# A randomized controlled trial comparing the safety and efficacy of IDegLira versus basal 3 bolus in patients with poorly controlled type 2 diabetes: IDegLira HIGH trial

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INVESTIGATOR-SPONSORED STUDY PROPOSAL

UNIVERSAL TRIAL NUMBER (UTN): U1111-1199-0366


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**Abstract:**

Basal-bolus insulin therapy is recommended for patients with poorly controlled type 2 diabetes and HbA1c >9%. However, basal-bolus insulin is labor intensive and associated with increased risk of hypoglycemia, glycemic variability, weight gain and poor compliance. Thus, there is a critical need for a simpler treatment regimen that could overcome these limitations. IDegLira, a fixed-ratio combination (FRC) therapy consisting of insulin degludec and liraglutide, is an attractive option for this population given its proven benefits on glycemic control, weight and compliance. *Accordingly, we propose a prospective randomized controlled trial comparing IDegLira and basal-bolus insulin therapy in achieving glycemic control (efficacy end-point), while preventing hypoglycemia and reducing glycemic variability and weight gain (safety end-point) in patients with uncontrolled T2D and HbA1c between ≥ 9-15%.* This study aims to show that a simpler regimen using a novel FRC agent (IDegLira) can improve glycemic control, decrease hypoglycemia, reduce the burden of diabetes care, and improve satisfaction/adherence in patients with poorly controlled T2D with HbA1c between ≥ 9-15%. This open-label, treat-to-target, two-arm parallel, controlled trial will randomize (1:1 ratio) patients with T2D and HbA1c ≥ 9%, treated with oral antidiabetic agents and/or basal insulin therapy (TDD ≤50 units), to IDegLira or basal-bolus insulin for 26 weeks. We will recruit a total of 150 patients from participating institutions. We anticipate recruiting 3-4 patients per week for a total recruitment period of approximately 12 months.

## BACKGROUND:

Extensive literature from landmark studies have shown that persistent hyperglycemia is associated with short- and long-term complications[1,2]. The UKPDS study, the largest study in patients with type 2 diabetes, showed that intensive glycemic control can reduce the risk of microvascular complications[1-3]. Sustained hyperglycemia, also known as glucotoxicity, leads to progressive loss of beta-cell function and is considered a key pathophysiological process in the development of T2D[4]. Patients with severe hyperglycemia may respond poorly to oral anti-diabetic agents (OAD) alone initially and frequently require insulin to achieve glycemic targets [5,6]. Current guidelines recommend to initiate therapy with basal insulin and progressively step-up to basal-bolus insulin in patients with high HbA1c >9%, particularly if symptomatic or with catabolic symptoms[6-8].

Basal-bolus insulin regimen increases the risk of hypoglycemia, weight gain and glycemic variability[9,10], which are limiting factors in achieving glycemic targets. Basal-bolus insulin regimen is also labor intensive and often requires multiple daily injections, further increasing the burden of diabetes care[11-14] and decreasing patient adherence [12,13]. In contrast, simplified treatment plans may improve adherence, leading to glycemic targets achievement[12,13,15]. Thus, there is a critical need for simpler regimens that could overcome clinical inertia, improve patient adherence, and decrease glycemic variability in patients with poorly controlled type 2 diabetes. With the advent of continuous glucose monitoring (CGM), we have recognized that hypoglycemia and glycemic variability are common events in many patients, even in patients with well-controlled T2D[16-20]. Despite large data supporting the efficacy and safety of combination therapy with basal insulin and GLP1-RA -including fixed-ratio combination (FRC) agents [21,22]; no previous studies have compared the efficacy and safety of IDegLira in patients with very high HbA1c vs the standard-of-care with basal-bolus insulin regimen. *Accordingly, this prospective randomized control trial will compare IDegLira to basal bolus insulin regimen in achieving glycemic control (efficacy end-point), while reducing hypoglycemia, glycemic variability and weight gain (safety end-point) in patients with uncontrolled T2D and HbA1c ≥9%.*

**SPECIFIC AIMS:**

**Specific Aim 1:**

1. ***To determine whether treatment with IDegLira will result in similar improvement in glycemic control, as measured by change in HbA1c (non-inferiority limit of 0.4%), compared to treatment with basal-bolus insulin regimen in patients with poorly controlled T2D (HbA1c ≥9-15%).***
   - Primary outcome: change in HbA1c from baseline after 26 weeks of treatment with IDegLira vs basal-bolus insulin (with metformin, unless contraindicated).
   - **Hypothesis:** After 26 weeks of treatment, IDegLira will result in similar improvement in glycemic control compared to basal-bolus insulin therapy.

**Specific Aim 2:**

2. ***To determine whether treatment with IDegLira will result in lower rate of hypoglycemic events and less glycemic variability (superiority), as measured by continuous glucose monitoring* (CGM)*, compared to basal-bolus insulin in patients with T2D and HbA1c ≥9-15%.***
   - Patients with poorly controlled T2D randomized to IDegLira or basal-bolus (with metformin, unless contraindicated) will have a one-week blinded CGM study performed during follow-up visits at 1, 12, and 26 weeks as well as 8-point self-monitored blood glucose (SMBG). CGM will allow better detection of hypoglycemic events, particularly asymptomatic and nocturnal hypoglycemia. It will also provide critical information on time in glycemic range and glycemic variability.
   - **Hypothesis:** IDegLira will result in less hypoglycemia and glycemic variability compared to basal-bolus insulin regimen.

**Specific Aim 3**:

3. ***To determine whether treatment with IDegLira will result in improved patient satisfaction compared to treatment with basal-bolus in patients with T2D and high HbA1c (≥9-15%).***
   - Patients with poorly controlled T2D randomized to IDegLira or Basal-Bolus will complete the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Treatment-related impact measures for diabetes (TRIM-D) survey during follow-up visits.
   - **Hypothesis:** Use of IDegLira is associated with higher patient satisfaction and adherence compared to a multiple-daily injection regimen with basal-bolus insulin.

## CURRENT STATUS OF WORK IN THE FIELD

### Epidemiology and treatment of patients with poorly controlled T2D and HbA1c >9%

Based on NHANES data from 2007-2010, up to 12.6% of patients with diagnosed diabetes (18.8 millions) have an HbA1c >9%[23]. In the Emory Health Care system, the largest academic health system in Georgia, over 64,000 patients have a diagnosis of diabetes, with ~16% having an HbA1c>9% (Figure 1). The evidence on the management of patients with T2D and very high HbA1c is very limited, with most studies excluding patients with HbA1c > 10%[24-27].

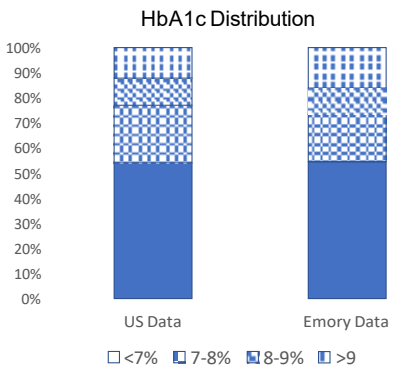



Figure 1. HbA1c Distribution in Patients with Diabetes: US and Emory Data

In a recent multi-national study of insulin-naïve patients with T2D, treated with or without oral agents, showed that only ~40% of patients with HbA1c > 9% were started on basal insulin. Moreover, the study showed that only 20.9% of such patients achieved HgA1c target (< 7%) at 3 months after initiating basal insulin, indicating a need for coverage of prandial-related hyperglycemic excursions. Notably, failure to achieve HbA1c targets at 3 months was associated with an increased risk of not achieving HbA1c targets at 24 months, with < 30% of patients achieving glycemic targets[28]. This study suggests that providers delayed initiation of basal insulin as recommended by national guidelines, and frequently failed to intensify therapy to cover prandial-related hyperglycemic excursions. A recent study in ambulatory patients with T2D and high HbA1c (>10%) on metformin and sulfonylurea treatment, randomized patients to combination (COMB) therapy with exenatide plus pioglitazone vs basal-bolus insulin regimen. COMB provided greater HbA1c reduction at 6 months, with significantly less weight gain. However, the rates of hypoglycemia were unusually high, up to 56% and 83% in COMB and BB, respectively[26]. Our group recently validated the efficacy of a hospital discharge algorithm based on the admission HbA1c[27]. Among those patients with high admission HbA1c> 9% (n: 81), 54 were discharged on basal-bolus insulin regimen. Mean admission HbA1c of 11.1% decreased to 8.8% and to 8.0% after 4 and 12 weeks of hospital discharge ($p<0.01$), respectively. However, up to 44% of patients had hypoglycemia (BG < 70 mg/dl) during follow-up. Thus, there is a critical need for effective but safe and simpler anti-diabetic regimen for this high-risk population.

