**Supplemental Material**

**Inclusion and exclusion criteria**

**Inclusion criteria**
1. Informed consent obtained before any trial-related activities. (Trial-related activities were defined as any procedure that would not have been performed during standard management of the subject.)
2. Males or females ≥18 years of age.
3. Type 1 diabetes mellitus (diagnosed clinically and treated on basal–bolus regimen) for ≥12 months, the last 3 months with injection-based therapies.
4. Current treatment with any basal insulin (e.g., insulin glargine [IGlar], insulin detemir, NPH insulin) using one or two daily injections and no fewer than three injections with bolus insulin (e.g., insulin aspart [IASp], insulin lispro, insulin glulisine, human insulin) as mealtime bolus insulin therapy.
5. HbA₁c ≤10.0% by central laboratory analysis.
6. BMI ≤35.0 kg/m².
7. Ability to self-manage insulin therapy as assessed by confirmation (verbal confirmation at screening visit) of a changed bolus insulin dose the preceding 2 months prior to screening.
8. Ability and willingness to adhere to the protocol, including performance of self-measured plasma glucose (SMPG) readings and self-adjustment of insulin doses according to protocol.

**Exclusion criteria**
1. Use within the last 3 months prior to Visit 1 of any antidiabetes glucose-lowering drug other than insulin.
2. Initiation or significant change of any systemic treatment which, in the investigator’s opinion, could interfere with glucose metabolism, such as systemic corticosteroids, beta-blockers or monoamine oxidase inhibitors (inhaled corticosteroids were allowed).
3. Cardiovascular disease, within the last 6 months prior to Visit 1, defined as: stroke; decompensated heart failure New York Heart Association class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty.
4. Uncontrolled treated/untreated severe hypertension (systolic blood pressure [BP] ≥180 mmHg and/or diastolic BP ≥100 mm Hg).
5. Impaired liver function, defined as alanine aminotransferase ≥2.5 times upper limit of normal (one retest analyzed at the central lab within a week of receipt of the result was permitted with the result of the last sample being conclusive).
6. Impaired renal function defined as serum-creatinine ≥180 μmol/L or ≥2.0 mg/dL.
7. Recurrent severe hypoglycemia (more than 1 severe hypoglycemic event during the last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for diabetic ketoacidosis during the previous 6 months.
8. Proliferative retinopathy or maculopathy requiring treatment, according to the investigator.
9. Pregnancy, breast-feeding, the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements. (In Germany, this referred to implants, injectables, combined oral contraceptives, hormonal intrauterine device, and sexual abstinence or vasectomized partner. In the UK, Belgium and Norway, this referred to established use of oral, injected or implanted hormonal methods of contraception, sterilization, intrauterine device or intrauterine system, or consistent use of barrier methods. In the USA, this referred to sexual abstinence, sterilization of either partner, including bilateral tubal ligation, oral, injected or implanted hormonal methods, intrauterine device or intrauterine system or consistent use of barrier methods.)
10. Cancer and medical history of cancer (except basal cell skin cancer or squamous cell skin cancer).
11. Any clinically significant disease or disorder, except for conditions associated with type 1 diabetes, which in the investigator’s opinion could interfere with the results of the trial.
12. Mental incapacity, psychiatric disorder, unwillingness or language barriers precluding adequate understanding or cooperation, including subjects not able to read or write.
13. Previous participation in this trial. Participation was defined as randomized. Re-screening of screening failures was to be allowed only once within the limits of the recruitment period.
14. Known or suspected allergy to any of the trial products or related products.
15. Receipt of any investigational drug within 1 month prior to Visit 1.
16. Donation of blood or participation in other trials within 1 month prior to Visit 1.
17. Known or suspected abuse of alcohol, narcotics, or illicit drugs.

Withdrawal criteria
A subject could choose to withdraw from the trial at any time. Subjects were to be withdrawn from the trial at the discretion of the investigator due to a safety concern or if judged noncompliant with trial procedures. Any subject randomized in error (not fulfilling inclusion and/or exclusion criteria) was to be withdrawn from the trial.

A subject was to be withdrawn if any of the following criteria applied:
1. Pregnancy or intention of becoming pregnant.
2. Hypoglycemia during the treatment period posing a safety problem as judged by the investigator.
3. Protocol deviation having influence on efficacy or safety data as judged by the investigator.
4. Initiation or significant change of any systemic treatment which in the investigator’s opinion could have interfered with glucose metabolism (inhaled corticosteroids were allowed).
5. Donation of blood or participation in other trials throughout the trial.
6. Lack of effect: After Week 12, if the subject had not had reduction in HbA1c and had a pre-breakfast SMPG reading >13.3 mmol/L (>240 mg/dL) on 3 consecutive days despite appropriate dose adjustments. The subject was to contact the investigator and come in for an unscheduled visit as soon as possible (within 2 weeks). The next scheduled visit was not to be awaited. An FPG was to be obtained and analyzed by the central laboratory. If this FPG exceeded 13.3 mmol/L (>240 mg/dL) and no treatable intercurrent cause for the hyperglycemia had been diagnosed, the subject was to be withdrawn.
7. During the main treatment period (i.e., Visit 2–Visit 28): Failure to comply with required SMPG assessments as assessed by more than two complete missing 4-point profiles (SMPG) per week for 2 consecutive weeks despite the reinforcement of such need by the investigator or trial coordinator.

