SUPPLEMENTAL MATERIAL

Supplemental Table 1. Study Inclusion and Exclusion Criteria

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| **Inclusion Criteria** |
| * Have a diagnosis of T2D treated with a stable dose of metformin (alone or in combination with a stable dose of a DPPIV inhibitor and/or a SGLT2 inhibitor) for at least 3 months prior to screening * No male contraception required except in compliance with specific local government study requirements * Female patients:   + Women of child-bearing potential who are abstinent or in a same sex relationship must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males   + Otherwise, women of child-bearing potential participating must agree to use contraception for the entirety of the study   + Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment * Are 18 to 75 years of age, inclusive, at the time of signing the informed consent * Have HbA1c values of 7.0% to 9.5% inclusive, at screening * Must have been treated with a stable dose of metformin (alone or in combination with a stable dose of a DPPIV inhibitor and/or a SGLT2 inhibitor) for 3 months prior to screening and be willing to continue stable dosing throughout the study * Have a body mass index (BMI) between 20 and 45 kg/m2, with no significant weight gain or loss in the past 3 months (≥5%) * Are well-motivated, capable, and willing to learn how to self-inject treatment, maintain study diaries, perform daily fingerstick blood glucose monitoring, and must have a normal wake/sleep pattern, in the investigator’s opinion * Are willing and able to follow the visit schedule during the complete duration of the trial |
| **Exclusion Criteria** |
| * Have a history of greater than 1 episode of ketoacidosis or hyperosmolar state/coma requiring hospitalization in the 6 months prior to screening * Have had any episodes of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to screening * Cardiovascular (CV): have had any of the follow CV conditions: acute myocardial infarction, New York Heart Association Class III or IV heart failure, or cerebrovascular accident (stroke) * Gastrointestinal: have gastroparesis or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (e.g., Lap-Band®) prior to screening * Hepatic: have acute or chronic hepatitis, or obvious clinical signs or symptoms of any other liver disease except non-alcoholic fatty liver disease (NAFLD), and/or have elevated liver enzyme measurements, as determined by the central laboratory at screening and as indicated below:   + Total bilirubin level >1.5x the upper limit of normal (ULN) in the absence of Gilbert’s syndrome   + Alanine aminotransferase/serum glutamic pyruvic transaminase >2.0x ULN   + Aspartate aminotransferase/serum glutamic oxaloacetic transaminase >2.0x ULN * Renal: have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2, calculated by the Chronic Kidney Disease-Epidemiology equation, as determined by the central laboratory at screening * Have fasting triglycerides >400 mg/dL or non-fasting >600 mg/dL * Have experienced significant weight loss or gain (>5%) in body weight in the 3 months prior to screening * Have active or untreated malignancy or have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years or are at increased risk for developing cancer or a recurrence of cancer in the opinion of the investigator * Have known hypersensitivity or allergy to any of the study medications or their excipients * Have any other serious disease or condition (e.g., known drug or alcohol abuse/regular consumption or psychiatric disorder) that, in the opinion of the investigator, would pose a significant risk to the patient, preclude the patient from following and completing the protocol, or interfere with the interpretation of safety, efficacy, or PD data * Have had a blood transfusion or severe blood loss within 3 months prior to screening or have any hematologic condition that may interfere with HbA1c measurement (e.g., hemoglobinopathy, hemolytic anemia, sickle-cell disease) * Are taking drugs that may significantly affect glycemic control (e.g., niacin [allowed if <1.0 g/day], bile acid sequestrants or pentoxyphylline) * Are receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy or intra-articular (but excluding topical, intraocular, intranasal, and inhaled preparations), or have received such therapy within 4 weeks immediately prior to screening with the exception of replacement therapy for adrenal insufficiency * Are currently taking or have taken within the 3 months preceding screening, prescription or over-the-counter medications to promote weight loss. Patients who participate must agree not to initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment * Have been treated with a sulfonylurea (SU), a glitazone, alpha-glucosidase inhibitor, a GLP-1 receptor agonist or insulin in the 3 months prior to screening with the exception of short-term use of insulin for acute conditions (≤14 days within the last 6 months prior to screening) * Are using or have used blood pressure-lowering medication at a dose that has not been stable for 1 month prior to screening * Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study * Have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed * Have previously completed or withdrawn from this study or any other study investigating BIF. |

Supplemental Table 2. HbA1c Results Presented by Subgroup above or below Median HbA1c at Baseline

