Title:

Study Protocol and Statistical Analysis Plan

The Effect of Simple Basal Insulin Titration, Metformin Plus Liraglutide for Type 2 Diabetes With Very Elevated HbA1c - The SIMPLE Study

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SIMPLE STUDY: SIMPLE BASAL INSULIN TITRATION, METFORMIN PLUS LIRAGLUTIDE FOR TYPE 2 DIABETES WITH VERY ELEVATED HBA1C

(A RANDOMIZED TRIAL COMPARING THE EFFICACY, SAFETY, AND HEALTHCARE RELATED COSTS OF TREATING PATIENTS WITH VERY ELEVATED HBA1C LEVELS WITH BASAL-BOLUS INSULIN REGIMEN OR BASAL INSULIN WITH A GLP-1 AGONIST)

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BACKGROUND AND SIGNIFICANCE:

1. Achieving glycemic goals in type 2 diabetes has multiple beneficial health consequences.

There are over 25 million patients with diabetes in the US [1], a disease with tremendous health, social, and economic implications. Studies like UKPDS [2, 3] and Kumamoto [4, 5] have established an undeniable link between hyperglycemia and micro- and even macrovascular complications. Such data serves as the background for the current glycemic targets recommended by the American Diabetes Association. Despite tremendous therapeutic advances and availability of numerous new classes of drugs in the past decade, more than a third of the population with diabetes, particularly in minority groups and those with lower level of education, still does not reach glycemic targets [6-8]. Given the large epidemic of obesity and type 2 diabetes, our efforts to curb diabetes related morbidity and mortality have a whole new meaning and huge potential impact, both on patient related outcomes as well as cost of healthcare – a very timely concern for our healthcare system[9-11].

2. Treatment guidelines for type 2 diabetes advocate insulin treatment for patients with a HbA1c>10%.

Treatment guidelines for diabetes have been published by ADA/EASD [12] and AACE [13], with the purpose of providing guidance to healthcare providers caring for patients with type 2 diabetes and ensure best possible outcomes. Currently metformin is well accepted as the first line therapy for patients with type 2 diabetes in addition to lifestyle changes [2, 12-14]. There is no general agreement as to what is the best way to advance treatment in those who have not achieved target HbA1c levels with monotherapy [12, 13]. The current ADA and AACE guidelines both recommend an individualized approach to treatment intensification which should take into consideration cost, patient's preference, and profile of available medications [12, 13] It is generally accepted that patients with HbA1c level >10 % have a low probability of achieving ideal glycemic target of <7.0% with any of the traditional oral hypoglycemic agents, or even after basal insulin-only initiation. Therefore such patients will require prandial insulin, whether administered as a mixed formulation or basal-bolus regimen in order to archive glycemic goals [6, 12, 13, 15-26].

3. Insulin is a very effective glucose lowering agent, but it is associated with multiple side effects and shortcomings.

Patients with a very elevated HbA1c (>10%) are traditionally thought to have more advanced disease [2, 6] as well as glucotoxicity [27, 28], which coupled with the need to lower HbA1c by >3% to reach glycemic targets, make insulin an obvious treatment choice [15, 29]. Insulin is considered the most effective hypoglycemic agent and therefore capable of lowering HbA1c into target range regardless of baseline glycaemia [15]. Yet an insulin based treatment regimen, when implemented correctly and intensively, takes a significant toll on the patient's lifestyle by requiring a higher commitment to disease management in the form of more frequent self-monitoring, multiple daily injections, requires more frequent dose adjustments, and a greater investment in insulin-related diabetes education [30, 31]. Furthermore, insulin treatment

is commonly associated with two most undesirable side effects: weight gain and hypoglycemia [30, 32].

4. Treatment-induced weight gain has a negative effect on the disease pathophysiology and fuels its progression.

Most patients with diabetes are overweight and obese, development of which is often the initial event in the pathophysiology of type 2 diabetes [1, 33, 34]. Using therapeutic agents that focus primarily on blood glucose control but promote further weight gain seems counterintuitive, as this further worsens insulin resistance, which in turns results in an increase in insulin requirement, thus fueling a vicious cycle which promotes disease progression [35]. A Swedish study confirmed the deleterious effects of weight gain after diabetes diagnosis, as it demonstrated that patients with newly diagnosed diabetes who gain, rather than lose or maintain weight, are at a significantly increased risk of cardiovascular death [36].

5. Hypoglycemia is a common side effect of intensive insulin treatment and has far reaching consequences.

Hypoglycemia has a greatly underestimated effect on patients' life and beyond. Even seemingly minor hypoglycemic events create treatment related anxiety, heighten social anxiety, can limit or interfere with the patients' professional and social life, and can lead to treatment noncompliance. Hypoglycemia, especially severe hypoglycemia, has also been associated with untoward medical consequences like dementia, cardiovascular risk, seizures, and even death [30]. It also carries a great financial burden both in direct cost related to the event, as well as indirect costs like lost wages and work absenteeism [31]. The effects of hypoglycemia reach beyond the patient, affecting the psychological, social, and financial well-being of the whole family [37].

6. We need treatment algorithms which are patient-centric and offer the best overall benefit, rather than a glucose-centric approach.

With an ever increasing focus on personalized patient-centric treatment [12, 13], there is a renewed focus on patient-related outcomes, including treatment burden and quality of life. Insulin treatment requires an increased level of diabetes education, more intensive glycemic monitoring, a heightened awareness for potential side effects, a larger daily time commitment, all with potential negative effect on quality of life and treatment satisfaction [31, 37, 38]. The increase in treatment acuity related to insulin translates into higher healthcare related costs, a very timely concern for our economy [9-11, 31].

7. GLP-1 agonist have pleiotropic effects which target the core pathophysiologic abnormalities in type 2 diabetes.

GLP-1 agonists have been a relatively recent addition to our diabetes treatment armamentarium. They exert many beneficiary actions, counteracting many of the basic pathophysiologic determinants of diabetes: enhance glucose stimulated insulin secretion, suppress glucagon production, promotes satiety, decreases food intake, improves insulin sensitivity, lower ectopic fat deposition (i.e. liver steatosis, visceral fat), etc. GLP-1 agonists lower HbA1c by 1.5-2%, have a very low risk of hypoglycemia, and promote weight loss – all very desirable effects in patients with type 2 diabetes [35]. While this

treatment does require an injection, it is very easy to use, does not require continuous treatment titration, and greatly reduces the need for frequent glucose self-monitoring. All these attributes make it quite an appealing treatment alternative for patients with type 2 diabetes. In the current diabetes treatment guidelines it is recommended as a second or third line agent after metformin failure.

