

Similar hypoglycemia duration with once-weekly insulin icodec versus degludec or glargine U100 in insulin-treated T2D: a *post hoc* CGM analysis from ONWARDS 2 and 4

Harpreet S. Bajaj,¹ Björg Ásbjörnsdóttir,² Lisbeth Carstensen,² Shannon O'Hara,³ Lars Lang Lehrskov,² Chantal Mathieu,⁴ Athena Philis-Tsimikas,⁵ Tadej Battelino⁶

Aim

- To quantify and to compare the continuous glucose monitoring (CGM)-derived duration of hypoglycemic episodes in adults with type 2 diabetes (T2D) switching from a daily basal insulin regimen to either once-weekly (OW) insulin icodec (icodec) or once-daily (OD) comparator (insulin degludec [degludec] or insulin glargine U100 [glargine U100]), using a *post hoc* analysis of CGM data from two phase 3a clinical trials (ONWARDS 2 and ONWARDS 4).^{1,2}

Introduction

- Hypoglycemia may occur in individuals receiving insulin treatment and can have numerous pathophysiological consequences depending on the severity and duration of the episode.³⁻⁶
- CGM-derived hypoglycemic episodes can be classified into levels indicating different amounts of urgency for action.
 - Level 1 hypoglycemia is considered an alert threshold, whereas level 2 hypoglycemia is considered clinically significant and requires immediate attention.⁷
- Icodec is a basal insulin analog currently in clinical development that is suitable for OW administration owing to its long half-life (~1 week).⁸
 - Given this long duration of action, the safety profile of icodec, particularly with respect to duration of hypoglycemia, needs to be further characterized.

Methods

Study design and treatment

- CGM data were analyzed from two 26-week, randomized, open-label, treat-to-target phase 3a trials in adults (age: ≥ 18 years) with T2D.
 - In ONWARDS 2, participants with inadequately controlled T2D (n = 526; mean ± standard deviation diabetes duration: 16.7 ± 8.1 years) treated with a basal-only insulin regimen were randomized (1:1) to OW icodec or OD degludec (ClinicalTrials.gov: NCT04770532).
 - In ONWARDS 4, participants with inadequately controlled T2D (n = 582; mean ± standard deviation diabetes duration: 17.1 ± 8.4 years) treated with a basal-bolus regimen were randomized (1:1) to OW icodec or OD glargine U100, both in combination with 2-4 daily injections of insulin aspart (ClinicalTrials.gov: NCT04880850).
- Double-blinded CGM (Dexcom G6) data were obtained during the switch period after randomization (weeks 0-4), end of treatment period (weeks 22-26) and follow-up period after the end of treatment (weeks 27-31) of both trials.
- Owing to the 3-4-week time period required to reach steady state,⁸ the trial protocols for both ONWARDS 2 and ONWARDS 4 recommended that individuals randomized