### "Standards-of-Care" for Patients with Severe Hyperglycemia

Based on expert consensus, the American Diabetes Association recommends "dual therapy" for patients with HbA1c >9% to achieve glycemic targets faster than with "sequential therapy" after 3 months of not achieving such targets. Based on historical availability and with no hierarchical preference by the ADA, dual therapy includes metformin and any of the following agents: sulfonylureas (SU), thiazolidinedione (TZD), glinides (GLN) dipeptidyl peptidase-4 inhibitors (DPP-4), SGLT-2 inhibitors, GLP-1 agonists and basal insulin[8]. Similarly, the American Association of Clinical Endocrinologists (AACE) based on expert consensus recommends the addition of insulin in patients with HbA1c >9% if symptomatic, or on maximum doses of dual therapy[6]. Moreover, in patients with HbA1c >8% on dual therapy and/or long history of diabetes, AACE suggests that the addition of insulin will more likely achieve glycemic targets over adding a third agent[6]. It was also suggested that the addition of GLP-1 to dual oral therapy may similarly help achieving glycemic targets[6], but still many patients will require insulin in this scenario[29,30]. In patients with HbA1c > 10%, or blood glucose > 300 mg/dl, and/or symptomatic hyperglycemia (polyuria or polydipsia) and catabolic symptoms (ketosis and weight loss), the ADA recommends "combination insulin injectable therapy". This regimen includes: basal-bolus insulin or basal plus GLP1-RA or pre-mixed insulin[8]. Notably, recommendations from national guidelines in this area are mostly based on expert consensus and the notion that "dual injectable therapy" for patients with HbA1c >9% may achieve glycemic targets faster than with "sequential therapy" after re-evaluation every three months, rather than based on strong clinical trials evidence[6,8]. Unfortunately, the evidence is very limited in patients with T2D and v e r y high HbA1c, with most studies excluding patients with HbA1c > 10%[24-27].

In clinical practice, many patients with uncontrolled T2D and HbA1c > 9% are started on basal insulin, followed by dose up-titration and addition of prandial insulin (basal bolus)–in concordance with national guidelines[6,8]. Intensive insulin therapy, by either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI), early in the disease course of patients with T2D results in rapid glycemic control within days, suggesting that avoiding the negative effects of long-term exposure to hyperglycemia may prevent further beta-cell failure[31-33]. However, the basal bolus regimen increases the risk of hypoglycemia and weight gain[9,10], which are well-recognized limiting factors to achieve glycemic targets. More importantly, basal bolus regimen is labor intensive and increases the burden of diabetes care, number of injections per day [11-14], which may lead to poor patient adherence, increase re-admission rates, and increased risk of hypoglycemia [12,13]. Studies comparing GLP1-RA therapy vs thrice-daily bolus insulin added to basal insulin plus oral agents have found similar HbA1c

reduction[30,34,35] accompanied by weight loss compared to weight gain in basal-bolus insulin regimen[30,35]. GLP1-RA therapy was also associated with better patient satisfaction and better quality of life[34]. *Indeed, the combination of basal insulin and GLP1-RA is an attractive and simpler option for many patients with uncontrolled diabetes – ideally in a single daily injection from a fixed-ratio combination agent.* Moreover, there is evidence suggesting that GLP-1 agonist therapy may preserve beta-cell function[36]. Based on data from meta-analysis and randomized studies[34,35,37], some authors favor this combination over basal-bolus insulin in patients with uncontrolled T2D on basal insulin[38,39].

**Combination of basal insulin and GLP-1 agonists – fixed-ratio combination agents**

The combination of basal insulin and GLP1-RA therapy offers a complementary mechanism to target the main physiologic defects in T2D, by addressing fasting and prandial hyperglycemia [21,22]. GLP1-RAs decrease post-prandial glycemic excursions and complement basal-insulin therapy by enhancing endogenous insulin responses in a glucose-dependent manner, inhibiting glucagon secretion, slowing gastric emptying and promoting satiety[40]. This combination has been shown to provide better glycemic control, less hypoglycemia, less weight gain, and reduce glycemic variability compared to basal bolus therapy or GLP1-RA alone[21,22,41,42]. IDegLira is a novel fixed-ratio combination of degludec 100 u/ml and liraglutide 3.6 mg in a pre-filled pen. IDegLira has been shown to improve glycemic control, with lower risk of hypoglycemia, less weight gain, and better patient satisfaction compared to basal-bolus or stepped-up basal therapy [43,44]. Pharmacokinetics studies showed that IDegLira provided coverage over the 24-hours interval at steady levels[43]. In the recent DUAL V trial, IDegLira resulted in greater HbA1c reduction, weight loss and less hypoglycaemia, compared to up-titration of insulin glargine in patients with T2D with HbA1c 7-10%[45]. More recently in the DUAL VII trial, patients with HgA1c 7-10% randomize to IDegLira had similar HbA1c reduction, but with an 89% reduction in the rate of severe or confirmed symptomatic hypoglycemia and weight loss compared to basal-bolus insulin[46]. Thus, IDegLira is an attractive and option for patients with severe hyperglycemia, due to potent HbA1c reduction, lower hypoglycemic risk, and flexibility of once-daily administration, compared to up to five injections per day in basal-bolus regimen. However, no previous studies have compared the efficacy and safety of IDegLira in patients with high HbA1c >9-15%.

**SIGNIFICANCE AND INNOVATION:**

The proposed study will test three innovative questions in patients with poorly controlled T2D and HbA1c ≥9%: 1) whether IDegLira, a novel FRC of degludec and liraglutide, results in similar glycemic control, 2) less hypoglycemia, less glycemic variability and less weight gain compared to a basal-bolus, and 3) whether IDegLira results in better patient satisfaction and treatment adherence compared to a more complex multiple-daily insulin injection regimen. If successful, this study will show that a once-a-day simpler regimen using IDegLira can improve glycemic control, decrease hypoglycemia, improve satisfaction and decrease the burden of diabetes care, which in turn will improve patient adherence. Since improvements in HbA1c strongly correlate with a reduction in the risk of microvascular and macrovascular complication[3], improved glycemic control with a simpler regimen like IDegLira have the potential to reduce the burden of complications associated with T2D. In addition, we will perform professional/blinded CGM at weeks -1, 12 and 26 of follow-up. By incorporating CGM, we will improve our ability to detect asymptomatic/unrecognized and/or nocturnal hypoglycemia and assess glycemic variability[17,47] compare to SMBG (standard-of-care). Since IDegLira therapy is expected to result in less clinical significant hypoglycemia (defined as interstitial glucose < 54 mg/dl), less nocturnal hypoglycemia and less glycemic variability (as measured by MAGE, %CV or SD) compared to basal-bolus, this simpler regimen could become the standard-of-care for patients with uncontrolled T2D and HbA1c ≥ 9%.

## RESEARCH DESIGN and METHODS

### ENDPOINTS:

The **primary outcome** of the study is to determine the difference in change in HbA1c at 26 weeks of treatment to a non-inferiority limit of 0.4% between IDegLira and basal-bolus insulin therapy.

The **secondary outcomes** are to compare differences between IDegLira and basal-bolus insulin therapy in any of the following measures:

- Mean fasting and mean daily blood glucose (per 8-point SMBG profile)
- Percent of patients with HbA1c <7.0% at 26 weeks and hypoglycemia
- Percent of patients reaching A1c < 7% without weight gain and no hypoglycemia" (responder's rate)
- Percent of patients reaching A1c < 7.5% without weight gain and no hypoglycemia"
- Percent of patients with A1c >10% and >11% that achieve A1c < 7.5% and < 8%

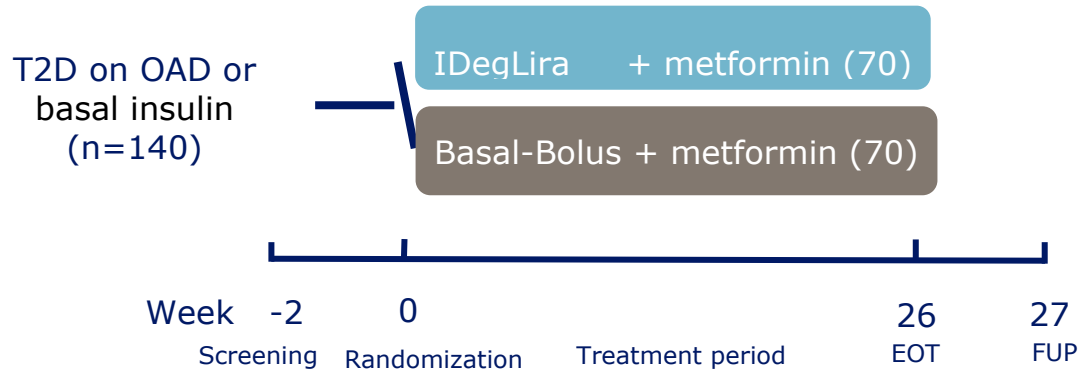
- Percent of patients with HbA1c <7.0% at 26 weeks and no weight gain
- Percent of patients with HbA1c <7.0% at 12 weeks and no hypoglycemia
- Incidence of documented symptomatic hypoglycaemia, defined as an event with typical symptoms of hypoglycaemia accompanied by SMBG or CGM (<70 mg/dL and < 54 mg/dL) that occurs at any time of the day
- Incidence of asymptomatic hypoglycaemia, defined as no typical symptoms reported by the subject but detected by SMBG or CGM (<70 mg/dL and < 54 mg/dL)
- Incidence of severe hypoglycaemia, defined as severe cognitive impairment requiring assistance from another person
- Incidence of nocturnal symptomatic hypoglycaemia, defined as an event with typical symptoms of hypoglycaemia accompanied by SMBG or CGM <70 mg/dL and < 54 mg/dL that occurs between 00:00 and 05:59 hrs
- Incidence of nocturnal asymptomatic hypoglycaemia, defined as SMBG or CGM <70 mg/dL and < 54 mg/dl between 00:00 and 05:59 hrs
- Percentage of time below 70 mg/dL and <54 mg/dl as obtained by CGM