8. The combination of basal insulin and GLP-1 agonists has been proven to be safe and very effective.

A meta-analysis of pooled data from across the LEAD program demonstrated that in patients with baseline HbA1c of > 9% liraglutide was better than glargine as an add on to oral hypoglycemic medications with average reduction in HbA1c of 1.9% [39]. Several other studies support equal or superior HbA1c reduction when a GLP-1 agonist is added to background therapy and compared to basal insulin, with the additional benefit of weight loss and minimal hypoglycemia [40-43]. GLP-1 agonist has also demonstrated superiority when added to maximized basal insulin therapy and metformin, when compared to prandial insulin alone [40, 44-48]. Furthermore, treatment with GLP-1 agonist in combination with basal insulin was shown to have a synergistic effect on glycemic control, with GLP-1 agonists exerting an insulin sparing effect, as well as ameliorating or eliminating the undesirable weigh gain associated with insulin therapy.

The current evidence suggests the combination of metformin, GLP-1 agonist, and basal insulin to be the most effective and simple strategy to achieve near normal glycemia in patients with a baseline HbA1c < 10%, while avoiding the side effects of weight gain, complexity of care, and hypoglycemia associated with insulin alone, or post-prandial hyperglycemia, weight gain, and hypoglycemia from the association of basal insulin to orals agents [40, 41, 43-48]. It is still not known whether these favorable effects extent to the more challenging group of patients with type 2 diabetes who have a baseline HbA1c >10%. Liraglutide reduces blood glucose by several mechanisms independent of insulin secretion and its superior effect on HbA1c and weight loss was found to be largely independent of diabetes duration and baseline HbA1c [39]. Treatment with GLP-1 agonists has also been associated with low secondary failure rates, durable and sustained long term blood glucose control, and durability of the initial weight loss [39, 42, 49].

Given all these distinct properties of GLP-1 agonists and simplicity of use, we propose they could represent a viable alternative to intensive insulinization in patients with very uncontrolled (HbA1c >10%) type 2 diabetes.

The aim of this study is to compare a GLP-1 plus basal insulin treatment regimen to a basal-bolus treatment regimen in patients with very uncontrolled (HbA1c>10%) type 2 diabetes. We will compare the two regimens with respect to efficacy in improving glycemic control, rate of hypoglycemia, change in weight, effect on patient quality of life, treatment burden, physician time, as well as healthcare related cost. We hypothesize that the two treatment regimens will have equal effectiveness, while the GLP-1 based regimen will be superior with respect to all other variables.

We chose to focus on a specific patient population which is generally considered to be most challenging to manage, use up greater heathcare resources, have higher potential for morbidity, and have traditionally been excluded from most clinical trials. Therefore this study will fill in an existing knowledge gap and provide high level evidence for future diabetes treatment guidelines pertaining to this patient population. We will obtain information not only in regards to the effectiveness of the treatment, but also safety and impact on healthcare cost beyond the cost of the drug.

Our findings will have great impact on the way we treat this – unfortunately – significant segment of the diabetic population, with huge potential benefits beyond just glycemic control, including quality of life, other metabolic co-morbidities, healthcare cost, etc. Additionally, if our proposed alternative regimen proves to be superior, this would represent a simple treatment alternative that primary care physicians can easily initiate and manage in their office, mitigating the need for referral to the specialist – representing a further healthcare cost control in addition to that observed in our study and a small step in alleviating the huge shortage of endocrinologists nationwide.

We are uniquely positioned to perform this study for multiple reasons: (1) we serve the largest county hospital in the US where this specific study population is greatly overrepresented; (2) our county hospital is a closed healthcare system, where all actual health-care related costs incurred by these patients can be readily captured; (3) the PI (and sub-I) have extensive clinical experience with this study population; (4) the PI has extensive clinical research experience, with proven track record of successfully designing clinically relevant studies and caring out to final completion even the most challenging research protocols.

SPECIFIC OBJECTIVES:

We plan to evaluate a new GLP-1 based treatment strategy for patients with very uncontrolled (HbA1c>10%) type 2 diabetes and compare it to a standard basal-bolus insulin regimen.

Primary Specific Aim: To determine the non-inferiority of the basal insulin-GLP-1 agonist combination therapy to full basal-bolus insulin combination therapy in patients with very uncontrolled (HbA1c>10%) type 2 diabetes.

Specific aims:

1. Compare the two treatment regimens with respect to a disease and patient-relevant composite outcome of effectiveness (HbA1c <7%) and safety (no hypoglycemia and no weight gain);
2. Compare the two treatment regimens with respect to treatment burden (number of daily shots, amount of glucose self-monitoring, need for treatment titration);
3. Compare the two treatment regimens with respect to quality of life [as measured by a disease specific (DQOL) questionnaire and general heath (SF-36) questionnaire];

4. Compare the two treatment regimens with respect to all healthcare related costs: actual cost of the pharmacologic agents, glucose monitoring supplies, all other pharmacologic (non-study related) and non-pharmacologic healthcare related costs (outpatient and inpatient, diabetes related and non-diabetes related). We will also compare actual physician time spent during office visits and non-visit related care of these patients. While no actual dollar amount can be attached to this (phone visits and longer office visits required by the need for extra patient education are not customarily reimbursable) time commitment is of great relevance to our physicians who care for these very complex patients.

Primary outcome:

Change in HbA1c from randomization to 26 weeks of therapy.

Secondary outcomes:

1. The main secondary outcome is a less traditional but very patient-centric and clinically meaningful composite outcome of HbA1c <7% AND no documented hypoglycemia (capillary glucose level <56 mg/dl) AND no significant weight gain (<3% body weight) during the 6-mo study follow-up;
2. % reaching target HbA1c of <7% at end of study;
3. 7-point glucose profile results;
4. % patients reaching pre-specified "treatment failure" outcome;
5. Change in weight from baseline (both absolute weight lost and percent of body weight);
6. % patients with weight loss >5% of body weight;
7. Number of hypoglycemic episodes defined as mild (symptoms of hypoglycemia confirmed by a CBG reading of <70 mg/dl), moderate (any CBG reading <56 mg/dl), severe (need for help to recover regardless of CBG reading);
8. Number of patients experiencing any hypoglycemic episodes;
9. DQOL questionnaire score;
10. SF-36 questionnaire score;
11. Number of daily injections;
12. Total daily dose of insulin;
13. Health care cost, total;
14. Health care cost, diabetes-related;
15. Total number of CBG checks/study;
16. Number of CBG checks/month;
17. Number of titration events by healthcare professional;
18. Number of titration events by patient;
19. Healthcare provider time during scheduled office (minutes/visit);
20. Healthcare provider time, unscheduled (total minutes);
21. Compliance with pharmacologic therapy;
22. Change in LDL cholesterol from baseline;
23. Change in Triglycerides from baseline;
24. Tolerability - defined as percentage of patients with side effects (other than hypoglycemia) related to the study medications;

25. Tolerability - defined by percentage of patients dropping out of the study due to side effects related to the study medications.

