Supplementary Materials to: Continuous Glucose Monitoring-Based Metrics and Hypoglycemia Duration in Insulin-Experienced Individuals With Long-Standing Type 2 Diabetes Switched From a Daily Basal Insulin to Once-Weekly Insulin Icodec: Post Hoc Analysis of ONWARDS 2 and ONWARDS 4

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Supplementary Table 1—Approximate mean time spent per day within each CGM outcome

		Time spent per day within range			
		TIR (3.9–10.0 mmol/L)	TAR (>10.0 mmol/L)	TBR (<3.9 mmol/L)	TBR (<3.0 mmol/L)
Switch					
ONWARDS 2	Icodec	12 h 17 min	11 h 32 min	11 min	3 min
	Degludec	12 h 49 min	11 h 1 min	10 min	2 min
ONWARDS 4	Icodec	13 h 35 min	9 h 58 min	27 min	8 min
	Glargine U100	13 h 28 min	10 h 7 min	24 min	6 min
End of treatment					
ONWARDS 2	Icodec	15 h 9 min*	8 h 32 min	19 min	5 min
	Degludec	14 h 17 min*	9 h 32 min	11 min	3 min
ONWARDS 4	Icodec	16 h 3 min†	7 h 19 min	38 min	11 min
	Glargine U100	15 h 57 min†	7 h 31 min	32 min	9 min
Follow-up					
ONWARDS 2	Icodec	13 h 17 min	10 h 34 min	9 min	3 min

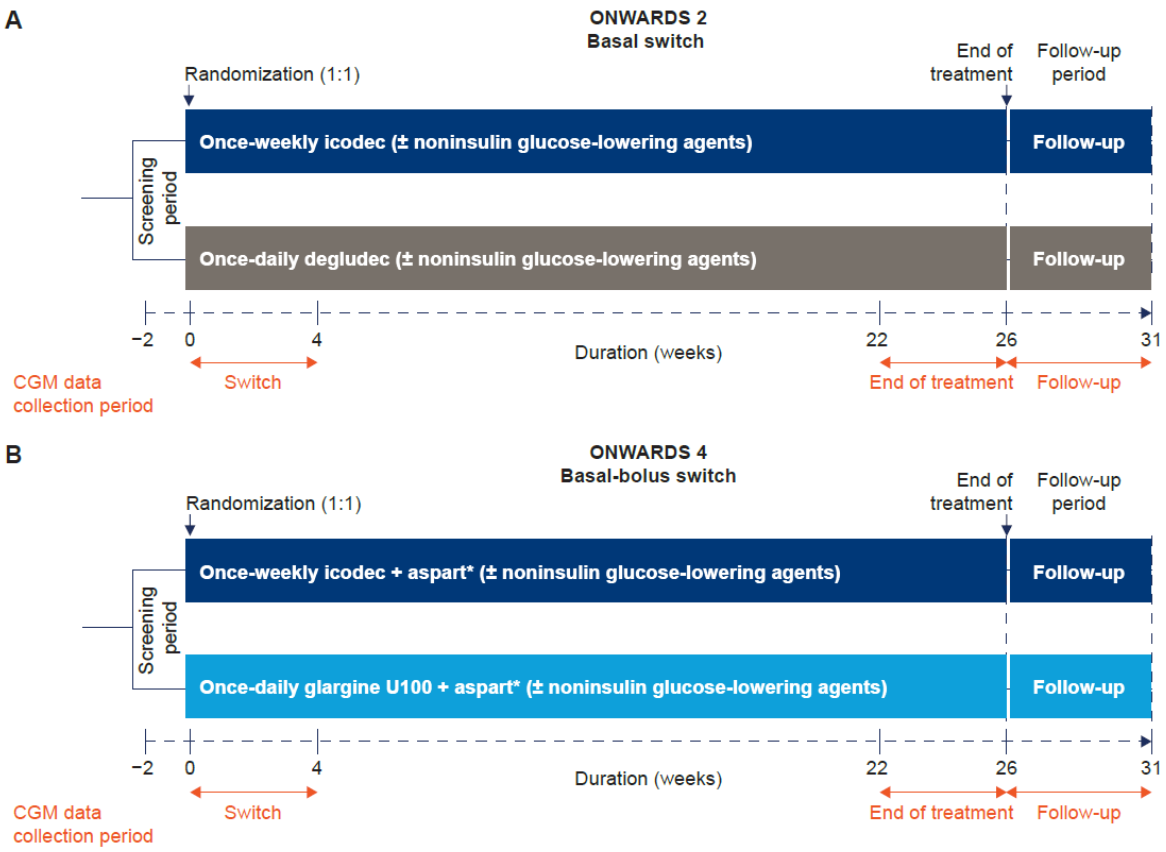
	Degludec	13 h 28 min	10 h 23 min	9 min	2 min
ONWARDS 4	Icodec	14 h 23 min	9 h 14 min	23 min	6 min
	Glargine U100	14 h 48 min	8 h 47 min	25 min	6 min

Approximate time spent per day was calculated based on the percentage of time within each glycemic range.