Masking:
Treatment group assignment was masked for individuals involved as titration surveillance monitors, internal safety committee members, external committee members responsible for cardiovascular event adjudication, and personnel involved in defining analysis sets until data was locked for statistical analysis. An independent ad hoc group was to be established to maintain masking if the internal safety committee members requested unmasking; however, this did not occur in this trial.

Insulin initiation, dosing and titration schedules

Basal insulin
Initiation: At randomization (Visit 2), the switch from prior basal insulin to insulin degludec (IDeg) Forced-Flex, IDeg or insulin glargine (IGlar) was to be done as described below.
Initiation of basal insulin in the IDeg or IGlar arms

| Prior treatment               | Starting dose of IDeg or IGlar |
|-------------------------------|--------------------------------|
| NPH or other basal insulin    | If prior basal insulin was a once-daily regimen, prescribe the same number of units once daily (1:1 transfer) |
|                               | If prior basal insulin was taken more than once daily, calculate total daily basal dose and dose once daily. If the subject is randomized to: |
|                               | - IGlar, it is recommended to reduce the dose by 20–30% according to approved labeling |
|                               | - IDeg, a dose reduction should be considered according to the investigator’s discretion |
|                               | - IDeg Forced-Flex, a dose reduction should be considered according to the investigator’s discretion and dosed as outlined in the dosing schedule below. |

Dosing schedule:
Injection schedule and dose intervals for the IDeg Forced-Flex regimen

| Day         | Injection time | Interval between IDeg injections |
|-------------|----------------|----------------------------------|
| Monday      | Morning*       | Minimum 8 hours                  |
| Tuesday     | Evening†       | Maximum 40 hours                 |
| Wednesday   | Morning*       | Minimum 8 hours                  |
| Thursday    | Evening†       | Maximum 40 hours                 |
| Friday      | Morning*       | Minimum 8 hours                  |
| Saturday    | Evening†       | Maximum 40 hours                 |
| Sunday      | Evening†       | Approximately 24 hours           |

*Morning defined as the time period from waking up to first meal of the day; †evening defined as the time period from start of main evening meal to bedtime.

Subjects randomized to the IDeg arm were to inject IDeg once daily in the evening with the main evening meal. Subjects randomized to the IGlar arm were to inject IGlar according to the approved labeling.

Titration:
Subjects measured pre-breakfast plasma glucose every day throughout the trial. Self-adjustment of basal insulin dose was to be performed three-times weekly (Monday, Wednesday, Friday) based on daily pre-breakfast SMPG.

Adjustment of basal insulin doses during the week as follows:

- Monday and Tuesday doses were determined based on the mean pre-breakfast SMPG value obtained Saturday, Sunday, and Monday.
- Wednesday and Thursday doses were determined based on the mean pre-breakfast SMPG value obtained Tuesday and Wednesday.
- Friday, Saturday, and Sunday doses were all determined based on the mean pre-breakfast SMPG value obtained Thursday and Friday.

The dose adjustment was to be performed using the titration algorithm below.
**Titration algorithm for adjustment of IDeg or IGlar doses**

| Previous days’ mean pre-breakfast SMPG (mmol/L) | Adjustment (U) |
|-----------------------------------------------|----------------|
| <4.0                                          | -2             |
| 4.0–5.0                                       | 0              |
| >5.0                                          | +2             |

**Bolus insulin**

**Initiation:**
At randomization (Visit 2), the switch from prior fast-acting insulin to insulin aspart (IAsp) was to be done as described below.

**Initiation of bolus insulin IAsp**

| Prior treatment                                      | Starting dose of IAsp |
|------------------------------------------------------|-----------------------|
| Human regular insulin or rapid-acting analogs at mealtime | Continue same doses of IAsp |

**Dosing:**
In all three basal–bolus regimens, IAsp was used as standard bolus therapy and was to be injected subcutaneously in connection with each main meal (three-times daily or more).

**Titration:**
Regardless of eating habits, subjects were to also self-measure plasma glucose values pre-lunch (approximately at noon), pre-dinner (main evening meal), and at bedtime. These SMPGs were to be used for the titration of IAsp, which was to be adjusted on a daily basis according to the recommendations outlined below, as appropriate.

Adjustment of daily mealtime doses of IAsp as follows:
- Pre-breakfast IAsp dose was to be titrated according to the preceding day’s pre-lunch SMPG.
- Pre-lunch IAsp dose was to be titrated according to the preceding day’s pre-dinner SMPG.
- Pre-dinner IAsp dose was to be titrated according to the preceding day’s bedtime SMPG.