RESEARCH DESIGN AND METHODS

Study type:

- Single Center (UT Southwestern Medical Center at Dallas, TX)
- Randomized
- Single blind (evaluator)
- Two treatment arms (treatment and control)
- Length of intervention: 6 months
- Efficacy & safety trial
- Non-inferiority trial for primary outcome

Study Design:

We will conduct a prospective, randomized, single blind, two-arm, parallel trial comparing two treatment regimens (liraglutide, detemir, and metformin versus aspart, detemir, and metformin) in patients with very uncontrolled (HbA1c>10%) type 2 diabetes. The investigator performing the study related measurements will be blinded to the patients' treatment assignment.

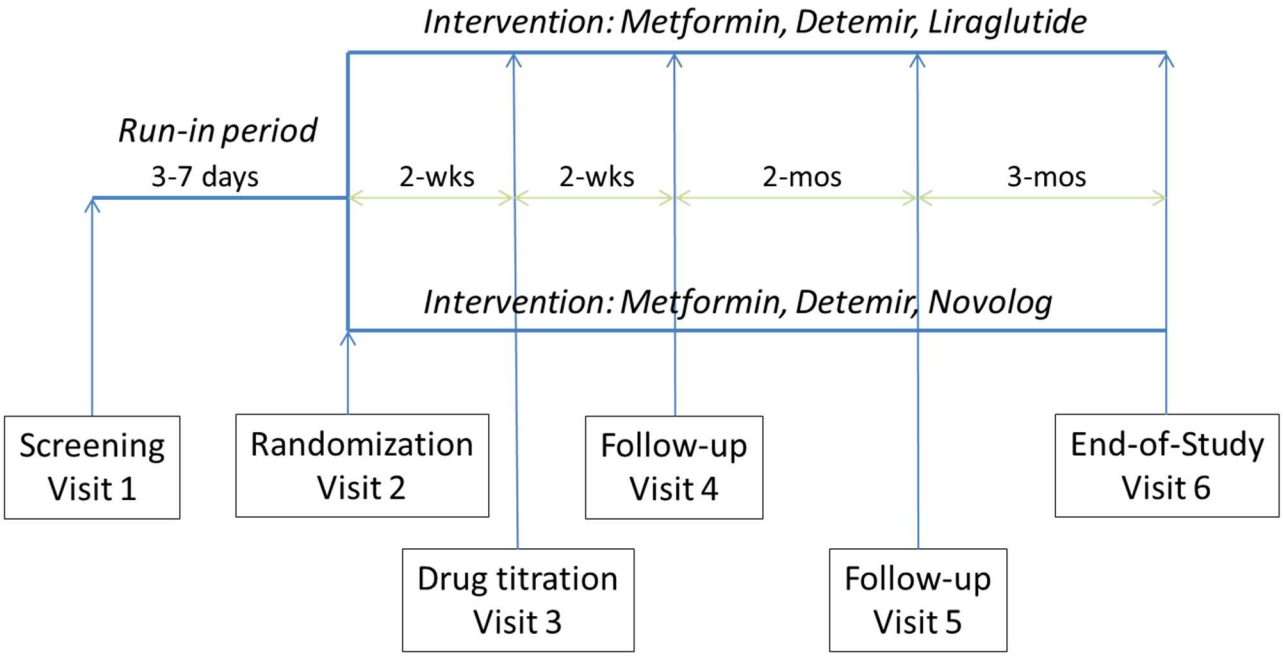

Figure 1: Study design showing the run-in period, followed by the randomization visit and the 6-mo intervention period.

The University of Texas Southwestern Medical Center Institutional Review Board will review the study and approve all relevant documents. Furthermore, study approval will be

obtained from Parkland Health and Hospital System (PHHS), which represents the study site.

Rationale for study Design

- The randomized design, with stratification for pertinent variables, will allow us to fully compare the effects of the two treatment algorithms in this hard to treat patient population.
- A 3-7 day run-in period was introduced in order to ensure patient compliance with study procedures prior to randomization.
- The patient-guided titration schedule for basal insulin is well validated in the literature and should help to lower fasting glucose level within a shorter period of time.
- A 6-month intervention period was chosen as nadir HbA1c after initiation of a treatment regimen is achieved by this time, therefore allowing us to evaluate the full effectiveness of these interventions.

Study Population:

Inclusion Criteria:

1. Informed consent obtained before any trial-related activities;
2. Both genders and all ethnicities;
3. Currently receiving medical care at Parkland Health and Hospital System (PHHS), Dallas, TX;
3. Age $\geq$ 18 years;
4. Diagnosis of Type-2 Diabetes, regardless of time since diagnosis;
5. Confirmed HbA1c >10%.

Exclusion criteria:

1. Age <18 as the feasibility and safety of this treatment regimen should be first established in the adult population; if successful, a subsequent pediatric study will be proposed;
2. Current use (within the past 30 days) of prandial-insulin;
3. Current use (within the past 30 days) of GLP-1 analogues or DPP-4 inhibitors;
4. Type 1 diabetes as purposefully withholding meal-time insulin is contraindicated;
5. Clinical state requiring inpatient admission/treatment;
6. Contraindication or strong cautions to any of the study medications:
    a. eGFR <30 ml/min if already on metformin, or eGFR<45 ml/min is not currently on metformin (per metformin label)
    b. History of lactic acidosis (per metformin label)
    c. Advanced hepatic or cardiac disease (per metformin label)
    d. Age >80 years (per metformin label)
    e. Chronic alcohol use (>14 drinks/week)
    f. History of pancreatitis (per liraglutide label)
    g. Personal or family history of medullary thyroid cancer or MEN syndrome (per liraglutide label)

h. Pregnancy, intention of becoming pregnant, or lactation (per liraglutide label)
i. Female of reproductive age not using adequate contraceptive methods (per liraglutide label). Adequate contraceptive measures include sterilization, intrauterine devices, oral contraceptives, approved hormonal implant, diaphragm with spermicide or condom with spermicide;

7. Any serious or unstable medical condition as it would interfere with treatment assignment as well as outcome measurement;
8. Any scheduled elective procedures/surgeries;
9. Active infections, including osteomyelitis;
10. Not willing to participate, unable to keep projected appointments, unwillingness to receive injectable treatment;
11. Known or suspected allergy to any of the trial products or related products;
12. Prior participation in this or another trial, or receipt of any investigational drugs within 3 months prior to screening;
13. Non-English speaking patients are excluded for safety reasons.