- Percentage of time in range (BG 70-180) as measured by CGM
- Glycemic variability, as measured by SD (standard deviation), %CV (coefficient of variance), Mean Amplitude Glucose Excursions (MAGE)
- Patient satisfaction and quality of life, as measured by the DTSQ and T R I M - D questionnaires
- Number of emergency room visits and hospital readmissions
- Change from baseline in total insulin dose (units/day)
- Number of treatment emergent AE

**STUDY DESIGN AND METHODS:**

The study is a 26-week, open-label, treat-to-target, two-arm parallel, randomized, controlled trial investigating the efficacy and safety of IDegLira versus basal-bolus insulin in patients with T2D. Patients with HbA1c ≥ 9% treated with oral antidiabetic agents and/or basal insulin therapy (TDD ≤50 units) will be randomized in a 1:1 manner to receive IDegLira or basal-bolus insulin regimen (plus metformin unless contraindicated), as shown in Fig 2. Subjects will have contact with the study team via clinic visits or phone contacts for a total of 29-weeks, as shown in the figure below (Fig 2 and Table 1).

Figure 2. Study design




Legend: OAD: Oral anti-diabetic agents, EOT: End-of-treatment, FUP: Follow-up safety visit

Visits will be distributed as follows: initial screening visit/CGM insertion (visit 1), 2 weeks of screening/run-in period, randomization visit (visit 2), 26-week treatment period (visits 4-18), and a follow-up safety visit after the end the 26-weeks treatment period (visit 19). Subjects will have contact with the study team via clinic visits or phone contacts for a total of 9 clinic visits and 9 telephone contacts. This study will include patients with a known history of T2D, age 18-80, treated with oral antidiabetic agents including metformin, sulfonylurea, repaglinide/nateglinide, pioglitazone, DPP4 inhibitors, SGLT2 inhibitors, (monotherapy + basal insulin) or in combination therapy (2-3 agents), and/or on basal insulin at a total daily dose (TDD) of ≤50 units. Participants previously using basal insulin [neutral protamine hagedorn (NPH), mixed insulin, detemir or glargine insulin], will be switched to study-provided Degludec or IDegLira and/or Aspart pens. Metformin will be continued at same dose during the study, unless contraindicated. Patients previously treated ambulatory with basal-bolus insulin therapy and/or GLP1-RA will be excluded. Patients transiently treated with basal-bolus insulin (standard-of-care treatment) during hospital admission can be included. Recommendations on insulin adjustment will be provided at each visit or phone encounter by a study physician.

**Rationale for study design**

Based on the DUAL trial program, a total of 26 weeks of treatment is sufficient to reach stable HbA1c levels, with a minimum of 12 weeks in the maintenance period. This timeline has been previously shown to be sufficient to collect data for efficacy and safety. A parallel design will allow for assessment of efficacy and safety in the shortest time in each group, compared to a cross-over design. An open label design allows us to use a simpler regimen with a single injection of IDegLira, as blinding the subjects will require a double dummy design with three extra subcutaneous injections per day, thus imposing a high burden on subjects, thereby increasing the non-compliance and withdrawal rates. Patients in both arms will receive the same degree of self-monitoring and follow-up. Patients will have

blinded CGM to avoid the bias of glycemic improvement by using real-time glucose data from CGM. The primary endpoint will use HgA1c changes, a standard laboratory test shown to correlate with risk of diabetes complication, thus limiting the assessment bias. Secondary endpoints will include rates of asymptomatic hypoglycemia or nocturnal hypoglycemia as detected by CGM, which will typically not be detected by the standard-of-care SMBG.

Table 1- Schedule of events during the study period

| Visit # (V)<br>Phone visit (P) | V1* | V2* | P3* | P4* | P5* | V6* | P7* | P8* | P9* | V10** | P11** | V12** | V13** | P14** | V15** | P16** | V17** | V18** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time-wks | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 | 12 | 14 | 16 | 20 | 24 | 26 | 27 |
| Inf. Consent | | X | | | | | | | | | | | | | | | | |
| Inc/exclusion | X | X | | | | | | | | | | | | | | | | |
| Rando@ | | X | | | | | | | | | | | | | | | | |
| Withdrawal cx | | X | X | X | X | X | X | X | X | X | X | X | X | x | X | X | x | x |
| Drug compl | | X | | | | X | | | | X | | X | x | | x | | X | x |
| Dose adjust | | | X | X | X | X | X | X | X | X | X | X | X | x | X | X | X | x |
| Efficacy | | | | | | | | | | | | | | | | | | |
| Vital signs@ | X | X | | | | X | | | | X | | X | x | | x | | X | x |
| Phys exam | x | | | | | | | | | | | | | | | | | |
| Pregnancy test* | X | X | | | | X | | | | X | | X | | | | | X | |
| Body Measurements | X | X | | | | X | | | | X | | X | X | | x | | X | |
| BMI | X | X | | | | X | | | | X | | X | x | | x | | | |
| Hba1c | x | | | | | | | | | | | X | | | | | X | |
| CMP | X[&] | | | | | | | | | | | X | | | | | X | |
| Fasting glucose[&] | | X | | | | X | | | | X | | X | | | | | X | x |
| Instruct 8-p SMBG | x | | | | X | | | | | | X | | | | | X | | |
| Collect 8-pt SMBG | | X | | | | X | | | | | | X | | | | | X | |
| Labs | X^ | | | | | | | | | | | | | | | | X^* | |
| 7d-CGM insert | X[1] | | | | | | | | | | | X | | | | | X | |
| 7d- CGM collect | | x | | | | | | | | | | | x | | | | | x |
| DTSQ&TRIM-D | | X | | | | | | | | | | X | | | | | X | |
| Safety | | | | | | | | | | | | | | | | | | |
| Adverse events | | | X | X | X | X | X | X | X | X | X | X | X | x | X | X | X | X |
| Hypoglycemia | | | X | X | X | X | X | X | X | X | X | X | X | x | X | X | X | X |
| Trial material | | | | | | | | | | | | | | | | | | |
| Drug dispensing | | X | | | | X | | | | X | | X | | | | | | |
| Drug account | | | | X | | X | | | | X | | X | | | | | x | |
| End-of-Trial | | | | | | | | | | | | | | | | | x | |

*+/- 3 days. **+/- 7 days. Labs: ^ pregnancy test, ketones, lipid panel^* and GAD65 (If concern for Type 1 diabetes, GAD65 and ketones will be ordered during screening, per PI discretion). Pregnancy test for WOCP as deemed by investigator [&]fasting defined as at least 8 hours without food or drinks or diabetes medications, except water and other prescribed medications. [1] +/- 7 days, but before randomization visit. Fasting glucose could be obtained from a chemistry sample obtained during the visit or POC BG. Body measurement includes: weight, height and waist and hip circumference. @ During "randomization" and "vital signs" visits, subjects will receive training on device use.