The subjects were allowed to eat extra meals every day and take additional IAsp. Additional pre-meal SMPG values were not to be monitored by the sponsor and were not to be entered into the electronic Case Report Form (eCRF). However, the total extra IAsp dose(s) was to be registered in the subject diary and entered into the eCRF.
Titration algorithm of bolus insulin IA\(\text{Asp}\)

| Pre-prandial SMPG | Dose change (U) |
|-------------------|-----------------|
| (\text{mmol/L})   | (mg/dL)         |
| <5.0              | <90             | 0               |
| 5.0–8.0           | 90–144          | +2              |
| 8.0–10.0          | 144–180         | +3              |
| \geq 10.0         | \geq 180        | +4              |

During the extension period it was recommended that self-titration of IA\(\text{Asp}\) continue on a daily basis under the guidance of the investigator as described above.

*Deviations from the algorithm*

It was recommended that the algorithm be followed. However, it was also important that the decision to adjust the basal and bolus insulin dose was based on all available information, such as symptoms of hypo-/hyperglycemia, previous responses to dose adjustments, and SMPG measurements other than those required as per protocol or dietary carbohydrate content (“carb-counting”). Deviations from the basal insulin algorithm were to be reported by the investigator in the subjects’ notes and entered into the eCRF.

*Initiation of NPH insulin during the follow-up period*

Since NPH insulin is an intermediate-acting insulin, it was to be administered twice a day. To determine the dose of NPH insulin to be taken during the follow-up period, the total daily basal dose at the end of the treatment period was to be reduced by 20% and divided by two, to be administered morning and evening. The first dose of NPH insulin was to be given, at the earliest, 24 hours after the last dose of IDeg or IGlar.

*Insulin initiation and titration – extension period*

- All subjects who completed the main trial period were invited to participate in the extension trial period after the 1-week follow-up period. No screening was performed for the extension trial period. There were only two treatment arms in the extension period (IDeg Free-Flex and IGlar, both administered with mealtime IA\(\text{Asp}\) as bolus insulin therapy).
- IDeg Free-Flex arm: IDeg was administered once daily at any time of the day, with a minimum time interval of 8 hours and a maximum time interval of 40 hours between injections. The subjects who had been randomized to the IDeg Forced-Flex or IDeg arms during the main trial period were allocated to this arm during the extension period.
- IGlar arm: IGlar was administered once daily according to local labeling. The subjects who had been randomized to the IGlar arm during the main trial period continued in this arm during the extension period.
IDeg Free-Flex subjects were allowed to administer IDeg at any time of the day, ensuring a minimum and maximum interval of up to 8–40 hours between injections.

The main/extension trial periods were conducted at 71/68 sites in 6 countries: Belgium (5/5 sites), Germany (7/7 sites), Norway (5/5 sites), Poland (5/5 sites), United Kingdom (UK) (12/11 sites), and United States of America (US) (37/35 sites).

*1-week wash-out period (Weeks 26–27); hence, 53 weeks = 52 weeks of exposure.

IAsp, insulin aspart; IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IDeg Free-Flex, insulin degludec once daily (free-flexible treatment arm); IGlar, insulin glargine once daily (same time daily).
Supplemental Figure 2: Participant flow

- 549 participants assessed for eligibility
- 56 participants excluded
- 493 enrolled and randomised 1:1:1

**IDeg Forced-Flex**
- 164 allocated to IDeg Forced-Flex and received treatment (100%)
- 26 withdrawn\(^{8}\) (15.9%)
  - 5 adverse events\(^{8}\) (3.0%)
  - 6 non-compliance (3.7%)
  - 2 ineffective therapy (1.2%)
  - 6 withdrawal criteria\(^{7}\) (3.7%)
  - 7 other\(^{8}\) (4.3%)
- 138 completed main (84.1%)

**IDeg**
- 165 allocated to IDeg and received treatment (100%)
- 26 withdrawn\(^{8}\) (15.8%)
  - 4 adverse events\(^{8}\) (2.4%)
  - 2 non-compliance (1.2%)
  - 1 ineffective therapy (0.6%)
  - 6 withdrawal criteria\(^{7}\) (3.6%)
  - 13 other\(^{8}\) (7.9%)
- 139 completed main (84.2%)

**IGlar**
- 164 allocated to IGlar
- 12 withdrawn\(^{8}\) (7.3%)
  - 1 adverse events\(^{8}\) (0.6%)
  - 4 non-compliance (2.4%)
  - 1 ineffective therapy (0.6%)
  - 2 withdrawal criteria\(^{7}\) (1.2%)
  - 4 other\(^{8}\) (2.4%)
- 152 completed main (92.7%)

**IDeg Free-Flex**
- 239 entered extension and received treatment (72.6%)
  - 16 withdrawn\(^{8}\) (4.9%)
    - 0 adverse events\(^{8}\) (0.0%)
    - 5 non-compliance (1.5%)
    - 2 ineffective therapy (0.6%)
    - 2 withdrawal criteria\(^{7}\) (0.6%)
    - 7 other\(^{8}\) (2.1%)
  - 223 completed extension (67.8%)

**EXTENSION**
- 133 entered extension and received treatment (81.1%)
  - 11 withdrawn\(^{8}\) (6.7%)
    - 1 adverse events\(^{8}\) (0.6%)
    - 2 non-compliance (1.2%)
    - 0 ineffective therapy (0.0%)
    - 4 withdrawal criteria\(^{7}\) (2.4%)
    - 4 other\(^{8}\) (2.4%)
- 122 completed main (74.4%)

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*†‡See Supplemental Table 1 for detailed explanations for subject withdrawal. §Withdrawn at/after randomization and before extension. ¶Withdrawn during extension.