Rationale for Study Population

Patients who have a very elevated HbA1c (>10%) are thought to have significant glucose and lipotoxicity and the current guidelines recommend initiation of a full insulin regimen. This is a difficult to treat population, as they generally have more advanced disease, less beta-cell reserve, and, often time, poor compliance. Finding a simpler, safer, and effective treatment algorithm for these patients would have a great impact on the rate of comorbidities, as well as healthcare cost. This is also a population traditionally excluded from all regulatory studies, therefore little information is available on how to best approach their treatment.

Rationale for Study Location

Only patients from the PHHS system will be recruited. PHHS is a county hospital that provides comprehensive care (primary, specialty, inpatient and outpatient) to the indigent population of Dallas County. EPIC is the electronic medical record that is deployed at all sites and covers all aspects of care, including financial data. Therefore PHHS is the ideal location to conduct this study, as all patient-related information is captured and can be queried at multiple levels, including cost.

Randomization Criteria

1. Patient returned a fully completed 7-point glucose profile – suggesting likely compliance with proposed study procedures.

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, or hypersensitive to any study drug.
3. Pregnancy or intention of becoming pregnant.
4. Subject's diabetes control remains unchanged or becomes worse.

5. Subject participation in the research is no longer safe
6. The researchers believe that other treatment may be more helpful.
7. The sponsor or the FDA stops the research for the safety of the participants.
8. The sponsor cancels the research.
9. Subject is unable to keep appointments or to follow the researcher's instructions.

Subject Replacement

Subjects who withdraw or become ineligible will not be replaced. A drop-out rate of 12% is estimated and already calculated in the recruitment plan.

Study Schedule

Recruitment:

We will recruit patients from the following locations within the PHHS: emergency room (only if discharged home after the evaluation), primary care clinics, any specialty clinic (including diabetes clinic). Eligible patients will be informed about the trial by their treating physician. If agreeable, they will be contacted by the study staff and a screening appointment scheduled as soon as feasible (within days).

Screening Visit (visit 1):

During the screening visit patients will complete the informed consent process and will undergo a complete assessment for all inclusion and exclusion criteria. A complete medical history and comprehensive physical examination will be performed. Blood will be drawn (if not done within the past 7 days) to assess for all eligibility criteria (HbA1c, creatinine, liver function tests and pregnancy test, if applicable). Patients will receive an identification card with information about participation in the study. Patients will be asked to complete a 7-point glucose profile on the day prior to their next visit.

Randomization (visit 2):

Randomization will occur at the second visit (3-7 days from visit 1-screening). The study statistician will generate a blocked randomization scheme (1:1) stratified by "any insulin treatment at time of screening" (yes/no) and BMI (cutoff 37 kg/m2 – the average BMI of this study population in our PHHS Diabetes Clinic).

At this visit we will obtain a full baseline evaluation of all outcome parameters. All patients will meet with the dietician to received education regarding recommended lifestyle modifications. Patient will undergo diabetes education as well as teaching regarding insulin injection and titration.

Phone follow-up/ Drug titration visit:

At 2-wk from randomization (visit 3) a phone visit will take place to assess for safety parameters (particularly hypoglycemia) and perform protocol-driven treatment titration.

Follow-up visits:

At 1-, 3-, and 6-months (visits 4, 5, 6) patients will be followed-up in person for interim (and end of study, respectively) evaluations of all outcome parameters, as well as

protocol-driven treatment titration. A 7-point glucose profile will be repeated prior to the last visit in the study.

Interventions:

Both groups will either continue or initiate treatment with metformin. To minimize gastrointestinal side effects metformin will be initiated at 500 mg daily (or continued at current dose) and titrated weekly in 500 mg increments to the final dose of 1000 mg twice daily (or maximum tolerated dose which should be at least 500 mg BID).

Both groups will be initiated on basal insulin detemir. If new to insulin, this will be started at 0.3 units/kg once daily at bedtime and self-titrated based on the study protocol (see detemir patient self-titration table). If already on basal insulin, will take the total daily dose of basal insulin and perform a 1:1 dose conversion to insulin detemir, which will be administered once daily at bedtime, followed by the same titration. Additionally, physician-directed titration will occur, if needed, during the scheduled phone and/or office visits, as well as any unscheduled patient-initiated visits (phone/in person, if applicable). All patients new to insulin will be seen by the diabetes educator to receive instruction in insulin injection techniques.

Detemir patient self-titration table:

Fasting Blood glucose	*Change in your insulin dose*
<45	Decrease by 5 units
<70 mg/dL	Decrease by 3 units
71- 100 mg/dL	No change in your insulin dose
101-120 mg/dL	Increase by 1 units

Patients randomized to liraglutide will stop any insulin products besides detemir (if applicable), initiate liraglutide at 0.6 mg/day, and dose escalate weekly to 1.2 mg/dl and final dose of 1.8 mg/dl. Patients who develop significant and persistent gastrointestinal side effects are allowed to down-titrate the dose of liraglutide to 1.2 mg/dl for 1 week or until the side effect resolve.

Patients randomized to meal-time insulin will initiate insulin aspart before each meal. Aspart insulin will be initiated at a dose of 0.3 units/kg/day divided among the number of meals taken daily. Meal-time insulin titration, if needed, can be either patient driven (see table below) or physician-directed during the scheduled follow-up visits (phone or in person), as well as any unscheduled patient-initiated visits (if applicable).

Novolog patient self-titration table:

Glucose prior to lunch	*Change in breakfast insulin dose*	*Glucose prior to dinner*	*Change in lunch insulin dose*	*Glucose prior to bedtime*	*Change in dinner insulin dose*
<54	-2 units	<54	-2 units	<54	-2 units
55-69	-1 unit	55-69	-1 unit	55-69	-1 unit
70-120	No change	70-120	No change	70-130	No change
121-160	+1 unit	121-160	+1 unit	131-180	+1 unit

>160	+2 units	>160	+2 units	>180	+2 units

Rescue therapy:

Should any patients randomized to liraglutide treatment experience persistent hyperglycemia (defined as a confirmed Hb1c>10%) at the 3-mo visit (visit 5), meal-time insulin aspart will be initiated per the same protocol as above. This is a pre-specified "treatment failure" end-point. Following initiation of rescue therapy patients will continue all scheduled visits and procedures through the end of the trial.

Should any patients randomized to the "standard of care" group experience persistent hyperglycemia (defined as a confirmed HbA1c >10%) at the 3-mo visit (visit 5), treatment and insulin titration will continue as scheduled. This is also a pre-specified "treatment failure" end-point.