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| --- | --- | --- | --- | --- | --- | --- |
| **Parameter** |  | **BIF** |  | **Degludec** |  | **Estimated Treatment Difference (90% CI) (%)** |
| **Timepoint** | **n** | **Estimate (SE) (%)a,b** | **n** | **Estimate (SE) (%)a,b** |  |  |
| **Median HbA1c < 7.9%** |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Baseline | 53 | 7.34 (0.042) | 62 | 7.31 (0.039) |  |  |
| Week 26 | 49 | 6.41 (0.097) | 55 | 6.49 (0.091) |  | -0.08 (-0.30, 0.14) |
|  |  |  |  |  |  |  |
| **Median HbA1c ≥ 7.9%** |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Baseline | 74 | 8.58 (0.061) | 68 | 8.55 (0.063) |  |  |
| Week 26 | 65 | 7.12 (0.109) | 63 | 6.94 (0.113) |  | 0.19 (-0.07, 0.45) |
|  |  |  |  |  |  |  |

a - MMRM model for post-baseline measures: Variable = Baseline + Pooled Country group 1 + SGLT2 Treatment at Baseline + DPP-4 Inhibitors Treatment at Baseline + Baseline BMI Group 2 + Treatment + Time + Treatment\*Time (Type III sum of squares). Variance-Covariance structure (Actual Value) = Unstructured. Variance-Covariance structure (Change from Baseline) = Unstructured.  
b - ANCOVA model for endpoint measures: Variable = Baseline + Pooled Country group 1 + SGLT2 Treatment at Baseline + DPP-4 Inhibitors Treatment at Baseline + Baseline BMI Group 2 + Treatment (Type III sum of squares).

Supplemental Table 3. Within- and Between- Day Glycemic Variability from CGM for 24-hour Time Period

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** |  | **BIF** |  | **Degludec** | **Estimated Treatment Difference (90% CI)** |
|  | **n** | **Estimate (SE)a,b** | **n** | **Estimate (SE)a,b** |  |
| **Within-Day Variability** |  |  |  |  |  |
| CV (%) |  |  |  |  |  |
| Baseline | 103 | 22.8 (0.48) | 106 | 22.8 (0.47) |  |
| Week 26 | 78 | 28.2 (0.57) | 84 | 28.0 (0.55) | 0.2 (-1.1, 1.5) |
| SD (mg/dL) |  |  |  |  |  |
| Baseline | 103 | 37.0 (0.99) | 106 | 35.6 (0.93) |  |
| Week 26 | 78 | 37.0 (0.98) | 84 | 35.0 (0.91) | 2.0 (-0.2, 4.2) |
|  |  |  |  |  |  |
| **Between-Day Variability** |  |  |  |  |  |
| CV (%) |  |  |  |  |  |
| Baseline | 103 | 20.5 (0.48) | 106 | 20.6 (0.48) |  |
| Week 26 | 78 | 24.0 (0.45) | 84 | 24.9 (0.45) | -0.9 (-1.9 0.2) |
| SD (mg/dL) |  |  |  |  |  |
| Baseline | 103 | 33.5 (1.04) | 106 | 32.5 (0.99) |  |
| Week 26 | 78 | 32.0 (0.90) | 84 | 31.4 (0.85) | 0.6 (-1.4, 2.7) |

Abbreviations: ANOVA = analysis of variance; CI = confidence interval; CGM = continuous glucose monitoring; CV = Coefficient of Variation; MMRM = mixed model repeated measures; SD = standard deviation; SE = standard error.

a MMRM model for postbaseline measures: log (Actual Measurement/Baseline) = log (Baseline) + Hemoglobin A1c Stratum at Baseline 1 + Treatment + Time + Treatment × Time (Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.

b ANOVA model for baseline measures: log (Actual Measurement) = Treatment (Type III sum of squares).

Supplemental Table 4. Safety summary

|  |  |  |
| --- | --- | --- |
| **n (%)** | **Degludec  (N=135)** | **BIFa (N=143)** |
| Treatment-emergent adverse events | 60 (44.4) | 70 (49.0) |
| Serious adverse event | 4 (3.0) | 7 (4.9) |
| Death | 1 (0.7)b | 0 |
| Treatment-Emergent Hepatic Disorder Events | 1 (0.7) | 0 |
| Treatment-Emergent Injection Site Reactions | 4 (3.0) | 5 (3.5) |
| Treatment-Emergent Systemic Hypersensitivity Reactionsc | 0 | 6 (4.2) |

aBIF group included patients randomized to both BIF algorithims, the paper, non-digital algorithm and the discontinued digital algorithm.

bDeath was due to COVID-19 pneumonia.

cThe count for hypersensitivity reactions was based on narrow search and 2 of them on BIF were related to study treatment (rash, reaction to excipient).

Abbreviations: BIF, Basal Insulin Fc; N, number of subjects in the analysis population; n, number of subjects in the specified category.