The trial was conducted March 3, 2010–November 12, 2010 (main) and September 14, 2010–May 23, 2011 (extension). The trial was completed as planned after 52 weeks of subject exposure to trial product. IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IDeg Free-Flex, insulin degludec once daily (free-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); OD, once daily.
### Supplemental Table 1: Reasons for withdrawal from trial

#### *Adverse events*

|                | Main                  | Extension |
|----------------|-----------------------|-----------|
| **IDeg Forced-Flex** | 5 subjects: rash/reduced visual acuity, night sweats (1), pyelonephritis/injection-site hematoma (1), adrenal insufficiency (1), hypoglycemic unconsciousness (1), transient ischemic attack (1) | None |
| **IDeg**            | 4 subjects: pain in extremity (1), hypoglycemia (2), completed suicide/hypoglycemic coma (1) | 1 subject: pruritis |
| **IGlar**           | 1 subject: pruritis | 1 subject: hypoglycemia |

#### Withdrawal criteria

|                | Main                  | Extension |
|----------------|-----------------------|-----------|
| **IDeg Forced-Flex** | 6 subjects: hypoglycemia (3), hypoglycemia and protocol deviation (1), initiation or significant change in treatment that could interfere with glucose metabolism (1), lack of effect (1) | 2 subjects: protocol deviation (1), hypoglycemia (1) |
| **IDeg**            | 6 subjects: failure to comply with required SMPG assessments (1), lack of effect (1), pregnancy (1), hypoglycemia (3) | 4 subjects: hypoglycemia and protocol deviation (1), pregnancy (2), hypoglycemia (1) |
| **IGlar**           | 2 subjects: hypoglycemia (1), pregnancy (1) | |

#### “Other”

|                | Main                  | Extension |
|----------------|-----------------------|-----------|
| **IDeg Forced-Flex** | 7 subjects: hypoglycemia (2), subject displeased with blood glucose meter device (1), busy schedule (1), withdrew consent/considered study too complicated (1), randomized in error (2) | 7 subjects: randomized in error (1), busy schedule (3), withdrew consent (2), lost to follow-up (1) |
| **IDeg**            | 13 subjects: subject not able to cope with variations in blood sugar and hypoglycemic episodes (1), subject exhausted by titration requirements (1), randomized in error (3), subject not content with study or products (1), subject did not like either insulin and wanted to revert to old regimen (1), busy schedule (2), lost to follow-up (2), withdrew consent (2) | 4 subjects: subject considered the study too demanding (1), withdrew consent (1), lost to follow-up (1), subject wished to resume pump therapy (1) |
| **IGlar**           | 4 subjects: randomized in error (2), subject displeased with once-daily regimen (1), withdrew consent (1) | 4 subjects: subject considered the study too demanding (1), withdrew consent (1), lost to follow-up (1) |

*†‡See Supplemental Figure 2.*

IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IDeg Free-Flex, insulin degludec once daily (free-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); SMPG, self-measured plasma glucose.
Supplemental Table 2: Descriptive statistics and statistical comparison of efficacy and weight parameters: change from baseline

| Endpoint       | Treatment               | Baseline mean (SD) | Change from baseline mean (SD) | ETD [95% CI]         |
|----------------|-------------------------|--------------------|-------------------------------|----------------------|
| **Main period (26 weeks)** |                         |                    |                               |                      |
| HbA1c (%) - FAS | IDeg Forced-Flex        | 7.7 (1.0)          | –0.40 (0.59)                 | IDegForcedFlex-IDeg: 0.01 [–0.13; 0.14] |
|                | IDeg                    | 7.7 (0.9)          | –0.41 (0.71)                 | IDegForcedFlex-IDeg: 0.17 [0.04; 0.30] |
|                | IGlar                   | 7.7 (0.9)          | –0.58 (0.72)                 |                      |
| HbA1c (%) - PP set* |                         |                    |                               |                      |
|                | IDeg Forced-Flex        |                    |                               |                      |
|                | IDeg                    |                    |                               |                      |
|                | IGlar                   |                    |                               |                      |
| HbA1c (%)†     | IDeg Forced-Flex        |                    |                               |                      |
|                | IDeg                    |                    |                               |                      |
|                | IGlar                   |                    |                               |                      |
| HbA1c (%)‡     | IDeg Forced-Flex        |                    |                               |                      |
|                | IDeg                    |                    |                               |                      |
|                | IGlar                   |                    |                               |                      |
| FPG (mmol/L) - FAS | IDeg Forced-Flex        | 9.6 (4.1)          | –1.28 (5.03)                 | IDegForcedFlex-IDeg: 0.95 [0.15; 1.75] |
|                | IDeg                    | 10.0 (4.0)         | –2.54 (5.11)                 | IDegForcedFlex-IDeg: 0.05 [–0.85; 0.76] |
|                | IGlar                   | 9.7 (4.2)          | –1.33 (5.21)                 |                      |
| Weight (kg) - FAS | IDeg Forced-Flex        | 81.7 (15.5)        | 1.2 (3.5)                    | IDegForcedFlex-IDeg: –0.04 [–1.14; 0.27] |
|                | IDeg                    | 79.5 (15.5)        | 0.8 (2.5)                    |                      |
|                | IGlar                   | 80.9 (15.3)        | 1.6 (3.7)                    |                      |
| **Main + Extension period (52 weeks)** |                         |                    |                               |                      |
| HbA1c (%) - FAS | IDeg Free-Flex          | 7.7 (1.0)          | –0.13 (0.67)                 | IDegFreeFlex-IDeg: 0.07 [–0.05; 0.19] |
|                | IGlar                   | 7.7 (0.9)          | –0.21 (0.73)                 |                      |
| HbA1c (%) - ETS | IDeg Free-Flex          | 7.6 (1.0)          | –0.08 (0.66)                 | IDegFreeFlex-IDeg: 0.08 [–0.06; 0.22] |
|                | IGlar                   | 7.7 (0.9)          | –0.18 (0.74)                 |                      |
| FPG (mmol/L) - FAS | IDeg Free-Flex          | 9.8 (4.0)          | –1.37 (5.32)                 | IDegFreeFlex-IDeg: –1.07 [–1.82; –0.32] |
|                | IGlar                   | 9.7 (4.2)          | –0.61 (5.23)                 |                      |
| Weight (kg) - FAS | IDeg Free-Flex          | 80.6 (15.5)        | 1.3 (3.6)                    | IDegFreeFlex-IDeg: –0.51 [–1.24; 0.22] |
|                | IGlar                   | 80.9 (15.3)        | 1.9 (4.5)                    |                      |