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

Visit	**1**	**2**	**3**	**4**	**5**	**6**
Time	**3-7 days**	**0**	**2 weeks**	**1 month**	**3 months**	**6 months**
Type	**Office**	**Office**	**Phone**	**Office**	**Office**	**Office**
Consent	x					
I&E criteria	x					
Randomization criteria		x				
Randomization		x				
Physical exam	x			x	x	x
Height	x					
Vitals (weight, BP, pulse)	x	x		x	x	x
Dietary counseling	x	x	x	x	x	x
Lifestyle counseling	x	x	x	x	x	x
7-point glucose		x				x
Labs (HbA1c, lipids, CMP, Hb)	x				x	x
Dispense trial drug		x		x	x	
Hypoglycemia assessment	X	X	X	x	x	x
Frequency of glucose monitoring				x	x	x
Titrate insulin		x	x	x	x	
Liraglutide titration (if applicable)			x			
Insulin dose assessment		x	x	x	x	x
Compliance assessment				x	x	x
# daily injections				x	x	x
QoL questionnaires (DQOL and SF36)		x				x
AE and SAE assessment		x	x	x	x	x
Pregnancy test (if needed)	x	x		x	x	x
Physician time assessment		x	x	x	x	x
Healthcare cost data extraction						x

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 dietitian at visit 2 and investigator at visits 3-5.

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, visit 5 (3-months) and end of study (6 months). Samples are processed immediately and stored at 0-5°C. It will be analysed 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. Weight - will be measured at each office visit using the same calibrated digital scale, while patients wearing no shoes and only light clothing.
3. Total daily insulin dose – will be calculated in units/kg 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.
4. 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.
5. Systolic and diastolic blood pressure - will be measured in sitting position using an Omron digital manometer, on the right arm, after 5 minutes of rest.
6. Lipid profile, liver function test, haemoglobin - will be collected at screening, 3-months, and end of study in fasting state. The blood will be processed and analysed immediately by PHHS Clinical Laboratory.
7. 7-point glucose measurement – will be performed by the patient on the day prior to the randomization visit and prior to the end-of-study visit.
8. Frequency of glucose monitoring – will be assessed by downloading the glucose monitor. Average number of readings/day will be recorded at each visit.

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 FDA in accordance with local guidelines.

1. Hypoglycemia – All plasma glucose values ≤ 70 mg/dL, as well as values >70 mg/dL when hypoglycemic symptoms have occurred, should be recorded by the subjects in the blood glucose diaries provided at each visit. The recording should include:

- date of hypoglycemic episode

- time of hypoglycemic 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
- whether the subject was able to treat him/herself
- the plasma glucose level before treating the episode

The following definitions for hypoglycemia will be used:

- Mild- Symptomatic or asymptomatic hypoglycemia with blood glucose 56-69 mg/dl and subject was able to treat him/herself
- Moderate- Symptomatic or asymptomatic hypoglycemia with blood glucose <56 mg/dl and subject was able to treat him/herself
- Severe- Blood sugar <70 mg/dl or symptoms highly suggestive of hypoglycemia and the subject needed assistance to be treated with carbohydrates, glucagon, or other resuscitative actions
- Nocturnal hypoglycaemia- blood glucose <70 with a time of onset between 00:01 and 05:59 (both included)
- Relative Hypoglycemia- Blood glucose >69 mg/dl with symptoms highly suggestive of hypoglycemia
- Probable symptomatic hypoglycemia- Symptoms highly suggestive of hypoglycemia but subject did not measure blood glucose.

2. Other treatment specific side effects
    - Nausea, vomiting, diarrhea, and headache;
    - Abdominal pain suspicious for pancreatitis would prompt immediate physician evaluation and laboratory testing for amylase and lipase measurement which would be processed immediately and analysed by PHHS Clinical Laboratory.
3. Pregnancy Test- females of childbearing potential will have urine pregnancy test (human chorionic gonadotropin, hCG) performed if clinically indicated in the assessment of the investigator. 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 randomization visit (Visit 2) and end of study (Visit 6) using a modified DQoL and SF-36 questionnaires. Total score as well as individual domain scores will be analysed 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.

Healthcare Cost Assessment: At the conclusion of the study, the EPIC integrated medical record system will be queried for the data regarding all healthcare related expenditures. From this information a data subset of diabetes-related expenditure will also be reported.

Physician Time Assessment: Each physician interaction (office visit or phone visit) will be timed to compare the two treatment regimens with respect to burden on healthcare provider's time.

RISKS ASSOCIATED WITH THE PARTICIPATION IN THE STUDY:

Risks of Liraglutide:

Very common (reported by more than 10 percent of the patients):

- - Gastrointestinal adverse events are the most common side effect of liraglutide and reported in up to 41% of patients. Nausea is seen in approximately 13% of patients treated with liraglutide and is usually developed in the first 2 weeks. It tends to be mild, dose-related and decline over time. In some patients the nausea can be more severe and be associated with vomiting which is usually transient and self-resolving.

Common (reported by 5-10 percent of the patients)

- Low blood sugar (hypoglycemia) - - The risk of having hypoglycemia with liraglutide is higher if taking it with another medicine that can cause hypoglycemia, such as a sulfonylurea or insulin. In some people, the blood glucose may get so low that they need another person to help them. The dose of your sulfonylurea medicine or insulin may need to be lowered while using liraglutide.
- Headache and upper respiratory tract infections have been reported in 7-9% of patients treated with liraglutide. A similar percentage of patients developed headaches with placebo or comparator drug.

Uncommon side effects (reported by 1-5 percent of the patients):

- Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of liraglutide treated patients in the five clinical trials of at least 26 weeks duration. Less than 0.2% of liraglutide-treated patients discontinued due to injection site reactions.

Very rare side effects (affects less than 1 percent of patients)

- Acute pancreatitis (inflammation of the pancreas) - there have been few reported event of acute pancreatitis presenting with persistent severe abdominal pain (usually accompanied by vomiting). Patients experiencing the above symptoms should contact the study doctor who will decide on whether they should discontinue the trial medication and /or require additional diagnostic procedures.
- Rarely, a severe form of allergic reaction (anaphylactic reaction) with additional symptoms such as breathing problems, swelling of throat and face, fast heart beat

etc. has been reported with marketed use of Liraglutide. Patients experiencing these symptoms should seek immediate medical help and inform the trial doctor as soon as possible.

- Kidney failure – Liraglutide may cause nausea, vomiting or diarrhea, leading to loss of fluids (dehydration). Dehydration may cause kidney failure which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce the risk of dehydration.

