**Dosing Guidance**

The general approach for dosing of BIF and degludec uses a similar fasting glucose target for both treatments and pre~~-~~specifies the FBG tier and corresponding dose increment for each treatment, as well as hypoglycemia criteria for considering dose reduction taking into account differences in their differing pharmacokinetic and pharmacodynamic characteristics.

**BIF (Paper Algorithm) Dosing**

The treat-to-target fasting glucose in the algorithm was 80-100 mg/dL (4.4 to <5.6 mmol/L). BIF dose adjustments were determined based on the median of the fasting glucose from SMBG of at least 3 days (up to 7 days) obtained in the previous week leading up to the visit. The BIF dose was not increased if any SMBG reading was documented at ≤70 mg/dL (<3.9 mmol/L) at any time in the preceding week. Dose decreases of 0.5 mg adjustment were permitted if multiple episodes of hypoglycemia with SMBG ≤70 mg/dL (<3.9 mmol/L) were recorded, or dose decrease of 1 mg if severe hypoglycemia (requiring assistance) occurred, or if any SMBG was documented at ≤54 mg/dL (≤3.0 mmol/L) in the preceding week.

The initial (Week 0, Visit 3) BIF dose was based on the baseline median fasting glucose

and body weight at Visit 3. The initial dose was increased 3-fold in order to achieve steady-state concentration within the first week. Directions provided below were used to determine the initial dose and for dose adjustments at subsequent visits

*Week 0, Visit 3 (Randomization Visit):*

Determine the initial dose by obtaining the participant’s body weight and median FBG in

the week prior to Visit 3 and consulting the table below.

**Determination of Initial Dosea of BIF at Visit 3 using Median of Baseline Fasting Glucose and Body Weight obtained at Visit 3**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Median Baseline Fasting Glucose** | **Median Baseline Fasting Glucose** | **BIF Dose for BW** | **BIF Dose for BW** | **BIF Dose for BW** | **BIF Dose for BW** |
| **(mg/dL)** | **(mmol/L)** | **≤80 kg** | **80.1–100 kg** | **100.1–120 kg** | **≥120.1 kg** |
| ≤140 | ≤7.7 | 3 mg | 4.5 mg | 6 mg | 7.5 mg |
| 141 – 180 | 7.8 – 10.0 | 6 mg | 7.5 mg | 10.5 mg | 12 mg |
| 181 – 220 | 10.1 – 12.2 | 9 mg | 10.5 mg | 12 mg | 13.5 mg |
| >220 | >12.2 | 12 mg | 13.5 mg | 15 mg | 16.5 mg |

a The initial dose reflects the 3-fold increase needed to reduce the time to target glycemic response and should ONLY be administered once at Visit 3.

b Conversions from mg/dL to mmol/L were rounded off to prevent overlap between threshold ranges and to address that the glucose meter displays 1 significant digit after the decimal when reporting mmol/L readings.

*Week 1, Visit 4:*

Calculate the total weekly dose BIF mg from the dose administered at Visit 3 (this is 1/3rd the dose administered at Visit 3)

Use the table below to determine the dose adjustment needed for Visit 5.

**Weekly Dose Adjustment of BIF using the Previous Week’s dose (D), Median Fasting Glucose and Hypoglycemic Episodes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Median Fasting Glucose (mg/dL)a** | **Median Fasting Glucose (mmol/L)a,e** | **Week 1 (Visit 4)** | **Week 2 (Visit 5)** | **Subsequent** | **Weekc** |
|  |  | **2nd dose** | **3rd dose** | **Dose ≤5 mg** | **Dose >5 mg** |
| <80 mg/dL or have any nocturnal hypoglycemia or multiple episodes of hypoglycemiad | <4.4 mmol/L or have any nocturnal hypoglycemia or multiple episodes of hypoglycemiad | Db – 1.5 mg | Db – 1.5 mg | Dc– 1.5 mg | Dc– 2 mg |
| 80 – 100 | 4.4 – 5.5 | Db – 1 mg | Db – 0.5 mg | No change | No change |
| 101 – 140 | 5.6 – 7.7 | No change | No change | Dc+ 0.25 mg | Dc+ 0.5 mg |
| 141 – 180 | 7.8 – 10.0 | Db + 3 mg | Db + 1.5 mg | Dc+ 0.5 mg | Dc+ 1 m |
| >180 | >10.0 | Db + 5 mg | Db + 3 mg | Dc+ 0.75 mg | Dc+ 1.5 mg |

a Based on median fasting glucose from at least 3 fasting glucose from previous week.