Supplemental Figure 1. Study design

**Screening/**

**Lead-In**

**Follow-up**

**Visit**

**Week**

**BIF (Paper Algorithm)**

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-2

2

-1

3

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4

1

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801

31

Randomization

End of treatment period

5 weeks

26 weeks

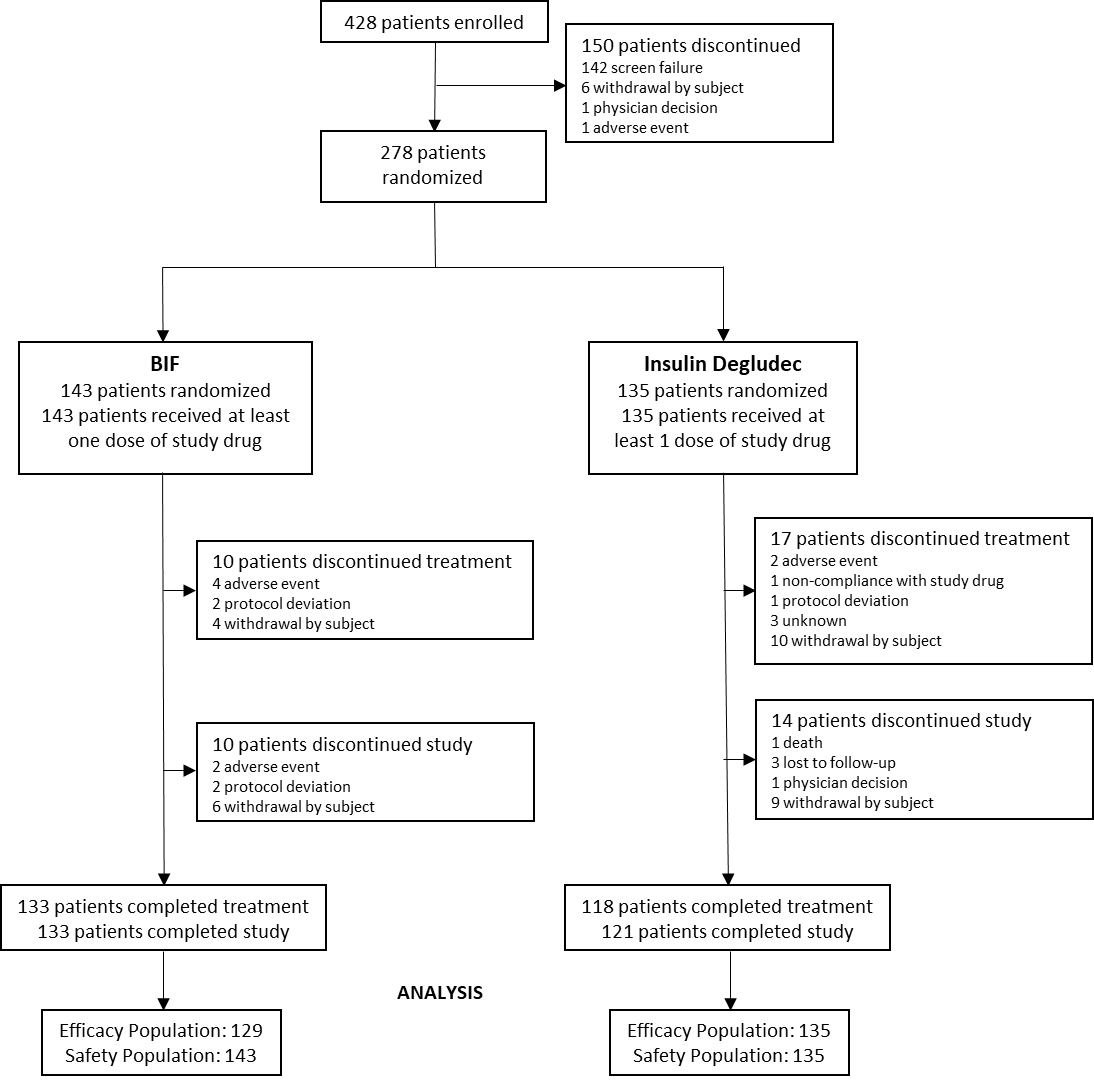
2 weeks

**Insulin Degludec**

**Treatment period**

**CGM Session**

Supplemental Figure 2. Participant disposition from enrolment to study completion



Supplemental Figure 3. Ambulatory glucose profiles

Chart, line chart

Description automatically generated

A

Chart, line chart

Description automatically generated

Baseline

B

Chart, line chart

Description automatically generatedChart, line chart

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Week 26

(A) Ambulatory glucose profiles for BIF (left) and insulin degludec (right) at baseline. (B) Ambulatory glucose profiles for BIF (left) and insulin degludec (right) at Week 26. Data presented as median (red line).

Abbreviations: BIF, weekly basal insulin Fc.

Supplemental Figure 4. Basal insulin dose

Basal insulin dose over the 26-week treatment period. Weekly BIF dose (left) and daily degludec dose (right). Data are mean. Abbreviations: BIF, weekly basal insulin Fc.