Other potential risks related to liraglutide:

- Hyperglycemia (too high blood glucose) can occur, especially if there is insufficient treatment. . The symptoms of hyperglycemia include increased urination, feeling thirsty, losing appetite, feeling sick (nausea or vomiting), feeling drowsy or tired, flushed, dry skin, dry mouth and a fruity (acetone) smell of the breath. If not treated, these symptoms may develop into a serious condition called diabetic ketoacidosis which may even lead to death.
- Thyroid tumors, including cancer -During the drug testing process, the medicine in Victoza caused rats and mice to develop tumors of the thyroid gland. Some of these tumors were cancers. It is not known if Victoza will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people. If medullary thyroid cancer occurs, it may lead to death if not detected and treated early. If you develop tumors or cancer of the thyroid, your thyroid may have to be surgically removed. Fibrosarcomas (cancer underneath the skin) were seen at the point of injection (skin) in male mice that underwent a 2 year study of liraglutide. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the preparation used for humans is 10 times higher than the concentration used in mice. It is not known if liraglutide will cause fibrosarcomas in people.

<u>Risk of insulin detemir and aspart:</u>

Very common (1-10 in 100 patients):

- Hypoglycemia (low blood sugar) is the most common adverse reaction of insulin therapy and may be life- threatening if severe and not treated appropriately.
- Mild-moderate weight gain is expected with any insulin therapy

Less common (less than 1 in 100 patients):

- Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with any insulin products, including detemir insulin or aspart insulin.
- Other adverse reactions associated with detemir insulin and/or aspart insulin include injection site reactions, lipohypertrophy, rash, itching.
- Needles and insulin pens should never be shared.

<u>Risk of Metformin:</u>

Very common (1-10 in 100 patients):

- Abdominal or stomach discomfort
- Decreased appetite
- Diarrhea
- Bloating
- Low serum Vitamin B12 levels without clinical manifestations

Precautions:

- Lactic Acidosis: Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to Metformin accumulation during treatment with Metformin HCl; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus. Metformin should be discontinued immediately and health care provider should be promptly notifed if unexplained increase in breathing rate, muscle aches, fatigue and unusual somnolence occur.
- Patients with Renal disease or renal dysfunction (e.g., as suggested by eGRF <30 ml/min) should not use metformin
- Metformin should be temporarily discontinued 48h prior to radiologic studies involving intravascular administration of iodinated contrast materials 48h prior to procedure to avoid increased risk of development of lactic acidosis and restarted 24h after the procedure.
- Excessive alcohol intake, either acute or chronic should be avoided while receiving Metformin.

SAFEGUARDS AND PRECAUTIONS TO MINIMIZE RISKS/HARMS:

- Hypoglycaemia episodes will very closely monitored trough the study using self-glucose monitoring. Review of blood glucose diary and hypoglycaemic events will be discussed during office, phone visits and as needed. Patient will be instructed during randomization visit on how to proper handle mild, moderate and severe hypoglycemic episodes and how to reduce their basal insulin doses according to study protocol. Those instructions will be reinforced as needed during the study.

- Should any patients randomized to liraglutide treatment experience persistent hyperglycemia (defined as Hb1c>10%) at the 3-mo visit (visit 5), meal-time insulin aspart will be initiated per the same protocol as the standard group

- Should any patients randomized to the “standard of care” group experience persistent hyperglycemia (defined as HbA1c>10%) at the 3-mo visit (visit 5), treatment and insulin titration will continue as scheduled.

- Patients will be monitored closely for any drug-related side effects. They will be provided with instruction on when to call the PI and a direct phone line, so they can immediately report any problems or concerns. Instructions will be given on possible side effects and how to avert/minimize them.

- Only qualified personnel will perform blood draws to minimize the risk of complications.

- Patients are allowed to skip questions on the questionnaire should they feel that the question might pose a psychological burden.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation

We propose to test a non-inferiority hypothesis comparing the 6-month change from baseline in HbA1c between the two treatment groups, with a non-inferiority margin of 0.4%. We conservatively estimate the standard deviation of the difference at 0.5% based on results from reported studies with similar design[44, 45, 47]. Using a one-sided alpha of 0.025, we determine that 44 subjects per group completing 6 months will provide power 0.96 to test this non-inferiority hypothesis, shown below amongst with other scenarios (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com). We will need to randomize 100 patients to test this hypothesis assuming a 12% drop-out rate (estimated drop-out rate based on our extensive prior experience with similar population and length of study). We plan to screen 120 patients to account for approximately 20% anticipated screen failures.

Power and sample size estimation for Non-Inferiority Test (H0: Diff >= NIM; H1: Diff < NIM)
Higher Means are Worse
Test Statistic: T-Test

Power	N1/N2	Non-Inferiority Margin (NIM)	Actual Difference (D)	Significance Level (Alpha)	Beta	Standard Deviation1 (SD1)
1.000	44/44	0.4	0	0.025	0.000	0.3
1.000	48/48	0.4	0	0.025	0.000	0.3
1.000	50/50	0.4	0	0.025	0.000	0.3
0.960	**44/44**	**0.4**	**0**	**0.025**	**0.040**	**0.5**
0.973	48/48	0.4	0	0.025	0.028	0.5
0.977	50/50	0.4	0	0.025	0.023	0.5
0.755	44/44	0.4	0	0.025	0.245	0.7
0.791	48/48	0.4	0	0.025	0.209	0.7
0.808	50/50	0.4	0	0.025	0.192	0.7

Further, this sample size will yield at least 80% power at two-sided alpha=0.05, superiority hypothesis, for the secondary composite outcome endpoint of HbA1c<7% with no hypoglycemia and no significant weight gain, expecting that 25% and 5% reach

this endpoint with liraglutide treatment and standard basal-bolus insulin treatment, respectively.

Randomization

Treatment assignment will occur at the second visit. The study statistician will generate a blocked randomization scheme (1:1) stratified by "any insulin treatment at time of screening" (yes/no) and BMI (cutoff 37 kg/m2 – the average BMI of this study population in our PHHS Diabetes Clinic), programmed using SAS Proc Plan.

Statistical Analysis Plan

All statistical analyses will be performed by the study statistician (Beverley Huet), who has extensive experience in clinical trials analysis.

Primary analysis: The primary analysis will be intention-to-treat (ITT) which will include all randomized participants who receive at least one dose of a study medication. The non-inferiority of liraglutide treatment strategy compared to standard basal-bolus insulin regimen will be assessed using a 95% confidence interval for the between treatment group net difference (month 6 minus month 0) in HbA1c at 6 months. This 95% confidence interval will be derived from the differences of least square means estimated from a mixed model repeated measures analysis. Non-inferiority of liraglutide treatment will be concluded if the upper limit of the 95% confidence interval is less than the non-inferiority margin of 0.4%.