Missing data are imputed using last observation carried forward.
*PP analysis set included participants who complied with all recruitment criteria (i.e., inclusion and exclusion criteria), had at least 12 weeks of exposure, and had valid HbA1c assessment at baseline and at or after 12 weeks of treatment. Remaining analyses are based on the full analysis set.
†Statistical sensitivity analyses using Simple Model: Response and change from baseline in the response after 26 weeks of treatment are analyzed using an ANOVA method with treatment as fixed effect, and baseline response as covariate.
‡Statistical sensitivity analyses using Repeated Measures Model: HbA1c (%) at scheduled time points after randomization are jointly analyzed in a linear mixed model with an unstructured residual covariance matrix, and with treatment, time, interaction between treatment and time, region, anti-diabetic treatment at screening and sex as fixed effects and age and baseline HbA1c (%) as covariates.
The subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment. The data for IDeg Forced-Flex and IDeg arms from the first 26 weeks are pooled into the IDeg Free-Flex arm in the main + extension portion of this table.
ETD, estimated treatment difference; ETS, extension trial set; FAS, full analysis set; FPG, fasting plasma glucose; IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once...
daily (forced-flexible treatment arm); IDeg Free-Flex, insulin degludec once daily (free-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); PP, per protocol; SD, standard deviation.
Supplemental Table 3: Hypoglycemic episodes.

### Main period (Weeks 0–26) – SAS

|                      | IDEg Forced-Flex (N = 164) | IDEg (N = 165) | IGLar (N = 161) | ERR [95% CI] (FAS) |
|----------------------|-----------------------------|----------------|-----------------|-------------------|
| Subjects             | n %                         | Subjects       | Rate            | Subjects          | Rate            | ERR [95% CI] (FAS) |
| Severe               | 17 10.4 0.3                 | 21 12.7 0.4    | 16 9.9 0.5      | IDEgforcedFlex/IGlar: 0.89 [0.40; 1.99] (NS) |
|                      |                             |                |                 | IDEgforcedFlex/IDeg: 1.09 [0.48; 2.48] (NS) |
| Overall confirmed    | 154 93.9 82.4               | 164 99.4 88.3  | 156 96.9 79.7   | IDEgforcedFlex/IGlar: 1.03 [0.85; 1.26] (NS) |
|                      |                             |                |                 | IDEgforcedFlex/IDeg: 0.92 [0.76; 1.12] (NS) |
| Nocturnal confirmed  | 111 67.7 6.2                | 121 73.3 9.6   | 117 72.7 10.0   | IDEgforcedFlex/IGlar: 0.60 [0.44; 0.82] |
|                      |                             |                |                 | IDEgforcedFlex/IDeg: 0.63 [0.46; 0.86] |
| Nocturnal severe     | 5 3.0 0.07                  | 5 3.0 0.07     | 5 3.1 0.17      | No statistical analysis performed due to small number of events |

### Main and extension period (Weeks 0–52) – SAS

|                      | IDEg Free-Flex (N = 329) | IGLar (N = 161) | ERR [95% CI] (FAS) |
|----------------------|--------------------------|-----------------|-------------------|
| Subjects             | n %                      | Subjects        | Rate             | ERR [95% CI] (FAS) |
| Severe               | 44 13.4 0.2              | 21 13.0 0.4     | IDEgFreeFlex/IGlar: 0.74 [0.38; 1.42] (NS) |
| Overall confirmed    | 319 97.0 68.1            | 157 97.5 63.4   | IDEgFreeFlex/IGlar: 1.09 [0.91; 1.29] (NS) |
| Nocturnal confirmed  | 256 77.8 6.4             | 126 78.3 8.5    | IDEgFreeFlex/IGlar: 0.75 [0.58; 0.97] |
| Nocturnal severe     | 14 4.3 0.05              | 6 3.7 0.14      | No statistical analysis performed due to small number of events |

