**Supplementary data**

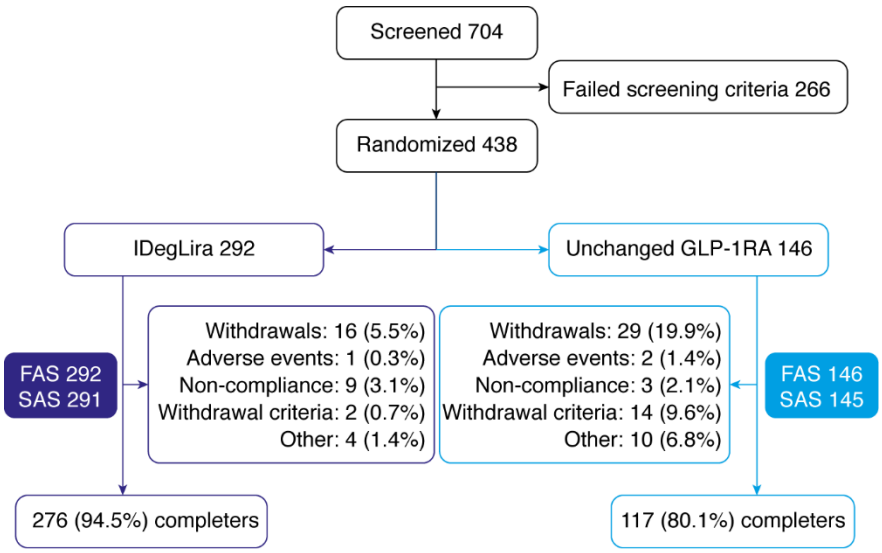
**Supplementary Table 1: Inclusion and Exclusion criteria:**

| **Inclusion criteria** |
|---|
| Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial |
| Type 2 diabetes |
| Male or female ≥18 years of age |
| $HbA_{1c}$ 7.0−9.0% (53–75 mmol/mol) (both inclusive) |
| Treatment with daily GLP-1RA at maximum dose according to local label (i.e. 1.8 mg once-daily liraglutide or 10 microgram twice-daily exenatide) or documented maximum tolerated dose (i.e. 1.2 mg OD liraglutide or 5 microgram BID exenatide) in combination with a stable daily dose of metformin (≥1500 mg or documented maximum tolerated dose) ± stable daily dose of pioglitazone (≥30 mg) ± stable daily dose of sulfonylurea (≥half of the max approved dose according to local label) ≥90 days prior to screening visit. |
| Body mass index ≤40 $kg/m^2$ |
| Able and willing to adhere to the protocol including performing self-monitored plasma glucose profiles, to keep a trial diary and to use pre-filled pen device |
| **Exclusion criteria** |
| Known or suspected hypersensitivity to trial product(s) or related products |
| Previous participation in this trial. Participation is defined as randomization |
| Females of child-bearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice) |
| Receipt of any investigational medicinal product within 30 days prior to screening visit (Visit 1) |
| Use of any drug (except metformin, pioglitazone, sulfonylurea and GLP-1RA) which in the investigator's opinion could interfere with the blood glucose level (e.g. systemic corticosteroids). |
| Treatment with any insulin regimen (short term treatment due to intercurrent illness including gestational diabetes is allowed at the discretion of the investigator) |
| Impaired liver function, defined as alanine aminotransferase (ALAT) ≥2.5 times upper normal range (UNR) |
| Impaired renal function defined as serum-creatinine ≥133 µmol/L (1.5 mg/dL) for males and ≥125 µmol/L (1.4 mg/dL) for females, or as allowed according to local contraindications for metformin |
| Screening calcitonin ≥50 ng/L |
| Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2) |
| Cardiovascular disorders defined as; congestive heart failure (New York Heart Association (NYHA) class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the past 52 weeks prior to Visit 1 and/or planned coronary, carotid or peripheral artery revascularisation procedures |
| Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg) |
| Proliferative retinopathy requiring acute treatment or maculopathy (macular edema) according to the investigator's opinion |
| Subjects with a clinical significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for the type 2 diabetes), neurological, genitourinary or haematological system that in the opinion of the Investigator, may confound the results of the trial or pose additional risk in administering trial product |
| Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedures or cooperation with the trial personnel |
| Known or suspected abuse of prescription drugs, alcohol or illicit substances |
| History of chronic pancreatitis or idiopathic acute pancreatitis |
| Suffer from a life threatening disease including malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer) |

**Supplementary Table 2: Titration algorithm**

| Fasting plasma glucose | | Dose adjustment |
|---|---|---|
| **mmol/L** | **mg/dL** | **Dose steps** |
| <4.0 | <72 | –2 |
| 4.0–5.0 | 72–90 | 0 |
| >5.0 | >90 | +2 |

**Supplementary Figure 1:** Patient disposition. FAS, full analysis set; GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide combination; SAS, safety analysis set.




**Supplementary Table 3: Hypoglycemia**

| | **IDegLira *n* = 291** | | | **Unchanged GLP-1RA *n* = 145** | | | **Estimated rate ratio [95% CI]** |
|---|---|---|---|---|---|---|---|
| | **N (%)** | **Events** | **Rate** | **N (%)** | **Events** | **Rate** | |
| Severe | 1 (0.3) | 1 | 0.007 | 0 (0) | 0 | 0 | N/A |
| Confirmed | 93 (32) | 397 | 2.82 | 4 (2.8) | 8 | 0.12 | 25.36 [10.6; 60.5], $p < 0.001$ |
| Nocturnal confirmed | 32 (11) | 64 | 0.45 | 1 (0.7) | 1 | 0.015 | 32.82 [4.13; 261.04], $p < 0.001$ |

N, number of subjects with ≥1 event; %, percentage of subjects; rate, unadjusted event rate (episodes per patient-year of exposure). Data are based on the SAS. Estimated rate ratio based on FAS. FAS, full analysis set; GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide combination; PYE, patient years of exposure; SAS, safety analysis set.