Secondary analyses: We will also perform a per-protocol analysis comparing HbA1c response because, in non-inferiority hypothesis testing, the ITT analysis may be biased toward the null hypothesis. The per-protocol population is defined as the population who continued the assigned intervention as randomized for the duration of the study period. Secondary outcomes include the composite endpoint of HbA1c<7% with no hypoglycemia and no significant weight gain, a binary variable, which will be compared between the randomized study groups with a logistic regression model. The odds ratio and corresponding 95% confidence intervals will be reported. From healthcare related cost data, cost-effectiveness ratios will be summarized as point estimates with 95% confidence intervals, accounting for the skewness in the distribution of the ratio[50]. Sensitivity cost analyses will be performed to further assess variables such as treatment failure and quality of life weights. Multiple logistic regression models will be constructed to evaluate any association of baseline covariates on treatment efficacy. Binary secondary endpoints will also be assessed with logistic regression models. Group comparisons and changes from baseline over time (study visits) of continuous secondary outcome variables will be analysed with mixed model repeated analysis. The logrank test will be used to compare the pre-specified "treatment failure" end-point between groups. Safety endpoints and hypoglycemic and other adverse events will summarize in detail with descriptive statistics. The analysis of safety data will be performed for the ITT population.

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.

DATA HANDLING AND RECORD KEEPING:

All data will be collected in strict compliance with the University's HIPPA rules. Research records (source documents) will be kept in a double-locked filing system in a secure locked room. Collected data will be stored in an electronic study database will be encrypted and password protected and saved on the University's secure network. Only study personnel will have access to these records.

The institutional review board (IRB) governing this study may inspect the medical records of any patient involved in this study at any time.

Laboratory specimens will be collected under standard of care protocol at Parkland hospital laboratory and handled in accordance with the hospital policy.

The study blind will be maintained by the designated statistician and only broken by request from a treating physician in case of a medical emergency.

ETHICS:

Ethical Considerations:

1. Exclusion of non-English speakers- while translators are available during working hours, the investigators are worried that no translator will be available to assure safety measures at all times.
2. Compliance with Insulin Regimen- At times patients are not compliant with complicated insulin regimens and providers often continue to uptitrate insulin dosage when patients remain above HbA1c goal. If patient compliance improves once enrolled in the study, there is a higher risk of hypoglycemia. Every effort will be made at all visits to determine exactly what amount of insulin the patient is taking and the overall compliance.

Informed Consent:
Informed consent will be obtained during the first face-to-face contact. Once a prospective subject is identified, we will explain the study details and preliminary eligibility is accessed either through phone or face-to-face interview. If the prospective volunteer remains interested in the study and fulfils preliminary eligibility criteria, baseline studies are scheduled. Only study personnel listed on the consent will be permitted to obtain consent. The subject will be provided informed consent and it will be signed and witnessed. The consent form will discuss the procedures to be performed at each visit, the number of visits, and what is expected of the patient, along with all possible side effects. A copy will be given to the subject and the original will be kept on file. Potential subjects may be screened for eligibility using a study-specific HIPAA waiver. Volunteers who call to inquire about the study will have their demographic and contact information collected over the phone, and the study will be described to them.

Once the subject has agreed to participate and appears in person, a study specific HIPAA Authorization will be signed, along with the consent form document.

Confidentiality/HIPAA:
Every effort will be made to keep all information about the patient confidential. Consent forms will be placed in the patient charts. Research records will be kept in a double-locked filing system in a secure locked room. The electronic study database will be encrypted and password protected and saved on the University's secure network. Only study personnel will have access to these records.

The institutional review board (IRB) governing this study may inspect the medical records of any patient involved in this study.

IRB Approval:
The study is approved by the UT Southwestern IRB.

FDA Approval:
An IND/NDA exception was granted by the FDA for possible use of rescue therapy with prandial insulin add-on to detemir-liraglutide combination should patients in the liraglutide arm reach the pre-defined failure end-point.

Declarations:
This study will be conducted in accordance with the Declaration of Helsinki.
This study will be conducted in accordance with the ICH GCP guidelines.
The sponsor-investigator will comply with all applicable regulatory and legal requirements, ICH GCP guidelines, and the Declaration of Helsinki in obtaining and documenting informed consent.

Study schedule:
IRB approval: December 2013
Start of Study: as soon as funding received (estimate March 2014)
Recruitment period: March 2014 – February 2015
First Patient First Visit: March 2014
Last Patient First Visit: February 2015
Last Patient Last Visit: August 2015
Final Report: October 2015
Final Manuscripts: December 2015

STUDY DRUGS AND MATERIALS:

Study medication
Liraglutide 6 mg/ml solution for subcutaneous injection delivered in a 3 ml prefilled disposable pen
Detemir insulin 300 units/prefilled disposable pen
Aspart insulin 300 units/prefilled disposable pen

Provided and manufactured by NovoNordisk A/S.

NovoFine Pen needles – provided by NovoNordisk US.

Storage and Drug Accountability of Study Medication(s)

Patients will be instructed as follows:

-Store unused pens in a refrigerator at a temperature between +2°C and + 8°C (36°F to 46°F). Keep away from the cooling element. Do not freeze and do not use if it has been frozen.

-Store pens in use for 30 days at room temperature (15°C to 30°C; 59°F to 86°F) or in a refrigerator (2°C-8°C; 36°F to 46°F).

-Do not freeze and do not use if it has been frozen.

-The pen must be protected from all sources of light, and the pen cap should be kept on when the pen is not in use.

-Product should not be used if it does not appear clear and colorless.

Investigator will ensure availability of proper storage conditions and record and evaluate the temperature. While at the site, drug will be stored in a temperature-monitored refrigerator at 4°C.

There will be no trial medication dispensed to any person not enrolled in the study.

Unused medication will be stored separately from used trial medication(s).

Procedures for Drug Accountability:

-At study site all trial products will be kept in locked refrigerator and counted at regular intervals

-At study site only enough medication will be dispensed to reach next appointment. All medication will be counted at visits and discussed at phone encounters.

Procedure for return of used/unused trial products:

-Unused product will be properly destroyed at the site or returned to sponsor if requested.

Auxiliary Supply

Subjects will use their own glucose monitors, lancet devices, and lancets. They will be provided with log books.

Randomization

Treatment assignment will be made using stratified blocked randomization at visit 2. The stratification variables will be prior insulin use and BMI (cut off 37 kg/m2). The randomization code will be generated by the study statistician using SAS software, and consecutively numbered envelopes will be created. The investigator opens the next envelope at the randomization visit to determine the group assignment of the patient.