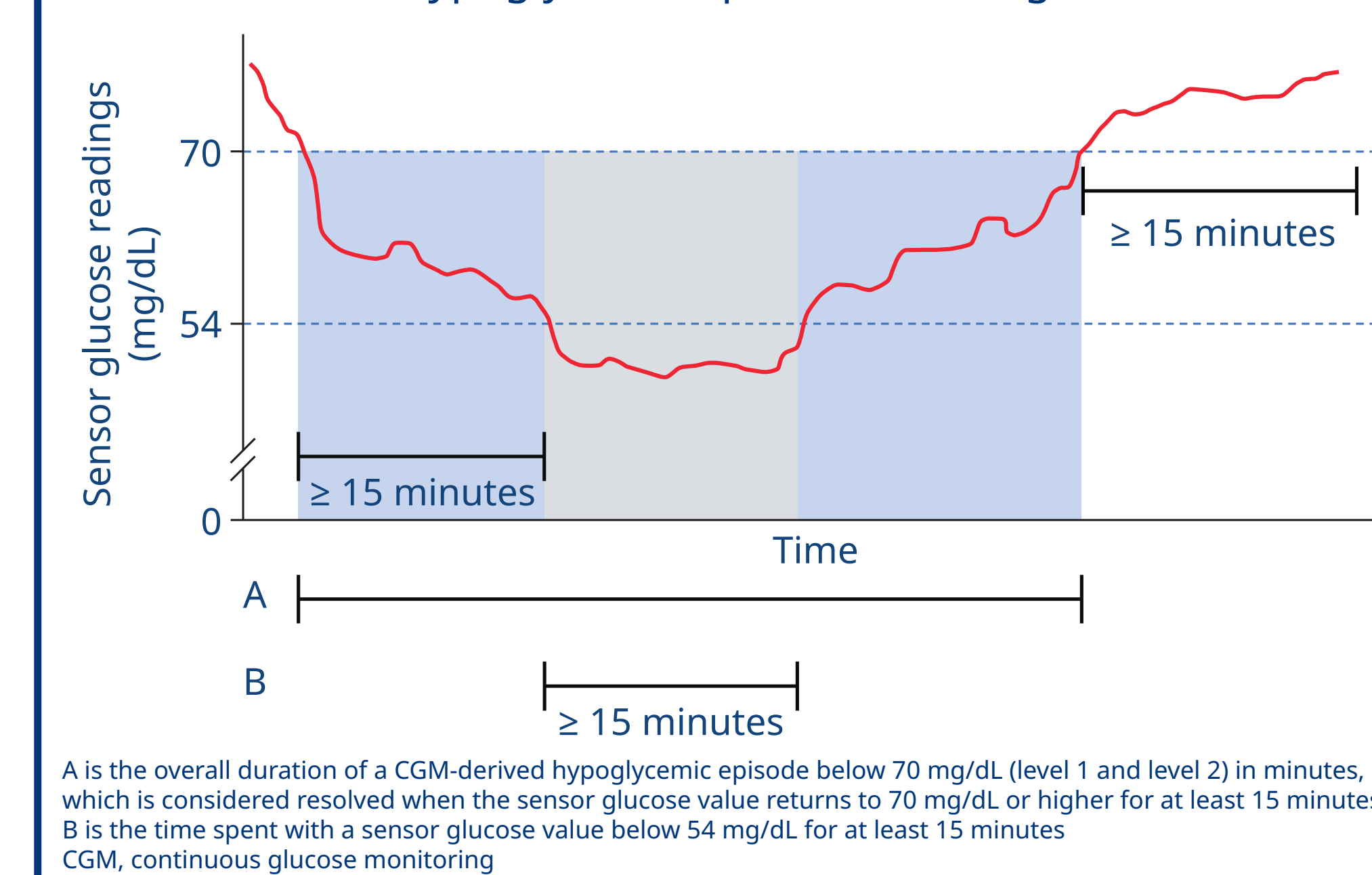
to icodec received a one-time additional 50% icodec dose at first injection only, in addition to the calculated weekly icodec dose (pre-trial daily basal insulin dose multiplied by seven). OD comparators were administered in accordance with local label guidelines.

- Both icodec and OD comparators were titrated weekly based on pre-breakfast self-measured blood glucose values (target: 80-130 mg/dL).
- At the end of the treatment period, the trial protocols for both ONWARDS 2 and ONWARDS 4 recommended that participants were transferred to any available basal insulin at the discretion of the investigator. For the icodec arm, it was recommended to initiate the new basal insulin 2 weeks after the last dose of icodec, but sooner if pre-breakfast self-measured blood glucose exceeded 180 mg/dL.