**Treatment of subjects:**

**Group 1) IDegLira Group**

- Discontinue OADs (SU, DPPIVi, glinides, and pioglitazone), except metformin (unless contraindicated) and SGLT2i.
- Start IDegLira at 16 dose steps (degludec 16 units/liraglutide 0.6 mg), per U.S labeling indications and/or provider discretion.
- IDegLira will be given once daily, at the same time of the day with or without food.
- IDegLira will be titrated until the maximum dose (50 steps) is reached, up to target fasting BG between 70 and 100 mg/dl (Treat-To-Target Trial protocol), see algorithm below.
- Titration will occur twice a week: 1) self-titration by patients once a week and 2) phone call/ contact by research team once a week, for the initial 8 weeks. After that, patients will self-titrate study medications per dosing algorithm.
- IDegLira will be titrated by 2-step-dose increment (2 IU of degludec and 0.072 of liraglutide), to a maximum of 8 steps per week.
- The maximum allowed dose of IDegLira 50 dose steps provide 50 U of degludec and 1.8mg of liraglutide.
- Titration will be performed twice weekly (every 3 to 4 days) based on the previous self-monitored fasting (pre-breakfast) BG measurement (mean of 3 consecutive days). Patients will be provided with self-titration algorithms for insulin adjustments.
- Subjects not at goal (fasting or mean SMBG from 3 consecutive days > 300 mg/dl) requiring > 50 dose steps of IDegLira, will be considered “treatment failures”. Degludec will be added to IDegLira as “rescue” basal insulin therapy. The dose of IDegLira will remain unchanged.
- The dose of “rescue” Degludec will be recorded and titrated twice weekly to target FPG of 70-100 mg/dl, per provider discretion, as shown below.

| Titration algorithm for IDegLira and Degludec pens | Insulin dosage IU/d)* |
|---|---|
| ≥181 | 8 |
| 141-180 | 6 |
| 121-140 | 4 |
| 101-120 | 2 |
| 71-100 | no adjustments |
| <70 | -2<br>If dose > 45 U/d, decrease by 10% |
| <56 | -4<br>If dose > 45 U/d, decrease by 10% |

* Maximum titration dose per week: 8 units

**Group 2: Basal-Bolus Insulin Group (Begin BB trial[48])**

- Discontinue OADs (SU, DPPIVi, glinides, and pioglitazone), except metformin (unless contraindicated) and SGLT2i.
- Insulin naïve participants will start at a daily dose of 10 units of degludec U-100 (or 0.2 u/kg/d per investigator discretion).
- Participants previously using basal insulin [neutral protamine hagedorn (NPH), mixed insulin, detemir or glargine U100] will be switched to study-provided degludec pens.
- For participants taking basal insulin prior to randomization, the conversion dose is 1:1 unit. The total daily basal dose could be the same or reduced by 20% at the investigator's discretion.
- Titration will be performed twice weekly based on the previous self-monitored fasting (pre-breakfast) BG measurement (mean of 3 consecutive days). Titration will occur as follows: 1) self-titration by patients once a week and 2) phone call/ contact by research team once a week, for the initial 8 weeks. After that, patients will self-titrate study medications per dosing algorithm.
- Degludec will be given once daily at the same time, and titrate up to fasting blood glucose 70-100 mg, with no maximum dose.
- Basal insulin should be adjusted before adjusting pre-meal aspart, as shown below.

**Degludec U100 Insulin adjustment**

| Mean fasting BG from preceding 3 days (mg/dl) | Insulin dosage IU/d) |
|---|---|
| ≥181 | 8 |
| 141-180 | 6 |
| 121-140 | 4 |
| 101-120 | 2 |
| 71-100 | no adjustments |
| <70 | -2<br>If dose > 45 U/d, decrease by 5% |
| <56 | -4<br>If dose > 45 U/d, decrease by 10% |

Aspart Insulin dosage:

- Aspart will be given before meals, to target pre-meal BG < 70-100 mg/dl.
- At the start of the trial, participants will be prescribed 4 U insulin aspart before the largest/main meal or; before each main meal (3 typical large meals per day: breakfast, lunch, and dinner, ≤4 times per day) per investigator discretion.
- For insulin naïve participants or per investigator discretion, total aspart dose will calculated at 0.2 u/kg/d, and equally divided in three doses to be started before the main/largest meal or before each meal (3 typical large meals per day: breakfast, lunch, and dinner, ≤4 times per day), per investigator discretion.
- If patients are started on only one dose for the largest meal, a second and third dose may be added, as detailed above. Subjects will be provided with titration algorithms.
- The dose adjustment of insulin aspart will be based on the pre-prandial BG of the subsequent meal or bedtime BG (i.e. the pre-dinner value will be based on the bedtime BG), per provider discretion, as shown below:

| Pre-prandial and bedtime BG (mean BG from preceding 3 days), mg/dl | Aspart dosage IU/d) |
|---|---|
| ≥181 | +4 |
| 141-180 | +3 |
| 101-140 | +2 |
| 71-100 | no adjustments |
| <70 | -2 |
| <56 | -4 |

**Study population:**

A total of 150 subjects (75 subjects in each arm) will be included in the study (screening about 300), randomized in a 1:1 manner, and started on study medications (as show in Fig 2). Based on an anticipated screening failure rate of 40% and an attrition rate of 20%, total of 300 patients will be screened. The study will be conducted at Emory University Hospital Midtown and Grady Hospital in Atlanta, Ga and second site TBA

**Inclusion Criteria**

1. Males or females between the ages of 18 to 80 years
2. Type 2 diabetes, diagnosed for ≥ 6 months
3. HBA1c ≥ 9% - 15%
4. Previously treated with oral antidiabetic agents, including metformin, sulfonylurea, repaglinide/nateglinide, pioglitazone, DPP4 inhibitors, SGLT2 inhibitors, (monotherapy + basal insulin) or in combination therapy (2-3 agents), and/or on basal insulin (neutral protamine hagedorn (NPH), mixed insulin, detemir or glargine U100) at a total daily dose (TDD) ≤50 units (stable doses of basal insulin for at least 90 days, defined as up to ±10% variability)
5. BMI ≤ 45 Kg/$m^2$

**Exclusion Criteria**

1. Age < 18 or > 80 years
2. Subjects with type 1 diabetes or LADA: positive GAD-65 antibody and/or ketones
3. Subjects with a BG > 400 mg/dL during the screening visit and laboratory evidence of diabetic ketoacidosis
4. Previous treatment with GLP-1 agonists (during prior 3 months)
5. Previous treatment with basal-bolus insulin (within prior 3 months, except transient treatment with during hospital admission)
6. Recurrent severe hypoglycemia or known hypoglycemia unawareness.
7. Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2
8. Patients with acute or chronic pancreatitis, pancreatic cancer
9. Patients with clinically significant hepatic disease (cirrhosis, jaundice, end-stage liver disease) or significantly impaired renal function (GFR < 30 ml/min).
10. Treatment with oral or injectable corticosteroid (equivalent or higher than prednisone 5 mg/day), parenteral nutrition and immunosuppressive treatment.
11. Mental condition rendering the subject unable to understand the nature, scope, and possible

consequences of the study

12. Hypersensitivity to study drugs
13. Participating in another investigational drug trial
14. The receipt of any investigational drug (within 3 months) prior to this trial.
14. Previously randomized in this trial
15. Heart Failure NYHA class 4 or uncontrolled hypertension (blood pressure > 180/110 mmHg)
16. Female subjects who are pregnant or breast-feeding at time of enrollment into the study
17. Females of childbearing potential who are not using adequate contraceptive methods (as required by local law or practice)
18. Known or suspected allergy to trial medications (degludec, liraglutide, aspart), excipients, or related products.
19. Subjects could be excluded based on PI's discretion
20. Unable to comply with trial protocol, and/or at investigator discretion
21. Patients receiving treatment for active diabetic retinopathy or with proliferative retinopathy

**Withdrawal Criteria**

- The subject may withdraw at will at any time during the trial.
- Pregnancy or intention of becoming pregnant.
- The subject may be withdrawn at the discretion of the investigator due to non-compliance or due to a safety concern
- The subject will be withdrawn if starting any drugs that interfere with glucose metabolism (steroids doses equivalent to prednisone > 5 mg/day)
- The subject may be withdrawn if diagnosed with acute pancreatitis (defined as meeting 2 of the following 3 rules: typical abdominal pain, amylase/lipase > 3x UNL and/or characteristic US, CT or MRI findings)
- If the fasting or mean SMBG during 3 consecutive days is > 300 mg/dl, the investigator will schedule an unplanned visit as soon as possible, to obtain confirmatory fasting BG and investigate the cause. If no apparent or intercurrent cause is detected, the patient may be withdrawn.
- Unable to comply with trial protocol, at investigator discretion.

**Subject Replacement**

There will be no replacement of subjects withdrawn after randomization in this trial.

**Rationale for Study Population**

The target population will include subjects with uncontrolled T2D with HbA1c ≥9%-15%, treated with oral anti-diabetic agents and low dose basal insulin (TDD ≤50 units/d), in whose treatment intensification is recommended. Subjects should have been on oral anti-diabetic agents or basal insulin for at least 90 days (with stable doses of insulin, 10% of dose fluctuations are acceptable). These subjects need intensification of therapy, and should start basal insulin and progressively step-up to basal-bolus insulin per national guidelines. However, these patients may benefit more from a simpler regimen consisting of a single daily injection, with lower risk of hypoglycaemia and less weight gain, which could improve treatment adherence. IDegLira is an attractive therapeutic option for these patients for its potency, flexibility, and potential lower risk of hypoglycaemia and weight gain.

