself (if not answered the Investigator must provide an explanation in the CRF)
   - the plasma glucose level before treating the episode (if available)

   The following definitions for hypoglycaemia will be used:
   - Minor: Subject is able to treat him/herself.
     - i. Asymptomatic Hypoglycemia- <70mg/dl with no symptoms
     - ii. Documented Symptomatic Hypoglycemia- <70mg/dl with symptoms
     - iii. Relative Hypoglycemia- >70mg/dl with symptoms
     - iv. Probable Symptomatic Hypoglycemia- Symptoms but no measurement
   - Severe: blood sugar <70mg/dl and the subject cannot treat him/herself. (Must be treated by another individual with carbohydrates, glucagon, or other resuscitative actions)
   - Nocturnal hypoglycaemia includes a time of onset between 00:01 and 05:59 (both included)

2. **Other treatment specific side effects**
• Nausea, vomiting, diarrhea, and headache
• Abdominal pain suspicious for pancreatitis would require interim amylase and lipase measurement which would be processed immediately, stored at 0-5°C, picked up by the currier same day, and analyzed at Quest laboratories, Irving, Tx.

3. Pregnancy Test- females of childbearing potential will have a serum or urine pregnancy test (human chorionic gonadotropin, hCG) performed at the screening visit and at visit 6 prior to MRI. Urine-stick pregnancy test will be performed for females of childbearing potential at any time during the trial, if a menstrual period is missed or if the participant voices concern.

Other Assessments
Treatment satisfaction and quality of life will be assessed at the run-in visit (Visit 1) and end of study (Visit 6) using a modified DQoL questionnaire. Total score as well as individual domain scores will be analyzed and reported.

Subject Compliance
Participants will bring all study medication to each appointment for review and study drug will be distributed at each appointment (visit 1, 2, 3, 4, and 5). Percent compliance will be calculated and recorded at each visit.

STATISTICAL CONSIDERATIONS:
Sample Size Calculation
The sample size was estimated using as guidance the results of the only published study that evaluated the addition of liraglutide to high dose insulin treatment (1). In this study the addition of liraglutide to high dose insulin lead to a reduction in HbA1c from 8.48+/-.084% to 7.08+/-1.1%. If such a difference between groups were assumed, eight subjects per study group would be sufficient to attain power of 80% or greater at alpha 5%. Yet this study did not have a control arm, and we do anticipate some glycemic improvement to occur in the control arm as well, due to closer observation and follow-up, and nutritional and lifestyle counselling. Taking a much more conservative approach and estimating the final HbA1c in the active group to be 7.1+/-0.9% in the active intervention group, and 7.6+/-0.9% in the control group (between groups HbA1c difference of 0.5+/-0.7%), 32 volunteers per group would have to complete the study to achieve 80% power and 5% alpha, rho=0.7 with either a compound symmetry or autoregressive covariance structure. Assuming 20% drop-out rate following randomization, 80 patients would have to be randomized. We plan to screen 100 patients to allow for screen failures and drop-outs during the run-in phase. Power estimates are calculated for between group comparisons in a repeated measures design using PASS 11 software, NCSS, Kaysville, Utah.

Statistical Methods
The study proposes to evaluate the effect of adding liraglutide to the treatment regimen of patients with uncontrolled type 2 diabetes on high doses of insulin. The primary hypothesis is that liraglutide will improve glycemia as measured by HbA1c.

An intention to treat (ITT) analysis will be performed with the ITT analysis data set consisting of all randomized subjects who received study medication and have at least one post-randomization study visit. All available data will be included in the analyses (repeated measures models), including subjects with missing data. Model parameter estimates in the presence of missing data will be made with restricted maximum likelihood. Missing values will not be imputed. Descriptive statistics will be used to summarize responses for each group and evaluation and 95% confidence intervals will be computed for differences between groups or visits within groups. Geometric means will be used to summarize data with log-normal distributions.

Post-treatment HbA1c will be compared between-groups using a mixed model repeated measures analysis for each measurement including the final visit and incorporating baseline HbA1c as a continuous covariate. The delta of last visit-baseline will be calculated and compared between groups as a secondary analysis. The area under the curve (AUC) for c-peptide, glucagon, and glucose measuring during the mixed-meal tolerance test will be computed using the trapezoidal rule and analyzed as described for HbA1c. All other secondary continuous endpoints described above will be compared between groups using a mixed model approach with intermediate study visit measurements (e.g., 1 month, 2 months, etc.) included as repeated measurement levels in the models. The repeated measures model will have a between treatment group factor, a repeated factor for study evaluation visits, and a group x visit interaction term. Pairwise comparisons will be made using least square contrasts derived from these Mixed Model Repeated Measures models. Covariates such as baseline c-peptide, age, BMI, and gender will be assessed and incorporated into the models as warranted. Categorical variables such as adverse event (see definition of hypoglycemia and other safety measures above) occurrence will be compared between groups with Fisher’s Exact test. Multiple hypoglycemic event occurrences will be evaluated with correlated binary regression via generalized estimating equations (GEE).

A per-protocol analysis is also planned using completers-only data, and excluding all patients in the active group who had an overall compliance rate of <50%.

As pre-planned exploratory analyses, we will compare (1) the effect of liraglutide on glucagon secretion in patients with high versus low beta-cell function at baseline; and (2) the HbA1c reduction in the group with higher (>8.5%) and lower baseline HbA1c (8.5% being the randomization stratification cutoff value).

All statistical analyses will be performed by the study statistician (Beverley Huet), who has extensive experience in clinical trials analysis. Model assumptions regarding normality and covariance structure will be carefully assessed. Nonparametric tests or data transformations will be used if necessary to meet assumptions. Statistical analysis will be performed with SAS software (SAS Institute, Cary NC), particularly Proc Mixed for linear models with both fixed and random effects.
A two-sided alpha <5% will be considered significant for all analyses.

**Interim Analysis**

No interim analysis is planned.

**REFERENCES:**