Post hoc analyses

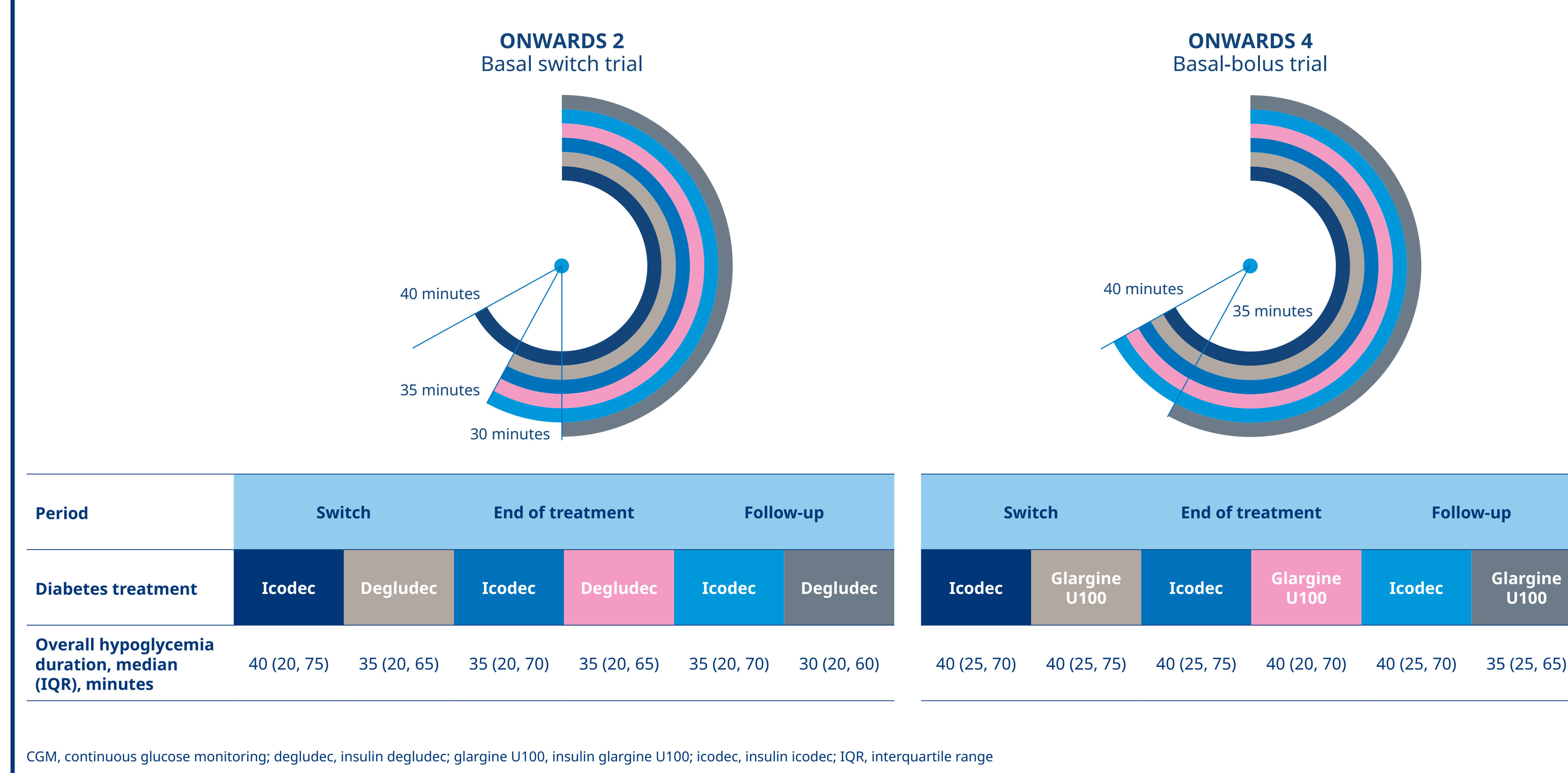
- CGM data were analyzed to assess the duration of hypoglycemic episodes with OW icodec compared with OD comparators.
- CGM-derived hypoglycemic episodes were defined according to the international consensus statement.⁷
 - CGM-derived level 1 hypoglycemic episodes are defined as a sensor glucose value below 70 mg/dL for at least 15 minutes (without any periods > 15 minutes spent below 54 mg/dL) and are considered resolved when the sensor glucose value returns to 70 mg/dL or higher for at least 15 minutes.
 - CGM-derived level 2 hypoglycemic episodes are defined as episodes including sensor glucose values below 54 mg/dL for at least 15 consecutive minutes (Figure 1).
- Median duration of CGM-derived overall hypoglycemic episodes below 70 mg/dL (level 1 and level 2) and the percentage of such episodes with time spent below 54 mg/dL (level 2) were assessed (Figure 1).