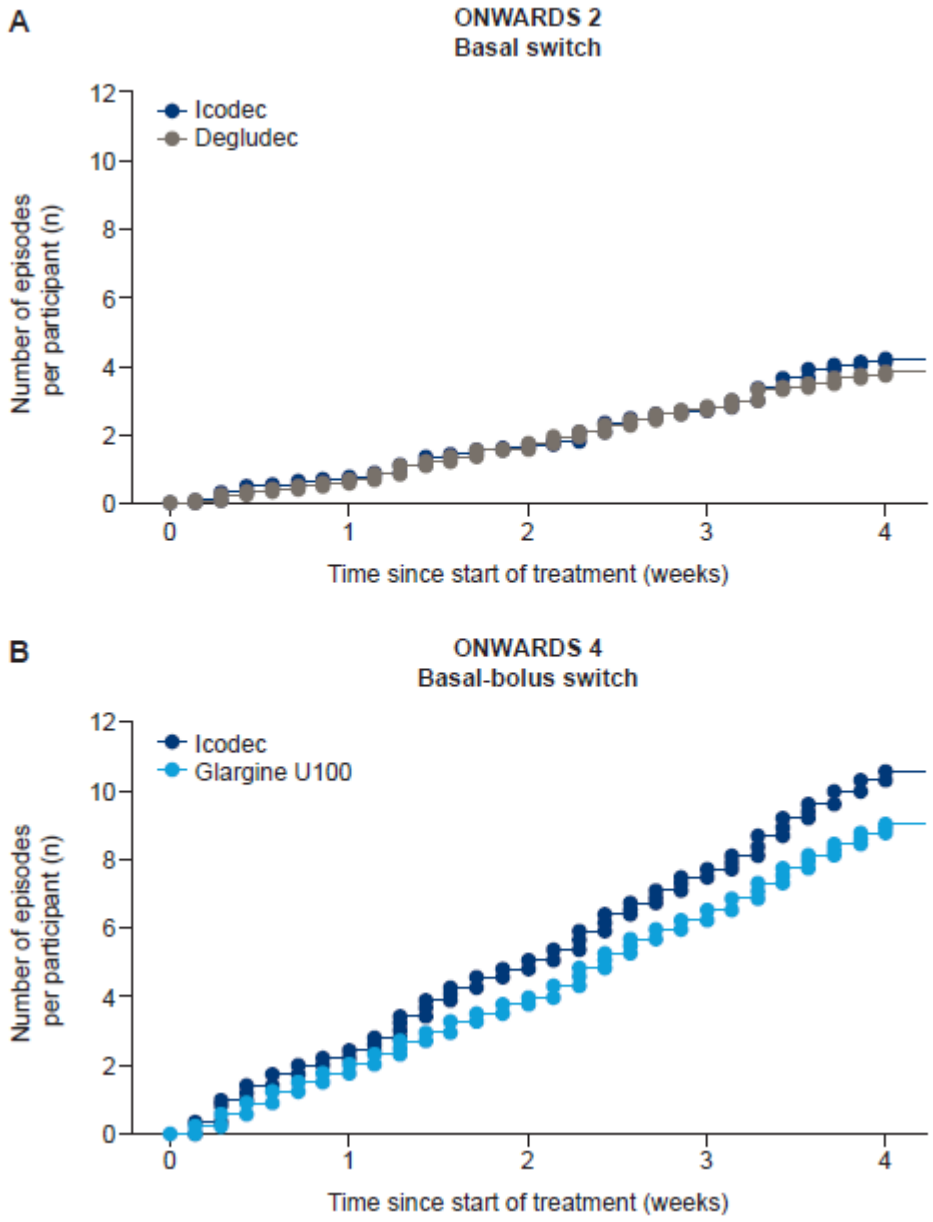
*ETD = 2.41%-points (approximately 35 min).