**Visit Procedures**

Figure 2 and Table 1 provides a description of procedures to be performed at each visit during the study period. Visits will be distributed as follows: initial/screening visit/CGM baseline insertion, (visit 1), 2 weeks of screening/run-in period, randomization visit (visit 2), 26-week treatment period (visits 4-18), and a follow-up safety visit after the end the 26- weeks treatment period (visit 19). Subjects will have contact with the study team via clinic visits or phone contacts for a total of 9 clinic visits and 9 telephone contacts. If subjects cannot participate in a scheduled visit (+/- 3 days), the investigators will arrange for an urgent (as soon as possible) visit. During follow-up, we will collect the following data (as described in Table 1): glycemic data, hypoglycemia events, drug compliance, protocol adherence, body measurements, and adverse events.

**Definitions:**

- CGM Hypoglycemia: CGM glucose levels < 70, < 54, ≤ 40 mg/dl, with a duration at least 15 minutes by CGM. The end of the event will be when glucose is ≥ 70 mg/dl for 15 minutes. A prolonged hypoglycemic event will be defined as CGM levels < 54 mg/dl for 120 minutes or more".[52]
- We will only analyze CGM data collected after the first 24 hours from insertion. Patients should have worn the CGM for at least > 4 days.
- Documented symptomatic hypoglycemia, defined as an event with typical symptoms of

hypoglycemia confirmed by SMBG or CGM (< 70 mg/dL and < 54 mg/dL) that occurs at any time of the day

- Incidence of asymptomatic hypoglycemia, defined as no typical symptoms reported by the subject but detected by SMBG or CGM (<70 mg/dL and < 54 mg/dL)
- Incidence of severe hypoglycemia, defined as severe cognitive impairment requiring assistance from another person
- Incidence of nocturnal symptomatic hypoglycemia, defined as an event with typical symptoms of hypoglycemia confirmed by SMBG or CGM < 70 mg/dL and < 54 mg/dL that occurs between 00:00 and 05:59 hrs
- Incidence of nocturnal asymptomatic hypoglycemia, defined as no typical symptoms reported by the subject but detected by SMBG or CGM (<70 mg/dL and < 54 mg/dL) between 00:00 and 05:59 hrs
- Confirmed hypoglycaemia includes: severe hypoglycemia and episodes with or without symptoms with biochemical confirmation of glucose < 54 mg/dL.
- Relative hypoglycemia includes: typical symptoms but with glucose > 70 mg/dL

**Body measurements (Visits V1, V2, V6, V10, V12, V13, V15, V17)**

**Body weight:** Body weight should be measured in kilogram or pound, without shoes and only wearing light clothing.

**Height:** Height (without shoes) should be measured in centimeters or inches and recorded without decimals.

**Waist and hip circumference:** The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest. The hip circumference is defined as the widest circumference around the buttocks. Three consecutive measurements of waist and hip circumference should be taken and recorded. Mean values will be used for result analysis. The waist and hip circumferences will be measured to the nearest 1.5 cm (0.2 inches) using a non-stretchable measuring tape.

The subject should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist and hip. The tape should touch skin, but not compress soft tissue and twist in tape should be avoided. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

**Body Mass Index (BMI): BMI will be calculated by the formula Body weight (Kg)/$m^2$.Screening Visit: (visit 1, week -2)**

Approximately 2 weeks prior to starting study medications, all potential study subjects will be

screened to check their eligibility. After providing the subjects with detailed information about the trial, subjects will sign the informed consent form and will be assigned a patient identification number.

During this visit, investigators will perform a comprehensive assessment, including: present and past medical history (concomitant illness), diabetes history (onset, prior complications, current and prior anti-diabetes medication's duration, allergies, or intolerances), physical examination, height, weight, vital signs, laboratory assessment (HbA1c, chemistry, pregnancy test for women of child-bearing potential (WOCBP), documentation of current medications, and prior intolerances or allergies. Investigators will notify the primary care physician that the subjects have consented to participate in the study. In WOCBP, the contraceptive methods will be documented.

After review of all inclusion and exclusion criteria, including laboratory results, patients who do not meet all the inclusion criteria at Visit 1 will be considered screen failures and will not be randomized to participate in the study.

During this visit, the investigator will insert the CGM to obtain baseline information (before drug exposure). During this visit, patients will receive training on CGM use and reinforce SMBG diary collection. Trained personnel will proceed with sensor insertion. After that, the sensor will be activated, the CGM session will be started.

Eligible patients will be trained on the use of the glucose meter to monitor their BG levels (i.e. 8-point SMBG). Patients will be given diabetes diaries and associated training to record all glucose levels, insulin doses, and episodes of hypoglycemia. Subcutaneous injections administration technique will be reviewed prior to randomization to ensure good technique. Reinforcement will be provided as needed during the follow-up visits.

Patients will be instructed in performing glucose testing at home before meals, with a minimum of 2 out of the 4 pre-meal and/or bedtime glucose measurements per day. In addition, patients must perform an 8-point SMBG for at least 1 day prior to week 0, 12, 26, as follows:

**Time-points for 8-point SMBG profile:**

The blood glucose levels should be measured and recorded in the diary (including date, actual clock time and blood glucose value) at the following time points, always starting with

measurement before breakfast. Subjects will be instructed to collect the SMBG on a day where the subject does not anticipate unusual strenuous exercise.

- Before breakfast
- 90 min after the start of breakfast
- Before lunch
- 90 min after the start of lunch
- Before dinner
- 90 min after the start of dinner
- At bedtime
- In the middle of the night at 3 or 4 am

Subject will also be instructed to check and record BG when hypoglycemia is suspected. Values < 70 mg/dl should trigger an intervention, as described below (safety section).

Instructions for Run-In Period (2 weeks):

The main purpose of this period is to ensure that patients can comply with 8-point SMBG, pen instructions and trial recommendations.

- Oral antidiabetic agents will be continued at same dose until randomization visit. Metformin dose will be titrated up to 1000mg twice daily or to the maximum tolerated dose, unless contraindicated, per investigator's discretion.
- Basal Insulin therapy [NPH, mixed insulin, or basal insulin (glargine U100, detemir)] at TDD ≤50 units will continue at same insulin dosage until randomization. Insulin can be initiated, or dose could be increased during run-in period in those subjects with severe hyperglycemia (BG>300 mg/dL) and/or glucotoxicity per investigator's discretion, for subject's safety reasons.
- Patients will be instructed in performing glucose testing at home before meals, with a minimum of 2 out of the 4 pre-meal and/or bedtime glucose measurements per day.
- Patient not randomized in the trial will be considered screening failures, and no data will be collected since these patients will not receive study medication.

Preparation for Visit 2 (Randomization visit)

- Patient will be instructed to complete the 8-point SMBG, and to titrate up metformin, unless contraindicated.
- All patients will be instructed to provide daily glucose records. In addition, they will

perform an 8-point SMBG done prior to Visit 3 (as described above).

- Patients who complied with the 8-point glucose testing (up to 6 points) and fulfill the eligibility criteria at Visit 2 will be randomized to participate in the study.
- Reminder to bring CGM sensor for collect and download.

**Randomization (Visit 2, Week 0)**

- Patients will be randomized to each treatment group
- Continue metformin therapy at same dose, unless contraindicated or for safety issues
- Discontinue other OADs and insulin formulation
- If BG > 400 mg/dl, patients will not be randomized, and considered screening failures.
- If BG > 300 mg/dl, investigator may order a confirmatory glucose test (at a different time) before considering the subject screen failure.
- Subjects will receive detailed instruction on the use of the IDegLira pen or IDeg and Aspart Pens and the titration algorithm.
- Patient will receive study medications. Subjects randomized to IDegLira will be instructed to not exceed 50 dose steps and to notify investigators if needed.
- Dose of insulin will be adjusted as needed.
- Patients will be instructed in performing glucose testing at home before meals, with a minimum of 2 out of the 4 pre-meal and bedtime glucose measurements per day.
- Patients will complete the DTSQ and TRIM-D questionnaires
- Investigator will collect CGM sensors

**Telephone Visits (weeks 1, 2, 3, 5, 6, 7, 10, 16, and 24)**

- Between each office visit, subjects will have a telephone visit with study personnel
- The purpose of these visits will be to monitor compliance with SMBG, CGM use, and study medication. Also hypoglycaemia and hyperglycemia data, as well as AEs, will be collected.
- Study diaries will be collected and reviewed for BG levels, episodes of hypoglycemia, SQ injections self-administration.

