## Supplementary material

### Supplementary Table 1. Dose titration schedule

|  |  |  |
| --- | --- | --- |
| Median\* fasting (pre-breakfast) SMPG | Current basal insulin dose | Dose adjustment of Gla-300 or Gla-100 |
| Above target range |  |  |
| * >180 mg/dL (>10.0 mmol/L)
 | <15 U/day | +2 U |
|  | ≥15 U/day | +4 U |
| No evidence of severe hypoglycemia† |  |  |
| Above target range |  |  |
| * >130–180 mg/dL
 | <15 U/day | +1 U |
| (>7.2–10.0 mmol/L) | ≥15 U/day | +2 U |
| No evidence of severe hypoglycemia† |  |  |
| In target range |  |  |
| * 90–130 mg/dL (5.0–7.2 mmol/L)
 | n/a | No change of BI dose |
| No evidence of severe hypoglycemia† |  |  |
| Below target range |  |  |
| * <90 mg/dL (<5.0 mmol/L)
 | <15 U/day | −1 U |
|  | ≥15 U/day | −2 U |
| In case of hypoglycemia |  | Doses may be reduced at any time |
| * Hypoglycemia is reported
 | <15 U/day | −1 U |
| Without explanation, e.g. unexpected exercise | ≥15 U/day | −2 U |
| * Severe hypoglycemia
 |  | In addition to dose reduction, upward titration may be stopped for 1 week |
| Neurological symptoms, assistance required |  |

\*Median = the middle value of fasting (pre-breakfast) SMPG out of the three values from last 3 days including the current day. †Severe hypoglycemia defined as a child/adolescent with altered mental status and inability to self-care, is semiconscious or unconscious, or in coma with or without convulsions, who may require parenteral therapy (glucagon or glucose).

SMPG, self-monitored plasma glucose

### Supplementary Table 2. Tanner puberty stage classification

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Classification of sexual maturity in girls** |  |  |
| **Stage** | **Pubic hair** | **Stage** | **Breasts** |
| P1 | Preadolescent | B1 | Preadolescent |
| P2 | Sparse, lightly pigmented, straight, medial border of labia | B2 | Breast and papilla elevated as small mound; areolar diameter increased |
| P3 | Darker, beginning to curl, increased amount | B3 | Breast and areola enlarged, no contour separation |
| P4 | Coarse, curly, abundant but amount less than adult | B4 | Areola and papilla from secondary mound  |
| P5 | Adult feminine triangle, spread to medial surface of thighs | B5 | Mature; nipple projects, areola part of general breast contour |
|  | **Classification of sexual maturity in boys** |  |  |
| **Stage** | **Pubic hair** | **Stage** | **Testes** |
| P1 | None | T1 | Preadolescent |
| P2 | Scanty, long, slightly pigmented | T2 | Enlarged scrotum, pink texture altered |
| P3 | Darker, starts to curl, small amount | T3 | Larger |
| P4 | Resembles adult type, but less in quantity; coarse, curly | T4 | Larger, scrotum dark |
| P5 | Adult distribution, spread to medial surface of thighs | T5 | Adult size |
|  | **Evaluation by stage** |  | **Classification** |
|  | P1, B1, T1 |  | Pre-pubertal |
|  | P2–P4, B2–B4, T2–T4 |  | Adolescent |
|  | P5, B5, T5 |  | Adult |

Categorization was straightforward if B or T was equal to P. In case of discordance, the lower score prevailed (e.g. P=1 and B/T = 2 or vice versa was classified as prepubertal; P=5 and B/T = 4 or vice versa was classified as adolescent).

B, breasts; P, pubic hair; T, testes

### Supplementary Table 3. Efficacy outcomes in the 12-month randomized period (6-month randomized period and 6-month extension period) (ITT population)

|  |  |  |
| --- | --- | --- |
| Efficacy outcomes at Week 52  | Gla-300 | Gla-100 |
|  | (N=233) | (N=230) |
| HbA1c, % |  |  |
| Mean (SD) | 8.61 (1.53) | 8.63 (1.31) |
| LS mean change (SE) | −0.051 (0.085) | 0.022 (0.083) |
| LS mean difference (95% CI) | −0.073 (−0.306 to 0.160) |

The 12-month randomized period is defined as the time from the randomization date to the study end, regardless of treatment discontinuation.