**Supplementary Table 4: Hypoglycemia by pre-trial oral anti-diabetic drugs**

| | IDegLira + met ± pio *n* = 223 | | | Unchanged GLP-1RA + met ± pio *n* = 111 | | | IDegLira + met + SU ± pio *n* = 68 | | | Unchanged GLP-1RA + met + SU ± pio *n* = 34 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (%) | Events | Rate | N (%) | Events | Rate | N (%) | Events | Rate | N (%) | Events | Rate |
| Severe | 1 (0.4) | 1 | 0.009 | 0 (0) | 0 | 0 | 0 (0) | 0 | 0 | 0 (0) | 0 | 0 |
| Confirmed | 62 (28) | 189 | 1.75 | 0 (0) | 0 | 0 | 31 (46) | 208 | 6.34 | 4 (12) | 8 | 0.51 |

N, number of subjects with ≥1 event; %, percentage of subjects; rate, unadjusted event rate (episodes per patient-year of exposure). Data are based on the SAS. Met, metformin, GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide combination; pio, pioglitazone; PYE, patient years of exposure; SAS; safety analysis set; SU, sulfonylurea.

**Supplementary Table 5: Lipase and amylase by treatment week**

| | IDegLira *n* = 290 | Unchanged GLP-1RA *n* = 145 |
|---|---|---|
| ***Lipase, U/L*** | | |
| Week 0 | 61.9 (44.3) [17.0; 388.0] | 57.3 (37.4) [17.0; 335.0] |
| Week 12 | 68.0 (55.6) [14.0; 438.0] | 60.8 (39.7) [18.0; 286.0] |
| Week 26 | 60.9 (40.1) [13.0; 418.0] | 55.5 (39.0) [17.0 429.0] |
| ***Amylase, U/L*** | | |
| Week 0 | 63.9 (31.1) [13.0; 256.0] | 62.2 (31.6) [11.0; 225.0] |
| Week 12 | 72.3 (37.7) [20.0; 291.0] | 63.3 (31.2) [20.0; 201.0] |
| Week 26 | 70.1 (36.8) [23.0; 241.0] | 61.2 (26.3) [13.0; 176.0] |

Values are mean (standard deviation) [min; max range]. N, number of subjects. Data are based on the SAS with LOCF. Met, metformin, GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide combination; LOCF, last observation carried forward; SAS; safety analysis set.

**Supplementary Table 6: Patient-reported outcomes**

| Score | IDegLira (*n* = 291) Observed score at EOT | Unchanged GLP-1RA (*n* = 146) Observed score at EOT | IDegLira (*n* = 290) Observed change from baseline | Unchanged GLP-1RA (*n* = 146) Observed change from baseline | Estimated treatment contrast [95% CI] ANCOVA analysis IDegLira – GLP-1RA |
|---|---|---|---|---|---|
| **TRIM-D** | | | | | |
| Total score | 82.3 ± 11.9 | 78.1 ± 13.9 | 8.7 ± 12.0 | 3.1 ± 12.2 | 5.0 [2.9, 7.2]; $p < 0.001$ |
| Treatment burden | 81.2 ± 15.9 | 76.6 ± 18.0 | 10.8 ± 18.8 | 5.7 ± 19.3 | 5.0 [1.9; 8.0]; $p = 0.002$ |
| Daily life | 84.5 ± 16.6 | 81.7 ± 18.7 | 6.3 ± 18.4 | 0.8 ± 18.2 | 3.7 [0.5; 6.8]; $p = 0.022$ |
| Diabetes management | 72.0 ± 18.5 | 67.2 ± 20.2 | 10.9 ± 21.3 | 4.1 ± 19.8 | 5.7 [2.2; 9.2]; $p = 0.002$ |

| | | | | | |
|---|---|---|---|---|---|
| Compliance | 87.2 ± 14.0 | 84.4 ± 16.9 | 8.9 ± 17.3 | 4.3 ± 15.9 | 3.5 [0.8; 6.2]; $p = 0.010$ |
| Psychological health | 85.9 ± 14.8 | 80.5 ± 18.4 | 7.3 ± 14.7 | 1.4 ± 16.5 | 5.4 [2.7; 8.1]; $p < 0.001$ |
| **DTSQs** | | | | | |
| Treatment satisfaction total score | 32.5 ± 4.2 | 30.7 ± 5.9 | 3.1 ± 5.6 | 1.1 ± 5.0 | 2.0 [1.1, 2.8]; $p < 0.001$ |
| Hyperglycemia | 1.5 ± 1.6 | 2.5 ± 2.0 | –1.8 ± 2.1 | –0.6 ± 1.9 | –1.0 [–1.4, –0.7]; $p < 0.001$ |
| Hypoglycemia | 1.1 ± 1.5 | 0.7 ± 1.4 | 0.2 ± 1.7 | –0.1 ± 1.5 | 0.4 [0.1, 0.6]; $p = 0.006$ |

Data are observed patient-reported outcome scores at 26 weeks, changes from baseline (LOCF), and estimated treatment contrast. Data are mean ± standard deviation unless otherwise indicated. TRIM-D: higher score indicates a better health state. DTSQs: higher scores indicate higher satisfaction; DTSQ hyperglycemia and hypoglycemia: higher scores indicate higher perceived frequency.

ANCOVA, analysis of covariance; CI, confidence interval; DTSQs, diabetes treatment satisfaction questionnaire status; EOT, end-of-trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide combination; LOCF, last observation carried forward; TRIM-D, treatment-related impact measure–diabetes.