**Dosing Guidance**

**BIF (Paper Algorithm)**

The initial dose of BIF was calculated based on the previously used basal insulin dose and the baseline fasting glucose with a target of 80-100 mg/dL for the first dose of BIF. A dose conversion of 7 IU of daily basal insulin (=49 IU weekly) per mg of BIF weekly was used to transform the previously used daily basal insulin dose into a BIF mg dose. This dose was then adjusted based on fasting glucose and then multiplied by 3 to obtain the one-time loading dose for BIF. The conversion factor was chosen based on data from previous Phase 1 studies and an interim analysis of another Phase 2 study in patients with T2D previously treated with basal insulin (Frias J, et al. Lancet Diabetes Endocrinol 2023.) as well as PK-PD modelling using virtual patients.

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 self-monitored fasting glucose from the CGM device (SMG) 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 SMG 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 was permitted if multiple episodes of hypoglycemia with SMG ≤70 mg/dL (<3.9 mmol/L) were recorded, or dose decrease of 1 mg if severe hypoglycemia (requiring assistance) occurred, or if any SMG was documented at ≤54 mg/dL (≤3.0 mmol/L) in the preceding week.

The starting BIF dose was determined based on both the prior basal insulin dose and

baseline fasting glucose. Participants entered the study using insulin glargine, detemir, or degludec. Consistent with product labeling these insulins were transitioned on a unit-for-unit basis and for the purposes of this protocol were considered equivalent. Directions are provided below to convert current basal insulin dose (in Units, U) to the dose of BIF (in mg) for determination of the starting weekly dose and for dose adjustments at subsequent Visits.

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

Obtain the prior daily basal insulin dose of insulin glargine, detemir, or degludec assessed

during the lead-in period. Calculate the “basal insulin equivalent dose” of BIF (in mg) by dividing the total daily dose of basal insulin (U) by the conversion factor of 7 U/mg.

The dose of BIF mg is then further adjusted according to median baseline fasting

glucose and the participant’s current basal insulin dose (U) category as shown in the table below.

The loading dose is obtained by multiplying the starting total BIF weekly dose (sum of basal insulin equivalent dose and the dose adjustment from table below) by 3.

**BIF Dose Adjustment (mg) Using the Median of Baseline Fasting Glucose and Prior Basal Insulin Dose (International Units, U)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Median Baseline Fasting Glucose (mg/dL)** | **Median Baseline Fasting Glucoseb (mmol/L)** | **BIF Dose Adjustment (mg)a** | | |
| **Basal Insulin Dose ≤15 U** | **Basal Insulin Dose 16 – 30 U** | **Basal Insulin Dose >30 U** |
| <80 | ≤4.4 | -0.25 | -1 | -1.5 |
| 80 – 100 | 4.4 – 5.5 | No change | No change | No change |
| 101 – 140 | 5.6 – 7.7 | +0.25 | +0.5 | +0.75 |
| 141 – 180 | 7.8 – 10.0 | +0.5 | +1 | +1.5 |
| 181 – 220 | 10.1 – 12.2 | +0.75 | +1.5 | +2 |
| >220 | >12.2 | +1 | +2 | +3 |

a This dose adjustment is added to the Basal Insulin Equivalent Dose to obtain the total weekly dose of BIF in mg. The starting total weekly dose of BIF is increased 3-fold (multiplied by 3) to obtain the first loading dose of BIF necessary to reduce the time to achieve target glycemic response.

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:*

Obtain the starting total weekly dose BIF mg determined 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 4.

**Weekly Dose Adjustment of LY3209590 Using the Previous Week’s Dose (D) using the Median Fasting Glucose and Hypoglycemic Episodes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Median Fasting Glucose (mg/dL)a** | **Median Fasting Glucose (mmol/L)a,e** | **Week 1 (Visit 4) (2nd dose)** | **Week 2 (Visit 5) (3rd dose)** | **Subsequent Weekc** |
| <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 mg | Dc– 0.5 mg |
| 80 – 100 | 4.4 – 5.5 | Db – 1 mg | Db – 0.5 mg | No change |
| 101 – 140 | 5.6 – 7.7 | No change | No change | Dc+ 0.25 mg |
| 141 – 180 | 7.8 – 10.0 | Db + 1 mg | Db + 0.5 mg | Dc+ 0.25 mg |
| >180 | >10.0 | Db + 2 mg | Db + 1 mg | Dc+ 0.5 mg |

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

b D for Week 1 (Visit 4) is 1/3 of the dose administered at (Week 0, Visit 3). D for Week 2 (Visit 5) is the dose administered at Week 1 (Visit 4).

c D for Subsequent Visits is the dose administered one week prior to the current visit.

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

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**

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

The insulin degludec dose should not have been increased if any SMG 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 fasting glucose of the last 3 days. If the patient only measured their fasting glucose on 2 of the last 3 days, then the lesser of those 2 fasting glucose values was to be used for dose assessment. If only 1 fasting glucose 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 fasting glucose value.

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

|  |  |  |
| --- | --- | --- |
| **If the median fasting glucose 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. |

**References**

Frias J, Chien J, Zhang Q, Chigutsa E, Landschulz W, Syring K, Wullenweber P, Haupt A, Kazda C. A Multi-centre, Open-label, Randomised Phase 2 Study to Investigate the Safety and Efficacy of Once Weekly Basal Insulin Fc (BIF) in Patients with Type 2 Diabetes Mellitus (T2DM) Previously Treated with Basal Insulin [In Press]. Lancet Diabetes Endocrinol 2023.