b D for Week 1 (Visit 4) was 1/3 of the initial dose. D for Week 2 (Visit 5) was Week 1 (Visit 4) dose.

c BIF dose adjustment starting at Week 3 (Visit 6) depended on whether previous (Week 2) dose (D) was ≤5 mg or >5 mg and was adjusted weekly up to Week 12 (Visit 15), then at Week 16 (Visit 17), Week 20 (Visit 18), and Week 24 (Visit 19).

d The BIF dose was not increased if any SMBG reading was documented at ≤70 mg/dL (<3.9 mmol/L) at any time in the preceding week. If multiple episodes of hypoglycemia with SMBG ≤70 mg/dL (<3.9 mmol/L) were recorded, guidance for dose reduction according to the applicable Visit number followed. Dose decreases of 1 mg were made when severe hypoglycemia (requiring assistance) occurred, or if any SMBG was documented at ≤54 mg/dL (≤3.0 mmol/L) in the preceding week.

e Conversions from mg/dL to mmol/L were rounded off to prevent overlap between threshold ranges and to address that the glucose meter displays 1 significant digit after the decimal when reporting mmol/L readings.

*Week 2, Visit 5:*

Confirm the dose of BIF mg administered at Visit 4.

Use the above table to determine the dose adjustment needed for Visit 5.

*Week 3, Visit 6:*

Confirm the dose of BIF administered at Visit 5 (Week 2).

Use the above table to determine the dose adjustment needed for Visit 6. Looking at the subsequent week column, apply the prior weekly dose information to the appropriate column (≤ 5 mg or >5 mg) to obtain the dose increment.

Subsequent visits were managed using the same approach as for Visit 6 (Week 3), always

confirming the BIF dose administered at the prior visit, the median fasting glucose

during the week prior to the visits, and hypoglycemia status since the last dose of study drug.

**Insulin Degludec Dosing**

The starting dose for insulin degludec for this study was 10 units.

The treat-to-target FBG is 80-100 mg/dL (4.4 to <5.6 mmol/L). Dosed adjustments based on FBG occurred approximately weekly consistent with specified protocol visits according to the table below.

The insulin degludec dose should not have been increased if any SMBG was documented at ≤70 mg/dL (<3.9 mmol/L) at any time in the preceding week.

The insulin degludec dose increase was determined using the median of the FBG of the last 3 days. If the patient only measured their FBG on 2 of the last 3 days, then the lesser of those 2 FBG values was to be used for dose assessment. If only 1 FBG measurement is available for the last 3 days, then the investigator was to use his/her discretion in determining whether there should be a dose adjustment based on that single FBG value.

Dose decreases of 2 to 4 U per adjustment were permitted if multiple episodes of hypoglycemia with SMBG ≤70 mg/dL (<3.9 mmol/L) were recorded, if severe hypoglycemia (requiring assistance) occurred, or if any SMBG was documented at ≤54 mg/dL (≤3.0 mmol/L) in the preceding week.

|  |  |  |
| --- | --- | --- |
| **If the median** | **FBG is...** | **Then...** |
| **mg/dL** | **mmol/L** |  |
| 80-100 | 4.4 to <5.6 | No change |
| 101-120 | 5.6 to 6.7 | increase the dose by 2 U. |
| 121-140 | 6.8 to 7.8 | increase the dose by 4 U. |
| 141-180 | 7.9 to 10.0 | increase the dose by 6 U. |
| >180 | > 10 | increase the dose by 8 U. |

Conversions from mg/dL to mmol/L were rounded off to prevent overlap between threshold ranges and to address that the glucose meter displays 1 significant digit after the decimal when reporting mmol/L readings.