### Main and extension period (Weeks 0–52) – ETS

|                      | IDEg Free-Flex (N = 239) | IGLar (N = 133) | ERR [95% CI] (ETS) |
|----------------------|--------------------------|-----------------|-------------------|
| Subjects             | n %                      | Subjects        | Rate             | ERR [95% CI] (ETS) |
| Severe               | 32 13.4 0.2              | 20 15.0 0.4     | IDEgFreeFlex/IGlar: 0.47 [0.23; 0.94] [
| Overall confirmed    | 236 98.7 65.5            | 130 97.7 61.4   | IDEgFreeFlex/IGlar: 1.02 [0.84; 1.24] (NS) |
| Nocturnal confirmed  | 200 83.7 6.3             | 108 81.2 8.4    | IDEgFreeFlex/IGlar: 0.73 [0.54; 0.98] |
| Nocturnal severe     | 11 4.6 0.05              | 6 4.5 0.15      | No statistical analysis performed due to small number of events |

‘Subjects’ and ‘Rate’ are based on SAS and ETS, as indicated. ‘ERR’ is based on FAS or ETS, as indicated. ERR, estimated rate ratio; ETS, extension trial set; FAS, full analysis set; IDEg, insulin degludec once daily at evening meal; IDEg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IDEg Free-Flex, insulin degludec once daily (free-flexible treatment arm); IGLar, insulin glargine once daily (same time daily); N, number of participants exposed to treatment; n, number of participants with events; NS, not significant; R, number of events per patient-year; SAS, safety analysis.
set; %, proportion of participants with events. The subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment. The data for IDeg Forced-Flex and IDeg arms from the first 26 weeks are pooled into the IDeg Free-Flex arm in the main + extension portion of this table.
Supplemental Table 4: Nocturnal confirmed hypoglycemic episodes by weekday – treatment emergent – main period – safety analysis set

|               | IDeg Forced-Flex (N = 164) |       |       |       |
|---------------|-----------------------------|-------|-------|-------|
|               | n  | %       | E    | R    |
| Total         | 111| 67.7    | 453  | 6.23 |
| Monday        | 48 | 29.3    | 64   | 6.16 |
| Tuesday       | 57 | 34.8    | 96   | 9.24 |
| Wednesday     | 38 | 23.3    | 51   | 4.92 |
| Thursday      | 52 | 31.7    | 91   | 8.76 |
| Friday        | 33 | 20.1    | 55   | 5.29 |
| Saturday      | 42 | 25.6    | 55   | 5.29 |
| Sunday        | 31 | 18.9    | 41   | 3.95 |

|               | IDeg (N = 165) |       |       |       |
|---------------|----------------|-------|-------|-------|
|               | n  | %       | E    | R    |
| Total         | 121| 73.3    | 732  | 9.61 |
| Monday        | 52 | 31.5    | 100  | 9.19 |
| Tuesday       | 58 | 35.2    | 123  | 11.30|
| Wednesday     | 58 | 35.2    | 129  | 11.86|
| Thursday      | 48 | 29.1    | 101  | 9.27 |
| Friday        | 60 | 36.4    | 120  | 11.03|
| Saturday      | 55 | 33.3    | 88   | 8.09 |
| Sunday        | 44 | 26.7    | 71   | 6.53 |

|               | IGlar (N = 161) |       |       |       |
|---------------|-----------------|-------|-------|-------|
|               | n  | %       | E    | R    |
| Total         | 117| 72.7    | 782  | 9.96 |
| Monday        | 53 | 32.9    | 123  | 10.96|
| Tuesday       | 64 | 39.8    | 124  | 11.04|
| Wednesday     | 61 | 37.9    | 141  | 12.56|
| Thursday      | 66 | 41.0    | 124  | 11.04|
| Friday        | 50 | 31.1    | 102  | 9.10 |
| Saturday      | 47 | 29.2    | 86   | 7.67 |
| Sunday        | 47 | 29.2    | 82   | 7.31 |

Confirmed hypoglycemia = subject unable to treat himself/herself and/or has a recorded plasma glucose <3.1 mmol/L (56 mg/dL).