**Follow-up Visits (visit 6-18)**

The following activities will occur during interim visits:

- Subjects will receive detailed instruction on the use of the insulin or IDegLira pens
- Study diaries will be collected and reviewed for BG levels, episodes of hypoglycemia,

insulin self-administration

- Dose of IDeglira or insulin will be adjusted as needed. Study medication will be dispensed
- Subjects will be instructed in performing glucose testing at home before meals, with a minimum of 2 out of the 4 pre-meal and bedtime glucose measurements per day.
- Drug compliance will be reviewed (see below "subject compliance" section)
- AE and hypoglycemia data will be collected, as well as concomitant medications.
- Laboratory blood work as indicated on page 12 (schedule of events during study period)

**Visit 12 (12 weeks follow up)**

The following activities will occur during interim visits:

- Study diaries (8p-SMBG) will be collected and reviewed for BG levels, episodes of hypoglycemia, insulin self-administration
- Dose compliance will be reviewed
- Dose of IDeglira or insulin will be adjusted as needed. Dispensing study medication.
- Body measurements, vital signs, BMI will be collected
- HbA1c, Fasting Glucose/CMP and pregnancy test (WOCP per PI discretion) will be obtained
- CMG will be inserted
- Patients will complete the DTSQ and TRIM-D questionnaires
- AE and hypoglycemia data will be collected, as well as concomitant medications.
- Drug dispensing

**CGM visits (insertion on weeks -2, 12, 26 and collection on week 0, 14, 27)**

All enrolled participants will have a blinded/professional CGM study performed during week -2, 12, and 26 weeks of follow-up.

During this visit, participants will receive training on CGM use and reinforce SMBG diary collection. Trained personnel will proceed with sensor insertion, transmitter placement and hook-up. After that, the transmitter will be activated, the CGM session will be started.

After 7 days, subjects will remove the sensor and return to the scheduled visit. Transmitter will be connected to the computer for data downloading. CGM summary will be reviewed to determine the quality.

Sensor will be stored following standard precautions. Onsite visits will be allowed for upload of the study devices and face-to-face discussion about hypoglycemia and hyperglycemia

episodes, insulin doses, AE/SAE evaluation, and replacement of study medication, if required. Trained personnel will input required clinical and demographic data into the sensor database software. Subjects will complete an 8-point SMBG for 1 day (as shown in Table 1) prior to clinic visit. Subjects will bring their glucose meter, CGM sensor (if applicable), BG diary, to each onsite visit.

**Visit 17 (Week 26, end-of-study)**

- Diabetes Treatment Satisfaction Questionnaire Status (DTSQs) and TRIM-D survey
- Blood sampling as indicated on page 12- schedule of events during the study period, including HbA1c assessment to determine efficacy of treatment
- Study diaries collected and reviewed for BG levels, episodes of hypoglycemia, insulin self-administration

**Visit 18 (week 27, case sign-off)**

- This visit should occur at least one week after the last treatment visit
- Since degludec has a prolonged duration of action, this visit will serve to monitor for adverse events.
- Sensor removal (after 7 days).

During each visit, participants will have their insulin dose titrated to achieve a fasting glucose 70-100 mg/dL as detailed in the insulin titration algorithm. Once the fasting glucose 3-day average is <100 mg/dL, insulin doses will be kept constant, unless the participant experiences recurrent or severe hyperglycemia.

**Assessments for Efficacy**

The primary outcome of efficacy will be determined by change of HbA1c from baseline after 26 weeks of treatment. HbA1c will be measured by the clinical laboratory of Grady Memorial Hospital and Emory University, a NGSP-certified laboratory. Subjects will complete an 8-point SMBG for at least 1 day before the CGM visits. We will also compare the time in target range (70-180) as detected by CGM, allowing us to assess glycemic control for > 7 days with frequent testing (CGM and POC BG). We will compare the rate of “responders”, defined as patients HbA1c <7.0% and no hypoglycemia at week 26.

**Assessments for Safety**

The safety endpoint of the study will be incidence of hypoglycaemia, as measured by the

current standard-of-care of POC monitoring. Subjects will complete an 8-point POC BG log before weeks -1, 12, 26. In addition, we will perform blinded/professional CGM studies for 7 days, during week -1, 12, and 26. CGM will allow better detection of hypoglycemic events, particularly asymptomatic and nocturnal hypoglycemia, usually not detected by POC monitoring. It will also provide critical information on time in glycemic range and glycemic variability. We will also compare differences in glycemic variability, by SD, %CV and MAGE. GV will be calculated by mean daily standard deviation (SD) of glucose values in absolute terms, and as a percentage of variance from the overall mean (%CV). These are measures of dispersion of glucose values around a measure of central tendency, which represents the overall glucose excursion during the study. We will also analyze GV by mean amplitude of glycemic excursion (MAGE), which represents the average of all BG excursions (up or down), with a magnitude of > 1 standard deviation of all BG measures[47].

**Potential Risks to the Subjects:**

**Hypoglycemia.** It is possible that following the proposed protocol, subjects receiving IDegLira or Basal-bolus may develop hypoglycemia, as defined above.

**Gastrointestinal side effects,** including nausea and vomiting are more common in patients treated with liraglutide compared to placebo. The frequency of nausea and vomiting is reported in up to 5-15% patients receiving IDegLira. The number of adverse events will be collected at each telephone contact or clinic visit. There have been few reported events of acute pancreatitis. Subjects should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Degludec-liraglutide should be discontinued. If the investigator suspects acute pancreatitis, all suspected drugs should be discontinued until confirmatory test have been conducted and appropriate treatment should be initiated. Subjects diagnosed with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase >3xUNR or characteristic findings on CT scan/ MRI should be withdrawn from the study. In a cardiovascular outcomes trial (LEADER trial) 3.1% of patients treated with liraglutide, versus 1.9% of placebo treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up will be indicated.

**Protection against Risks:**

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor response to medical treatment every 1-2 weeks by telephone contact and every 1-2 months

during clinic visits, b) women of reproductive age who are sexually active will undergo a urine pregnancy tests prior to participation in the study and in-person visits as deemed by the investigator, c) female subjects who are pregnant, breast-feeding, or not willing to use appropriate contraception at time of enrollment will not be included in the study, d) patients with significant comorbidities such as chronic kidney disease greater than stage III, liver cirrhosis, gastroparesis, and pancreatic disorders will be excluded from the study. Hypoglycemia: Patients will receive diabetes education and will be instructed on hypoglycemia sign/symptoms and treatment. Patients will be asked to call the diabetes center and/or PCP in the event of hypoglycemia. If a patient develops hypoglycemia, the dose of basal insulin will be reduced (see treatment algorithm). Gastrointestinal side effects including nausea and vomiting may be expected, more commonly in patients treated with liraglutide. In subjects with suspected acute pancreatitis liraglutide and other potentially suspect medicinal products should be discontinued until confirmatory tests have been conducted and appropriate treatment initiated.

**Other Assessments**

We will assess patient satisfaction by using the DTSQs at baseline and the DTSQc at the end-of-study, as recommended by Health Psychology Research.

*For treatment satisfaction*, subjects' responses to questions 1, 7 and 8 of the DTSQc will be used. A comparison of the score on the DTSQs from week 0 to week 24, as well as using the score on the other questions of the DTSQc, which would overcome the ceiling limitation of using the DTSQs by itself[49]. The Diabetes Treatment Satisfaction Questionnaire Status (DTSQs) form will be administered at weeks 0, 12 and the DTSQc will be administered at week 26. The amplitude of the score on the DTSQc gives the degree of change in satisfaction, while the direction (positive or negative) will provide guidance on the preference of one treatment regimen over the other one.

*For quality of life, we* will use the "Treatment-related impact measures for diabetes" (TRIM-D)" in order to determine the impact of the type of therapy on this outcome. Subjects will be given the questionnaire at baseline, and weeks 12 and 26 to assess their quality of life and any potential impact of the treatment regimen [50].

**Subject Compliance**

Subject compliance will be assessed by monitoring of drug accountability. Subjects will be encouraged at every visit to adhere to the study medications and follow-up schedule. Unused trial medications will be compared with dispensed amount at each corresponding visit. If discrepancies are noted, the subject will be asked.

## STATISTICAL CONSIDERATIONS:

### Sample Size Calculation

The primary outcome is the change in HbA1c from baseline after 26-weeks of treatment. The primary hypothesis is that HbA1c change is similar between the IDegLira group and the basal-bolus group. Given the data reported for the DUAL V study, we assume the HbA1c change from baseline has a standard deviation bounded above by 0.85 (%). We assume the margin of equivalence is 0.4 (%) and the true mean difference in the primary outcome is 0 (%). Given 57 subjects per study group, based on a one-sided, two-sample t-tests, we would achieve 80% power to detect non-inferiority, with alpha (type-1 error) set as 0.05. Accounting for 20% attrition rate of 20%, we need to recruit 75 subjects per group (150 in total).

### Statistical Methods

This is a randomized, open-label study. We will first compare the primary outcome (i. e. change in HbA1c from baseline to after 26 weeks of treatment) between the two study groups using nonparametric and parametric two-sample tests, such as Wilcoxon tests and t-tests. A logarithm transformation may be employed to make the data better conform to the normality assumption. We will apply standard variable selection and model checking procedures to decide the final model.