†ETD = 0.29%-points (approximately 4 min).

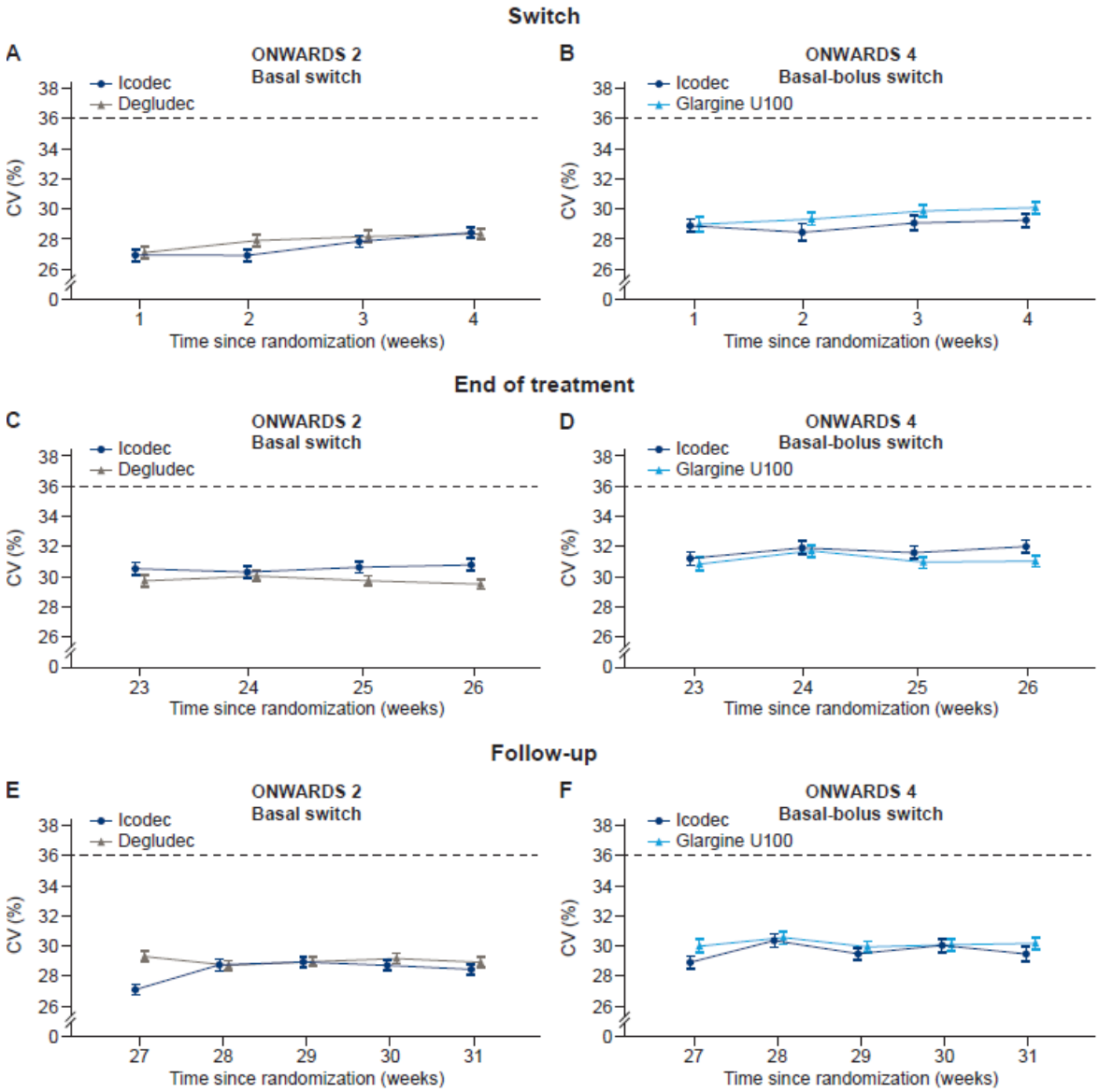
CGM, continuous glucose monitoring; degludec, insulin degludec; ETD, estimated treatment difference; glargine U100, insulin glargine U100; icodec, insulin icodec; TAR, time above range; TBR, time below range; TIR, time in range.