CI, confidence interval; SD, standard deviation; SE, standard error

### Supplementary Table 4. Safety outcomes in the 12-month study period (6-month treatment period and 6-month safety extension period) (safety population)

|  |  |  |
| --- | --- | --- |
| **Safety outcomes in the**  | **Incidence: n (%)** | **Event rates: E (R),** |
| **12-month TEAE period\*** | **Relative risk (95% CI)** | **Rate ratio (95% CI)** |
|  | **Gla-300** | **Gla-100**  | **Gla-300** | **Gla-100**  |
|  | **(N=233)** | **(N=228)** | **(N=233)** | **(N=228)** |
| **Hypoglycemia** |  |  |  |  |
| Anytime (24 h) documented (≤70 mg/dL [≤3.9 mmol/L]) or severe | 231 (99.1) | 224 (98.2) | 18289 (81.70) | 17268 (79.63) |
|  | 1.01 (0.99–1.03) | 1.02 (0.86–1.20) |
| Nocturnal documented (≤70 mg/dL [≤3.9 mmol/L]) or severe (00:00–05:59 h) | 193 (82.8) | 176 (77.2) | 1767 (7.89) | 1481 (6.83) |
|  | 1.07 (0.98–1.17) | 1.13 (0.90–1.42) |
| Anytime (24 h) severe | 20 (8.6) | 25 (11.0) | 36 (0.16) | 38 (0.18) |
|  | 0.78 (0.45–1.36) | 0.93 (0.47–1.87) |
| **Hyperglycemia with ketosis** |  |  |  |  |
| **Preferred Term** |  |  |  |  |
| Participants with ≥1 TEAE of hyperglycemia with ketosis | 22 (9.4) | 36 (15.8) | 58 (0.26) | 64 (0.30) |
| **Hyperglycemia with ketosis**  |  |  |  |  |
| **Biochemical** |  |  |  |  |
| Any hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L) | 23 (9.9) | 31 (13.6) | 379 (1.69)† | 178 (0.82)‡ |
| **Sensitivity analysis§** |  |  |  |  |
| Any hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L) |  |  | 79 (0.35) | 91 (0.42) |
| **Adverse Events**: |  |  |  |  |
| Participants with |  |  |  |  |
| Any TEAE | 167 (71.7) | 168 (73.7) | 673 (3.01) | 606 (2.79) |
| Any treatment emergent SAE | 35 (15.0) | 31 (13.6) | 52 (0.23) | 44 (0.20) |
| Any TEAE leading to death | 1 (0.4) | 0 | 2 (0.01) | 0 |
| Any TEAE leading to permanent treatment discontinuation | 3 (1.3) | 3 (1.3) | 5 (0.02) | 3 (0.01) |

\*The 12-month TEAE period was defined as the period from first basal insulin treatment up to two days after the last treatment dose. †One participant in the Gla-300 group presented with 300 events of hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L) ‡One participant in the Gla-100 group presented with 87 events of hyperglycemia with ketosis (SMPG ≥252 mg/dL [≥14 mmol/L] and ketone ≥1.5 mmol/L). **§**Ad-hoc sensitivity analysis for number of biochemical events (excluding 2 participants with >30 events of hyperglycemia with ketosis).

CI, confidence interval; E(R), number of events (event rate per participant-year); ITT, intent-to-treat; SAE, serious adverse event; SMPG, self-monitored plasma glucose; TEAE, treatment-emergent adverse event

### Supplementary Table 5. Incidence and event rates of hyperglycemia with ketosis during the main 6-month treatment period (safety population)

|  |  |  |
| --- | --- | --- |
|  | Gla-300 | Gla-100 |
|  | (N=233) | (N=228) |
| Preferred Term\* | Number of participants  | Number of events  | Number of participants  | Number of events  |
|  | (%) | (events per participant-year) | (%) | (events per participant-year) |
| Hyperglycemia with ketosis | 15 (6.4) | 34 (0.30) | 27 (11.8) | 46 (0.41) |
| Ketosis | 15 (6.4) | 33 (0.29) | 23 (10.1) | 41 (0.37) |
| Diabetic ketoacidosis† | 1 (0.4) | 1 (0.01) | 4 (1.8) | 5 (0.04) |

\*A single descriptor for a defined medical condition or area of interest, defined by MedDRA. †Incidence and event rates of diabetic ketoacidosis were reported as SAEs

MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment emergent adverse event

### Supplementary Figure 1. Participant flow diagram during the main 6-month treatment period and 6-month safety extension period



### Supplementary Figure 2. Time course of mean daily total, basal, and mealtime insulin dose over the entire 12-month study (safety population)



### Supplementary Figure 3. (A) Relative risk of participants experiencing anytime and nocturnal hypoglycemia and (B) rate ratios of anytime and nocturnal hypoglycemia, for Gla-300 versus Gla-100, during the main 6-month treatment period (safety population)

A)

A)



B)

B)



CI, confidence interval

### Supplementary Figure 4. Cumulative mean number of hypoglycaemia events per participant at any time of day (24 h) during the entire 12-month treatment period: (A) severe or documented (≤70 mg/dL [≤3.9 mmol/L]) events; (B) severe events (safety population)