Secondary outcomes include various measurements (related to glycemic control, qualify of life, adverse effects, and etc.) collected at a single or multiple time points. For continuous outcomes measured a single time point (i.e. non-longitudinal outcome), we shall analyze them following the same strategy designed for the primary outcome. For discrete non-longitudinal outcome, we will use Chi-square (or Fisher's Exact) tests to compare them between the two study groups. This will be followed by logistic regression or Poisson (or Negative Binomial) regression to assess other potential confounders. We will perform appropriate model selection and diagnostic procedures to ensure adequate fit to the data. For outcomes measured at multiple time points (i.e. longitudinal outcome), we will first conduct cross-sectional analyses as planned for the non-longitudinal outcomes. Next we will perform repeated measures analyses that account for with-subject correlations in the longitudinal outcomes. We will analyze longitudinal continuous outcomes based on repeated measures ANOVA followed by repeated measures linear regression, and we will analyze longitudinal discrete outcomes by using repeated measures generalized linear model (GLM). If the assumption of missing completely at random (MCAR) is reasonable, we shall handle missing data by excluding them from the cross-

sectional and the longitudinal data analyses. When MCAR assumption is questionable, we will assume missing values are missing at random and deal with them by the standard multiple imputation methods. We plan to conduct statistical analyses using SAS 9.4.

**Interim Analysis**

We plan to perform interim analysis on the primary safety endpoint every 6 months. The trial will be stopped if there is evidence beyond a reasonable doubt of a difference in the rate of death (two-sided alpha level, <0.01) between the treatment groups. In addition, the trial will be stopped if the rate of severe hypoglycemic events (BG <40 mg/dl) in either group is > 40%.

**Explorative Statistical Analysis for Pharmacogenetics and Biomarkers**

N/A

**DATA HANDLING AND RECORD KEEPING:**

Data collection records with personal identifiers will be stored in locked file cabinets. Sponsor site expects data to be entered in REDCap within 10 days of phone call or outpatient visit. The study coordinators will enter data from each visit into data collection paper forms and into an electronic database (REDCap) that meets HIPPA and confidentiality regulations, provided by the Emory Research Information Technology Department. Baseline data will include demographics/history form (subject's gender, date of birth, ethnicity, history of diabetes, and treatment of diabetes and comorbid conditions, body weight, BMI. During follow-up visits, data from SMBG, laboratory and/or CGM will be also collected. Data on adverse events will also be collected and enter into the database. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, research coordinators, and the IRB at Emory University.

**ETHICS:**

**Informed Consent.**

After identification of eligible patients these individuals will be provided basic information regarding the study and, if interested, a member of the research staff using inclusion/exclusion criteria delineated elsewhere in the protocol will enroll patients. Informed consent will be obtained before any trial related procedures including screening procedures. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have questions, and a member of the research staff will answer questions. The principal investigator

will also be available at all times to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office.

Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important and key points of the study. One of the investigators or research coordinators will obtain an informed consent prior to inclusion of a patient into the study.

The study will be conducted in accordance with the Declaration of Helsinki and 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 the informed consent.

**STUDY SCHEDULE:**

The study will be conducted at two sites: at 1) Emory University Hospital Midtown and Grady Memorial Hospital in Atlanta, GA; and at 2) TBA. An additional site will be considered if funds are available.

Based on our prior trials experience, we anticipate 3-4 potential candidates per week, including the collaborating institutions, for a total recruitment period of approximately 12 months. Since the study requires a 6-month follow up period, we anticipate a study length of 18-24 months.

| | |
|---|---|
| First subject in | 2019 January |
| Screening | ~300 |
| Randomized | 150 |
| Last subject recruited | 2020 June/July |
| Last subject in (completed) | 2021 Nov/Dec |
| Data analysis | 2021 DEC |
| Submission to congress or journal | ADA 2021, Major journal and/or Diabetes Care 2021 |

**Study DRUGS and materials:**

**Study medication(s) / devices(s)**

- Group 1: IDegLira pens will be supplied by the sponsor and given free of charge to the study subjects. IDegLira is a FRC agent, including basal insulin degludec and GLP-1 agonist

liraglutide. The starting dose of IDegLira is at 16 dose steps (degludec 16 units/liraglutide 0.6 mg). The maximum allowed dose of IDegLira 50 dose steps provide 50 U of degludec and 1.8mg of liraglutide.

- Group 2: Degludec U-100 and Aspart U-100 insulin pens will be supplied by the sponsor and given free of charge to the study subjects.
- We will use a professional CGM device. The investigator will keep the sensor readers, and will store the transmitters after the completion of each sensor study for up to 5 years- as part of the study information.

**Packaging and Labelling of Study Medication(s)**

Trial products will be packed and labelled by Emory and Grady Investigational Drug Service. Labelling will be in accordance with local law and study requirements.

**Storage and Drug Accountability of Study Medication(s)**

Emory and Grady Investigational Drug Service, is a full-service research pharmacy with all required conditions for proper storage and dispensing of study medications. The investigator will ensure the availability of proper storage conditions and record and evaluate the temperature. There will be no trial medication(s) dispensed to any person not enrolled in the study. Any unused medication(s) will be stored separately from used trial medication(s). Subject compliance will be assessed by asking subjects to return all unused, partly used and unused cartridges and vials of liraglutide and degludec insulin at each visit. Subjects will be instructed to return all used, partially used or unused study products before each dispensing visit. Subjects will be encouraged at every visit to adhere to the study medications and follow-up schedule. Any partially used or unused study medications will be destroyed accordingly to local procedures. After study completion, any surplus of study medications or supplies will be disposed as per local regulations.

**Auxiliary Supply**

Investigator will provide the following supplies:

- Needles for insulin pens, IDegLira, Degludec and Aspart pens

**Randomization and Blinding**

This is an open label randomized controlled trial. Patients will be randomized consecutively using a computer-generated randomization table provided by Dr. Limin Peng, Professor of Statistics at the Emory School of Public Health. Patient will be randomized based on HbA1c (HbA1c <10 or ≥10). The randomization table will be mailed to each institution where

a member of the research team will be in charge of the randomization process and group assignment.

**Breaking of Blinded Codes**

N/A

**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 must be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication must be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the sponsor must be informed.

The information collected for each concomitant medication includes, 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, should be recorded.

**ADVERSE EVENTS:**

The investigator will be responsible for reporting of all adverse events including serious adverse events (SAE), serious adverse drug reactions (SADRs) to the competent authority and independent IRB boards based upon federal regulations and local/IRB policies. The investigator will report to the sponsor all S A R D s at the same time it's reported to the IRB or within 15 days of the investigator becoming aware.

The investigators will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification (e.g. initials, sex, age)
3. Diagnosis
4. Drug
5. Reporter identification (e.g. Name, or initials)

Also 6) Causality, and 7) Outcome might be reported, but this is not mandatory.

**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.

**Adverse Reaction (AR)**

An AR is an adverse event for which the causal relationship between the product and the adverse event is suspected.

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 hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- 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 jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Suspicion of transmission of infectious agents

*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 is an adverse event (AE) for which a causal relationship to the trial product is at least possible i.e. causal relationship is conceivable and cannot be dismissed. Serious adverse reaction (SAR): Adverse event which fulfils both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.

**Suspected Unexpected Serious Adverse Reaction (SUSAR):**

An SAE which is unexpected and regarded as possibly or probably related to the trial/study product by the investigator.

**Medical Events of Special Interest (MESI):** A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

**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 ethology other than the trial product

**The US PI, will be used to evaluate all unexpected events and adverse reactions.**

**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, paralyzed). 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 must be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the posttreatment follow-up period as stated in the protocol.

**Follow-up of Adverse Events**

During and following a subject's participation in a clinical trial, the investigator will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study, 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 the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.

**Pregnancy**

Subjects will be instructed to notify the sponsor-investigator immediately if they become pregnant.

The investigator will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by investigator should occur within the same timelines described

above for reporting of Adverse Events.

Pregnancy complications should 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**

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor capillary blood glucose and reported symptoms. To minimize significant clinical events, we will exclude patients with history of significant liver, renal or cardiac failure in this study.

Hypoglycemia can occur during the treatment with insulin. Hypoglycemia will be treated accordingly to the best local practices, and insulin will be adjusted as per a predefined algorithm. Subjects will be instructed to not exceed the maximum dose of IDegLira of 50 steps. Subjects will be instructed to maintain good hydration, and to report the presence of severe nausea, vomiting, or diarrhea. Insulin doses will be adjusted for hypoglycemic values.

**LIABILITY AND SUBJECT INSURANCE:**

No additional cost to patients or to the institution will be incurred for research purposes. Patients will not be billed for the laboratory work or any test that is being done only for study purposes. Novo Nordisk will provide IDegLira, Degludec and Aspart at no cost to participants. Patients will be responsible for the cost of their usual ongoing medical care, including procedures (glucose meter supplies) and/or non-study medications that your doctor requires as part of your usual medical care.