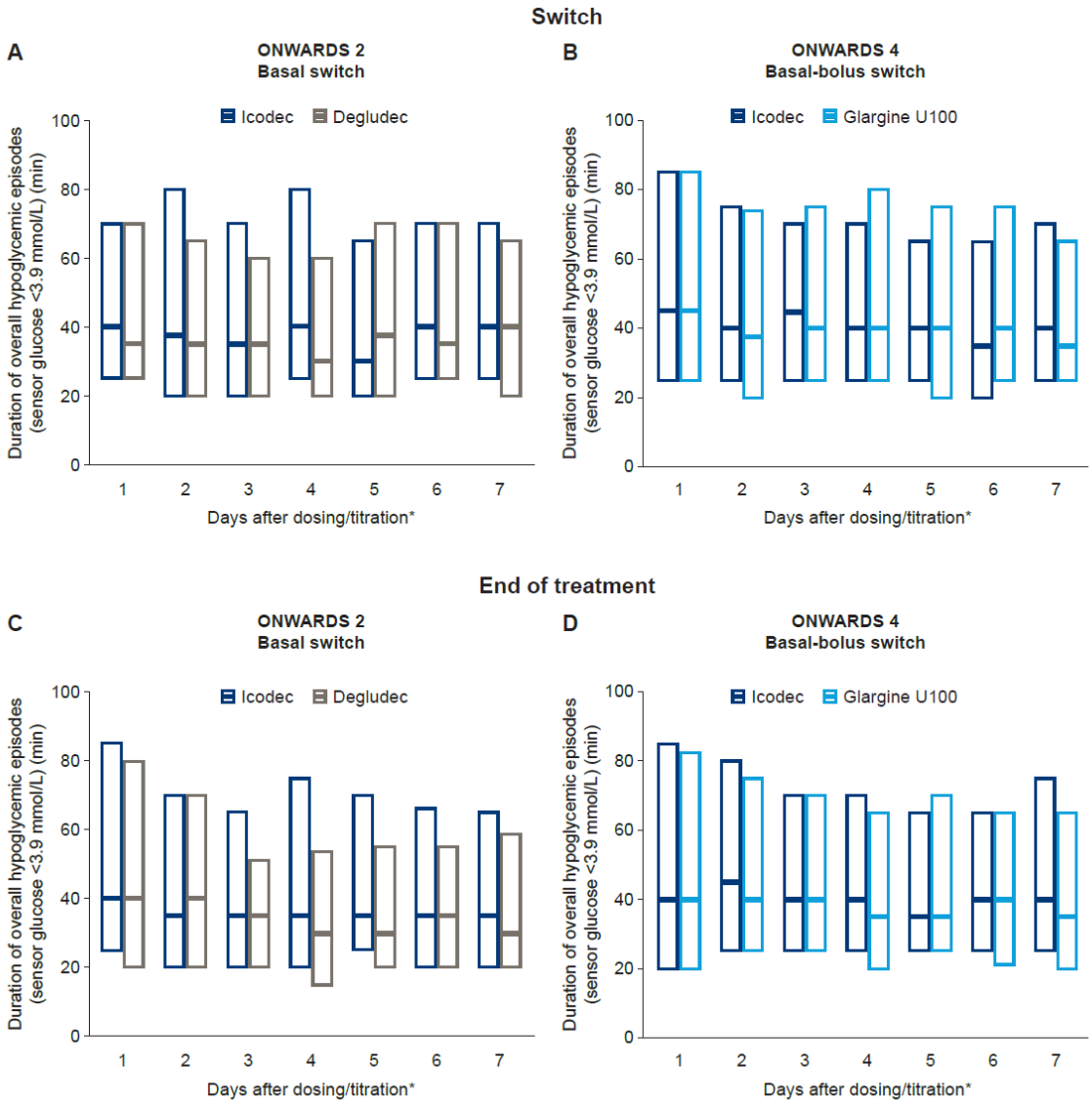
Supplementary Figure 1—Trial design for ONWARDS 2 (*A*) and ONWARDS 4 (*B*). *2–4 daily injections of aspart. Aspart, insulin aspart; CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec. Adapted from Philis-Tsimikas A et al. Diabetes Obes Metab 2023;25:331–41. doi: 10.1111/dom.14871. Copyright © 2023. Reproduced with permission of John Wiley & Sons Ltd.