E, number of events; IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); N, number of participants exposed to treatment; n, number of participants with events, R, event rate per exposure year of the weekday; %, proportion of participants with events.
Supplemental Table 5: Summary of AEs – safety analysis set

|                      | IDeg Forced-Flex (N = 164) | IDeg (N = 165) | IGlar (N = 161) |
|----------------------|----------------------------|----------------|---------------|
|                      | n  | %  | R  | n  | %  | R  | n  | %  | R  |
| AEs                  | 111| 67.7| 443| 125| 75.8| 550| 116| 72.0| 527|
| SAEs                 | 9  | 5.5 | 17 | 7  | 4.2 | 12 | 8  | 5.0 | 10 |
| Severity             |    |     |    |    |     |    |    |     |    |
| Severe               | 19 | 11.6| 36 | 24 | 14.5| 47 | 20 | 12.4| 47 |
| Moderate             | 46 | 28.0| 139| 45 | 27.3| 114| 51 | 31.7| 118|
| Mild                 | 88 | 53.7| 268| 104| 63.0| 388| 102| 63.4| 362|
| AEs possibly/probably related to basal insulin | 34 | 20.7 | 72 | 32 | 19.4 | 60 | 25 | 15.5 | 57 |
| AEs possibly/probably related to bolus insulin | 37 | 22.6 | 74 | 25 | 15.2 | 47 | 23 | 14.3 | 51 |
| Injection-site reactions | 8  | 4.9 | 15 | 3  | 1.8 | 4  | 4  | 2.5 | 5  |

|                      | IDeg Free-Flex (N = 329) | IGlar (N = 161) |
|----------------------|--------------------------|----------------|
|                      | n  | %  | R  | n  | %  | R  |
| AEs                  | 268| 81.5| 447| 134| 83.2| 481|
| SAEs                 | 25 | 7.6 | 13 | 12 | 7.5 | 10 |
| Severity             |    |     |    |    |     |    |    |     |    |
| Severe               | 53 | 16.1| 32 | 26 | 16.1| 42 |
| Moderate             | 131| 39.8| 121| 66 | 41.0| 113|
| Mild                 | 232| 70.5| 294| 117| 72.7| 326|
| AEs possibly/probably related to basal insulin | 70 | 21.3 | 42 | 28 | 17.4 | 43 |
| AEs possibly/probably related to bolus insulin | 68 | 20.7 | 38 | 26 | 16.1 | 40 |
| Injection-site reactions | 12 | 3.6 | 6  | 4  | 2.5 | 4  |

AE, adverse event; IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); N, number of participants exposed to treatment; n, number of participants with events; R, number of events per 100 patient-years of exposure; SAE, serious adverse event; %, proportion of participants with events.

The subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment. The data for IDeg Forced-Flex and IDeg arms from the first 26 weeks are pooled into the IDeg Free-Flex arm in this table.
Supplemental Table 6: AEs occurring with a frequency ≥5% – main and extension periods – safety analysis set

|                              | IDeg Free-Flex (N = 329) | IGlar (N = 161) |
|------------------------------|--------------------------|-----------------|
|                              | n | % | E | R | n | % | E | R |
| Events                       |   |   |   |   |   |   |   |   |
| Infections and infestations  |   |   |   |   |   |   |   |   |
| Gastroenteritis              | 19 | 5.8 | 22 | 8 | 6 | 3.7 | 6 | 4 |
| Gastroenteritis viral        | 9  | 2.7 | 11 | 4 | 10 | 6.2 | 14 | 10 |
| Nasopharyngitis              | 99 | 30.1 | 174 | 65 | 48 | 29.8 | 85 | 59 |
| Sinusitis                    | 23 | 7.0 | 28 | 10 | 13 | 8.1 | 18 | 13 |
| Upper respiratory tract infection | 28 | 8.5 | 39 | 15 | 21 | 13.0 | 30 | 21 |
| Nervous system disorders     |   |   |   |   |   |   |   |   |
| Headache                     | 33 | 10.0 | 61 | 23 | 24 | 14.9 | 48 | 33 |
| Gastrointestinal disorders   |   |   |   |   |   |   |   |   |
| Diarrhoea                    | 9  | 2.7 | 15 | 6 | 12 | 7.5 | 15 | 10 |
| Nausea                       | 18 | 5.5 | 21 | 8 | 8  | 5.0 | 13 | 9  |
| Vomiting                     | 18 | 5.5 | 22 | 8 | 11 | 6.8 | 12 | 8  |
| Metabolism and nutrition disorders |   |   |   |   |   |   |   |   |
| Hypoglycemia                 | 32 | 9.7 | 50 | 19 | 15 | 9.3 | 46 | 32 |
| Respiratory, thoracic and mediastinal disorders |   |   |   |   |   |   |   |   |
| Cough                        | 17 | 5.2 | 20 | 7 | 11 | 6.8 | 13 | 9  |
| Oropharyngeal pain           | 28 | 8.5 | 36 | 13 | 14 | 8.7 | 15 | 10 |
| Injury, poisoning and procedural complications |   |   |   |   |   |   |   |   |
| Wrong drug administered      | 19 | 5.8 | 20 | 7 | 7  | 4.3 | 8  | 6  |

Treatment-emergent AEs (AEs occurring on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment with insulin degludec or insulin glargine) by system organ class and preferred term reported by ≥5% in any one group.

Interpretation of n and E must take the 2:1 randomization (IDeg Free-Flex:IGlar) into consideration.

The subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment. The data for IDeg Forced-Flex and IDeg arms from the first 26 weeks are pooled into the IDeg Free-Flex arm in this table. AE, adverse event; E, number of events; IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IDeg Free-Flex, insulin degludec once daily (free-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); N, number of participants exposed to treatment; n, number of participants with events; R, number of events per 100 patient-years of exposure; %, proportion of participants with events.
Supplemental Table 7: SAEs possibly/probably related to trial product – safety analysis set

|                      | IDeg Forced-Flex (N = 164) | IDeg (N = 165) | IGlar (N = 161) |
|----------------------|-----------------------------|----------------|-----------------|
|                      | n  | %  | E  | R  | n  | %  | E  | R  | n  | %  | E  | R  |
| **Events**           |    |    |    |    |    |    |    |    |    |    |    |    |
| Hypoglycemia         |  6 | 3.7|  8 | 11 |  4 | 2.4|  5 |  7 |  5 | 3.1|  5 |  6 |
| Hypoglycemic unconsciousness |  3 | 1.8|  3 |  4 |    |    |    |    |    |    |    |    |
| Hypoglycemic seizure |    |    |    |    |    |    |    |    |    |    |    |    |
| Hypoglycemic coma    |    |    |    |    |    |    |    |    |    |    |    |    |
| Retinal hemorrhage   |  1 | 0.6|  1 |  1 |    |    |    |    |    |    |    |    |
| Completed suicide    |    |    |    |    |    |    |    |    |    |    |    |    |

|                      | IDeg Free-Flex (N = 329) | IGlar (N = 161) |
|----------------------|--------------------------|-----------------|
|                      | n  | %  | n  | %  | n  | %  |
| **Events**           | 13 | 4.0| 18 | 7  | 5  | 3.1|
| Hypoglycemia         |  7 | 2.1| 11 | 4  | 2  | 1.2|
| Hypoglycemic unconsciousness |  3 | 0.9|  3 |  1 | 2  | 1.2|
| Hypoglycemic seizure |    |    |    |    |    |    |
| Hypoglycemic coma    |  2 | 0.6|  2 |  1 |    |    |
| Retinal hemorrhage   |  1 | 0.3|  1 |  0 |    |    |
| Completed suicide    |  1 | 0.3|  1 |  0 |    |    |

E, number of events; IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); N, number of participants exposed to treatment; n, number of participants with events; R, number of events per 100 patient-years of exposure; SAE, serious adverse event; %, proportion of participants with events.

Treatment-emergent SAEs possibly/probably related to the trial product by system organ class and preferred term. Interpretation of n and E must take the 2:1 randomization (IDeg Free-Flex:IGlar) into consideration. The subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment. The data for IDeg Forced-Flex and IDeg arms from the first 26 weeks are pooled into the IDeg Free-Flex arm in this table.
Supplemental Table 8: Antibodies – main and extension periods – safety analysis set

|                  | n     | IDeg-specific antibodies (% B/T) Median [min; max] | Cross-reacting antibodies* (% B/T) Median [min; max] |
|------------------|-------|---------------------------------------------------|---------------------------------------------------|
| **Baseline**     |       |                                                   |                                                   |
| IDeg Free-Flex   | 327   | 0.0 [–13.0; 3.0]                                   | 6.0 [–1.0; 65.0]                                   |
| **Week 27**      |       |                                                   |                                                   |
| IDeg Free-Flex   | 286   | 0.0 [–12.0; 4.0]                                   | 11.0 [0.0; 75.0]                                  |
| **Week 54**      |       |                                                   |                                                   |
| IDeg Free-Flex   | 229   | 0.0 [–6.0; 6.0]                                    | 7.0 [0.0; 72.0]                                   |

|                  | n     | IGlar-specific antibodies (% B/T) Median [min-max] | Cross-reacting antibodiesa (% B/T) Median [min-max] |
|------------------|-------|---------------------------------------------------|---------------------------------------------------|
| **Baseline**     |       |                                                   |                                                   |
| IGlar            | 160   | –1.0 [–3.0; 6.0]                                   | 6.0 [0.0; 61.0]                                   |
| **Week 27**      |       |                                                   |                                                   |
| IGlar            | 154   | –1.0 [–3.0; 7.0]                                   | 9.0 [0.0; 76.0]                                   |
| **Week 54**      |       |                                                   |                                                   |
| IGlar            | 126   | Not measured                                      | 5.0 [0.0; 65.0]                                   |

Data are for all exposed patients with antibodies measured. The antibodies are measured by a subtraction radioimmunoassay method at follow-up visits conducted after 1-week NPH washout periods begun at Weeks 26 and 53. The reported result represents the % B/T values after subtraction of background. Due to the assay variation, the resulting difference can be negative. Samples that do not contain insulin antibodies will therefore give values that vary around zero.

*Antibodies cross-reacting between insulin degludec and human insulin.

The subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment. The data for IDeg Forced-Flex and IDeg arms from the first 26 weeks are pooled into the IDeg Free-Flex arm in this table. IDeg, insulin degludec once daily at evening meal; IDeg Forced-Flex, insulin degludec once daily (forced-flexible treatment arm); IDeg Free-Flex, insulin degludec once daily (free-flexible treatment arm); IGlar, insulin glargine once daily (same time daily); % B/T, % bound over total radioactivity.
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