Figure 1: Schematic defining a CGM-derived overall level 1 and level 2 hypoglycemic episode (< 70 mg/dL)



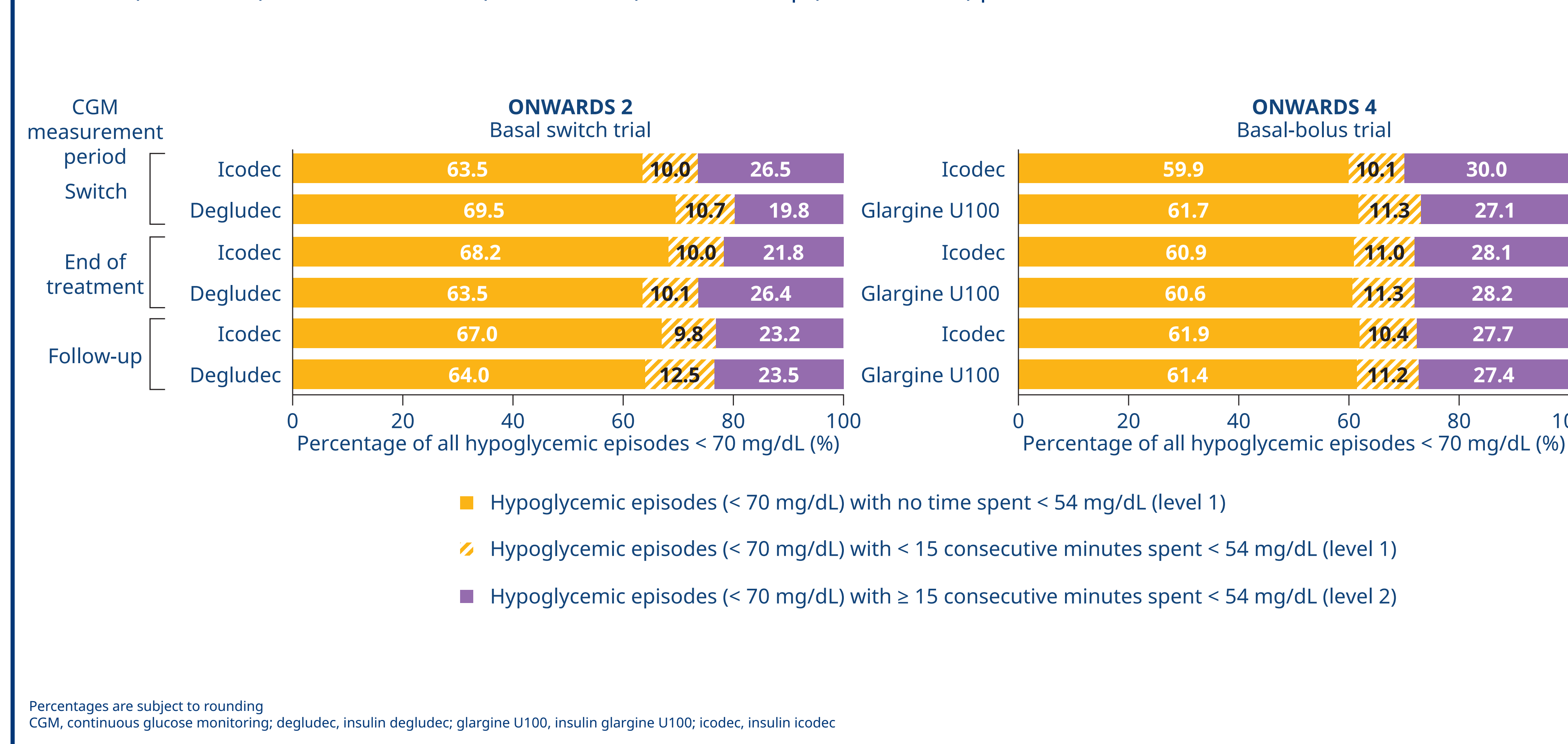
A is the overall duration of a CGM-derived hypoglycemic episode below 70 mg/dL (level 1 and level 2) in minutes, which is considered resolved when the sensor glucose value returns to 70 mg/dL or higher for at least 15 minutes. B is the time spent with a sensor glucose value below 54 mg/dL for at least 15 consecutive minutes. CGM, continuous glucose monitoring