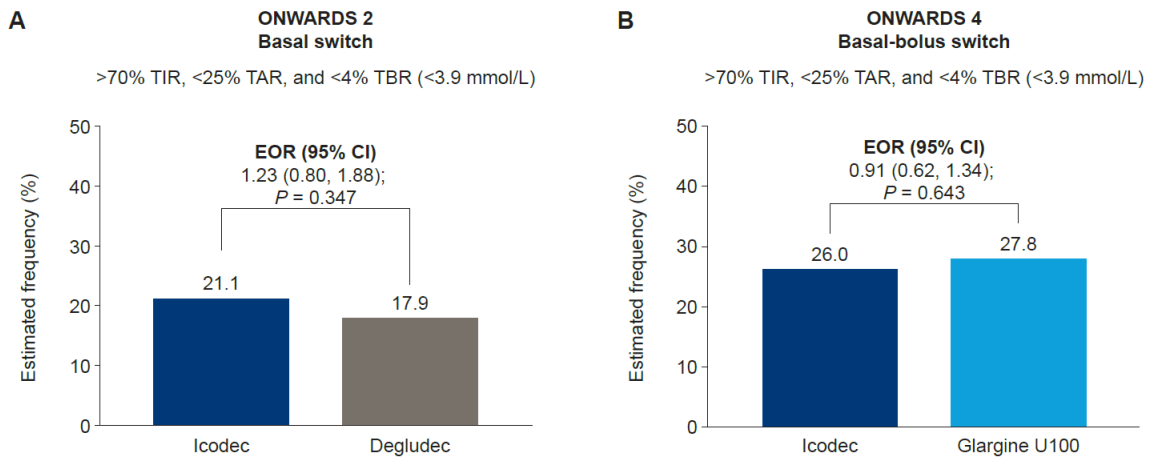
Supplementary Figure 2—Mean cumulative function of overall CGM-derived hypoglycemic episodes (sensor glucose <3.9 mmol/L) by week during the switch periods of ONWARDS 2 (*A*) and ONWARDS 4 (*B*). Observed data are presented. CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec.