During and following a subject's participation in a clinical trial, the 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 at patient own cost, regardless of their insurance status. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

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

representations; 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.

**PREMATURE TERMINATION OF STUDY:**

The investigator may decide to stop prematurely the trial. In this case, the investigator will notify the subjects promptly and ensure appropriate follow up. The investigator will also notify the IRB and local regulatory authorities.

**PUBLICATION PLAN:**

We anticipate completion of the study in Dec 2019. Data will be analyzed between October and December 2019. One abstract will be submitted to the 2020 American Diabetes Association meeting and manuscript(s) will be submitted during the first six months of 2020. The investigator will register the study with a publicly assessable database, such as clinicaltrials.gov.

**REFERENCES:**


1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):837-853.
2. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):854-865.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359(15):1577-1589.
4. Kahn SE. Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. *J Clin Endocrinol Metab.* 2001;86(9):4047-4058.
5. Ferrannini E. The stunned beta cell: a brief history. *Cell Metab.* 2010;11(5):349-352.
6. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. *Endocr Pract.* 2017;23(2):207-238.
7. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2012;97(1):16-38.
8. American Diabetes A. 8. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care.* 2017;40(Suppl 1):S64-S74.
9. Garber AJ. Insulin intensification strategies in type 2 diabetes: when one injection is no longer sufficient. *Diabetes Obes Metab.* 2009;11 Suppl 5:14-18.
10. Garber AJ. The importance of titrating starting insulin regimens in patients with type 2 diabetes. *Diabetes Obes Metab.* 2009;11 Suppl 5:10-13.
11. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet Med.* 2012;29(5):682-689.
12. Peyrot M, Rubin RR, Khunti K. Addressing barriers to initiation of insulin in patients with type 2 diabetes. *Prim Care Diabetes.* 2010;4 Suppl 1:S11-18.
13. Rubin RR, Peyrot M, Kruger DF, Travis LB. Barriers to insulin injection therapy: patient and health care provider perspectives. *Diabetes Educ.* 2009;35(6):1014-1022.
14. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. *J Gen Intern Med.* 2005;20(5):479-482.
15. Josse RG, Woo V. Flexibly timed once-daily dosing with degludec: a new ultra-long-acting basal insulin. *Diabetes Obes Metab.* 2013;15(12):1077-1084.
16. Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose

measurements for improving metabolic control. *Diabetes Care.* 2003;26(4):1153-1157.
17. Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. *J Diabetes Complications.* 2017;31(1):280-287.
18. Munshi MN, Segal AR, Suhl E, et al. Frequent hypoglycemia among elderly patients with poor glycemic control. *Arch Intern Med.* 2011;171(4):362-364.
19. Leinung M, Nardacci E, Patel N, Bettadahalli S, Paika K, Thompson S. Benefits of short-term professional continuous glucose monitoring in clinical practice. *Diabetes Technol Ther.* 2013;15(9):744-747.
20. Gehlaut RR, Dogbey GY, Schwartz FL, Marling CR, Shubrook JH. Hypoglycemia in Type 2 Diabetes--More Common Than You Think: A Continuous Glucose Monitoring Study. *J Diabetes Sci Technol.* 2015;9(5):999-1005.
21. Tibaldi J. Achieving glycemic goals with addition of incretin-based therapies to insulin in patients with type 2 diabetes mellitus. *Am J Med Sci.* 2014;347(6):491-501.
22. Vora J, Bain SC, Damci T, et al. Incretin-based therapy in combination with basal insulin: a promising tactic for the treatment of type 2 diabetes. *Diabetes Metab.* 2013;39(1):6-15.
23. Ali MK, Bullard KM, Gregg EW. Achievement of goals in U.S. Diabetes Care, 1999-2010. *N Engl J Med.* 2013;369(3):287-288.
24. Palermo NE, Modzelewski KL, Farwell AP, et al. Open Access to Diabetes Center from the Emergency Department Reduces Hospitalizations in the Susequent Year. *Endocr Pract.* 2016;22(10):1161-1169.
25. Magee MF, Nassar CM, Mete M, White K, Youssef GA, Dubin JS. The Synergy to Enable Glycemic Control Following Emergency Department Discharge Program for Adults with Type 2 Diabetes: Step-Diabetes. *Endocr Pract.* 2015;21(11):1227-1239.
26. Abdul-Ghani M, Mujahid O, Mujahid A, DeFronzo RA, Zirie M, Jayyousi A. Efficacy of Exenatide Plus Pioglitazone Versus Basal/Bolus Insulin in T2DM Patients With Very High HbA1c. *J Clin Endocrinol Metab.* 2017.
27. Umpierrez GE, Reyes D, Smiley D, et al. Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes. *Diabetes Care.* 2014;37(11):2934-2939.
28. Mauricio D, Meneghini L, Seufert J, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. *Diabetes Obes Metab.* 2017.
29. DeVries JH, Bain SC, Rodbard HW, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care.* 2012;35(7):1446-1454.
30. Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care.* 2014;37(8):2317-2325.
31. Ilkova H, Glaser B, Tunckale A, Bagriacik N, Cerasi E. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care.* 1997;20(9):1353-1356.

32. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care.* 2004;27(5):1028-1032.
33. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet.* 2008;371(9626):1753-1760.
34. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care.* 2014;37(10):2763-2773.
35. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet.* 2014;384(9961):2228-2234.
36. Retnakaran R, Kramer CK, Choi H, Swaminathan B, Zinman B. Liraglutide and the preservation of pancreatic beta-cell function in early type 2 diabetes: the LIBRA trial. *Diabetes Care.* 2014;37(12):3270-3278.
37. Buse JB, Han J, Miller S, MacConell L, Pencek R, Wintle M. Addition of exenatide BID to insulin glargine: a post-hoc analysis of the effect on glycemia and weight across a range of insulin titration. *Curr Med Res Opin.* 2014;30(7):1209-1218.
38. Wilding JP, Rajeev SP, DeFronzo RA. Positioning SGLT2 Inhibitors/Incretin-Based Therapies in the Treatment Algorithm. *Diabetes Care.* 2016;39 Suppl 2:S154-164.
39. Owens DR, Monnier L, Barnett AH. Future challenges and therapeutic opportunities in type 2 diabetes: Changing the paradigm of current therapy. *Diabetes Obes Metab.* 2017.
40. Owens DR, Monnier L, Bolli GB. Differential effects of GLP-1 receptor agonists on components of dysglycaemia in individuals with type 2 diabetes mellitus. *Diabetes Metab.* 2013;39(6):485-496.
41. Investigators F-ST. Glucose Variability in a 26-Week Randomized Comparison of Mealtime Treatment With Rapid-Acting Insulin Versus GLP-1 Agonist in Participants With Type 2 Diabetes at High Cardiovascular Risk. *Diabetes Care.* 2016;39(6):973-981.
42. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab.* 2014;16(7):636-644.
43. Freemantle N, Mamdani M, Vilsboll T, Kongso JH, Kvist K, Bain SC. IDegLira Versus Alternative Intensification Strategies in Patients with Type 2 Diabetes Inadequately Controlled on Basal Insulin Therapy. *Diabetes Ther.* 2015;6(4):573-591.
44. Hughes E. IDegLira: Redefining insulin optimisation using a single injection in patients with type 2 diabetes. *Prim Care Diabetes.* 2016;10(3):202-209.
45. Lingvay I, Perez Manghi F, Garcia-Hernandez P, et al. Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The DUAL V Randomized Clinical Trial. *JAMA.* 2016;315(9):898-907.
46. A/S NN. Xultophy® demonstrates similar glucose control with reduced risk of

hypoglycaemia and a superior weight profile compared to basal-bolus therapy.
47. Bergenstal RM. Glycemic Variability and Diabetes Complications: Does It Matter? Simply Put, There Are Better Glycemic Markers! *Diabetes Care.* 2015;38(8):1615-1621.
48. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet.* 2012;379(9825):1498-1507.
49. Bradley C. Diabetes treatment satisfaction questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. *Diabetes Care.* 1999;22(3):530-532.
50. Brod M, Christensen T, Hammer M, Busk AK, Bushnell DM. Examining the ability to detect change using the TRIM-Diabetes and TRIM-Diabetes Device measures. *Quality of Life Research*. 2011;20(9):1513-1518. doi:10.1007/s11136-011-9886-7
51. Philis-Tsimikas A, Brod M, Niemeyer M, et al. Insulin Degludec Once-Daily in Type 2 Diabetes: Simple or Step-Wise Titration (BEGIN: Once Simple Use). *Advances in Therapy*. 2013;30(6):607-622.
52. Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continous Glucose Monitoring. *Diabetes Care*. 2017; Dec; 40 (12): 1631-1640