Figure 2: Duration of CGM-derived overall level 1 and level 2 hypoglycemic episodes (< 70 mg/dL) during the switch (weeks 0-4), end of treatment (weeks 22-26) and follow-up (weeks 27-31) periods



CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec; IQR, interquartile range

Figure 3: Classification of CGM-derived overall hypoglycemic episodes (< 70 mg/dL) by time spent below 54 mg/dL in the switch (weeks 0-4), end of treatment (weeks 22-26) and follow-up (weeks 27-31) periods



Percentages are subject to rounding. CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec

Results

Duration of CGM-derived overall hypoglycemic episodes (< 70 mg/dL)

- In both trials, the median duration of CGM-derived overall level 1 and level 2 hypoglycemic episodes (< 70 mg/dL) was comparable for icodec and the OD comparators during the switch, end of treatment and follow-up periods, within the range of 30-40 minutes (Figure 2).

Classification of CGM-derived overall hypoglycemic episodes (< 70 mg/dL) by time spent below 54 mg/dL

- During the switch, end of treatment and follow-up periods, the majority of CGM-derived hypoglycemic episodes below 70 mg/dL either did not include any time spent below 54 mg/dL or had a duration of time spent below 54 mg/dL of less than 15 minutes (level 1 hypoglycemia) (Figure 3).
- There were no substantial differences between icodec and OD comparators in the percentage of hypoglycemic episodes with time spent below 54 mg/dL for at least 15 minutes (level 2 hypoglycemia), irrespective of time period of CGM measurement (Figure 3).

Conclusion

- In insulin-experienced participants with long-standing T2D:
 - the CGM-derived duration of overall hypoglycemic episodes below 70 mg/dL was comparable between OW icodec compared with OD comparators during all three CGM time periods, with all medians being 40 minutes or less
 - for individuals receiving icodec, the majority of all hypoglycemic episodes below 70 mg/dL did not develop into level 2 hypoglycemia (< 54 mg/dL for ≥ 15 minutes), with a comparable percentage of such episodes to OD comparators, during any of the CGM time periods
 - these findings suggest that, despite its long half-life, OW icodec treatment does not lead to prolonged duration of CGM-derived level 1 or level 2 hypoglycemia compared with OD comparators.

¹LMC Diabetes & Endocrinology, Brampton, ON, Canada; ²Novo Nordisk A/S, Søborg, Denmark; ³Novo Nordisk Inc, Plainsboro, NJ; ⁴Clinical and Experimental Endocrinology, University of Leuven, Leuven, Belgium; ⁵Scripps Whittier Diabetes Institute, San Diego, CA, USA; ⁶UMC-University Children's Hospital, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
Presenting author contact details: Shannon O'Hara PharmD, BCPS, 800 Scudders Mill Rd, Plainsboro, NJ 08536, US. Tel: (+1) 425-229-3588. Email: SOQH@novonordisk.com
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