Blinding

This study is only blinded to the investigator performing the study assessments. The study is not blinded to the patient, nor the study doctor who will be providing diabetes care to the patient and aid in insulin titration.

CONCOMITANT ILLNESSES AND MEDICATIONS:

Definitions:

Concomitant illness: any illness that is present at the start of the trial *(i.e. at the first visit).*
Concomitant medication: any medication other than the trial product(s) that is taken during the trial, including the screening and run-in periods.
Details of all concomitant illnesses and medication will be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication will be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the Sponsor will be informed.
The information collected for each concomitant medication will include, at a minimum, start date, stop date or continuing, and indication.
For each concomitant illness, date of onset, date of resolution or continuing, at a minimum, will be recorded.

ADVERSE EVENTS AND PREGNANCY:

During each contact (phone or face-to-face) the subject will be asked about adverse events. All serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSAR), and serious adverse drug reactions (SADR) will be evaluated by the investigator and recorded in the patients record. Other adverse events (AE) will be evaluated and documented according to standard clinical practice
The sponsor-investigator will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification (e.g. initials, sex, age)
3. Event (preferably a diagnosis)
4. Drug
5. Reporter identification (e.g. Name, or initials)
6. Causality
7. Outcome.

Definitions

Adverse Event (AE):

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

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

Clinical Laboratory Adverse Event:

A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a

severity, which requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE):

A serious AE is an experience that at any dose results in any of the following:

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

*The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

Serious Adverse Drug Reaction (SADR):

An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study drug and the occurrence of the event is suspected. The ADR should be classified as **serious** if it meets one or more of the seriousness criteria. Clinical judgement following thorough review of any event will be used to determine the relatedness of the event to the study drug. .

Non-Serious Adverse Event:

A non-serious AE is any AE which does not fulfil the definition of an SAE.

Severity Assessment Definitions:

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

Relationship to study medication Assessment Definitions:

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

Outcome Categories and Definitions:

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial

• Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
• Not recovered
• Fatal
• Unknown

Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the study. This will be monitored by an independent committee (see below). All serious and unexpected adverse events will be reported using FDA form 3500. All reports of SAEs/SAR/SUSARs or any events reported to the local health authorities must be sent to Novo Nordisk A/Swithin the same timeline used for reporting to regulatory authorities (see below). Further information about safety related events will be provided to Novo Nordisk A/S if specific requests are received.

Data Safety Monitoring Board (DSMB)

An independent DSMB will be set up for the trial to oversee safety and perform ongoing safety surveillance. The DSMB will be composed of 3 members who cover the relevant specialty as well as an independent statistician:

- Maria Ramos, MD (Endocrinology)
- Sumitha Hathiramani, MD (Endocrinology)
- Naim Maalouf, MD (Endocrinology)
- Song Zhang, PhD (Statistician)

The first meeting will occur after the enrolment of 15 subjects or three months after the first patient is enrolled, whichever comes first. The meetings will then occur on a quarterly basis, although the board may request more frequent meetings as needed. A formal report approved by all DSMB members will be sent to the PI and study coordinator within 3 weeks of the meeting and then forwarded to the IRB.

All AEs will be presented at each meeting and will be available for informal review by the DSMB at any time after study initiation. All SAE and unanticipated but related AE will be promptly reported to the IRB (within 2 working days of PI's awareness for SAEs and within 10 working days for other reportable AEs). We intend to comply with all local legal, regulatory, and IRB requirements. We will also report to Novo Nordisk all SAEs, SUSARs, and SADRs at the same time such events are reported to regulatory authorities or within 15 working days from the sponsor-investigator becoming aware of such adverse events, whichever comes first.

Follow-up of Adverse Events

During and following a subject's participation in a clinical trial, the sponsor-investigator and institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.

All adverse events classified as serious or severe or possibly/probably related to the trial product must be followed until the subject has recovered and all queries have been resolved. For cases of chronic conditions follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered".
All other adverse events must be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered" or until the end of study, whichever comes first, and until all queries related to these AEs have been resolved.

Pregnancy
Study subjects will be instructed to notify the sponsor-investigator immediately if they become pregnant. If using liraglutide this medication will be discontinued immediately.

The sponsor-investigator will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by sponsor-investigator should occur within the same timelines described above for reporting of Adverse Events**.**

Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

Precautions/Over-dosage
The following precautions and procedures will be observed in the event of overdose by any trial product provided during the study: if asymptomatic, the patient is instructed to call the study doctor immediately after discovering the overdosage and obtain case-specific instructions; if symptomatic, the patient is instructed to call the EMS for immediate treatment.

LIABILITY AND SUBJECT INSURANCE:
During and following a subject's participation in trial, the sponsor-investigator and his/her institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.

The sponsor-investigator will be responsible for the conduct of the study and that the sponsor-investigator agrees to defend, indemnify, and hold harmless Novo Nordisk, any of its parent companies, affiliates, or subsidiaries, and their respective officers, directors, employees, agents, representatives, distributors, salespersons, customers, licensees, and end-users from and against any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from or related to: (a) any breach of sponsor-investigator's obligations; or (b) sponsor-investigator's negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived therefrom. This indemnification shall not apply in the event and to the extent that a court of competent jurisdiction or a duly appointed arbiter determines that such losses or liability arose as a

result of Novo Nordisk's gross negligence, intentional misconduct, or material breach of its responsibilities.

EVALUABILITY OF SUBJECTS:

All patients and collected data will be included in the intention to treat analysis.
A secondary confirmatory analysis will be performed using only completers data, where all data from patients with an overall compliance rate during the study period of <50% will be excluded. The subjects and observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible prior to database release. The documentation must be stored together with the remaining trial documentation.

PREMATURE TERMINATION OF STUDY:

Study can be discontinued if funding is withdrawn or by the Data Safety Monitoring Board (DSMB) if there is evidence of futility or excess harm. The study statistician will monitor the data quarterly and discuss any observed trends with the other members of the DSMB who will make such decision following pre-established guidelines.

PUBLICATION PLAN:

We plan to publish the data from this clinical trial in peer reviewed scientific journals (i.e. Diabetes Care). We anticipate at least two manuscripts to results from this work (possibly one on clinical efficacy and safety, one on healthcare utilization and cost data).We expect the final manuscripts to be completed around December 1st, 2016. All manuscripts will be submitted to Novo Nordisk for review and commenting 1 month before external submission. We also plan to present the data at the American Diabetes Association and/or The Endocrine Society scientific meetings as poster or oral presentations.
We have registered the study with clinicaltrials.gov.

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