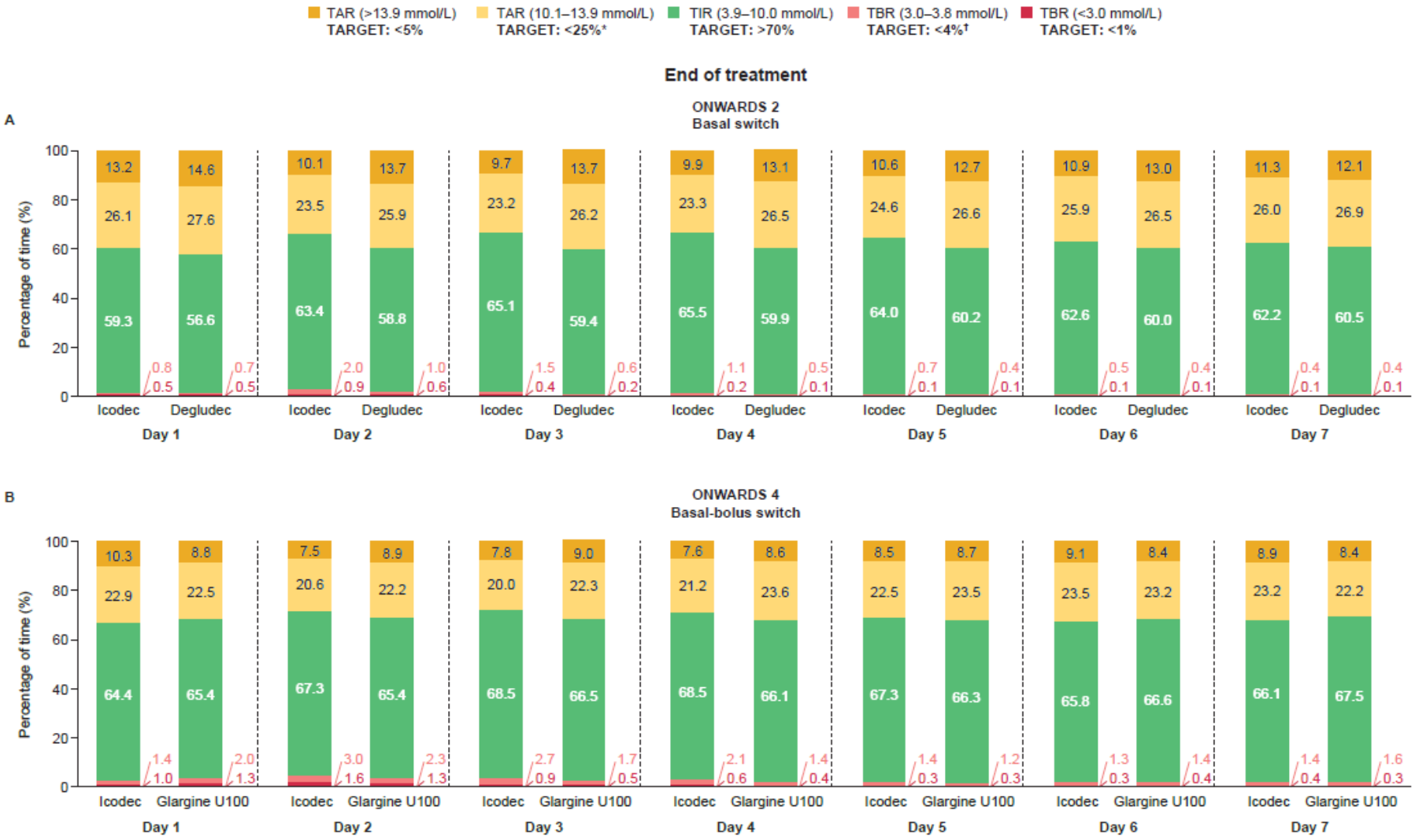
Supplementary Figure 3—Glycemic variability (CV%) during the switch periods of ONWARDS 2 (*A*) and ONWARDS 4 (*B*), end of treatment periods of ONWARDS 2 (*C*) and ONWARDS 4 (*D*), and follow-up periods of ONWARDS 2 (*E*) and ONWARDS 4 (*F*). Geometric mean (symbols) and geometric error (error bars) are illustrated on the plot. Dashed lines indicate internationally recognized threshold for stable glucose levels – unstable glucose levels are defined when CV% ≥36% (1). CV%, coefficient of variation; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec.



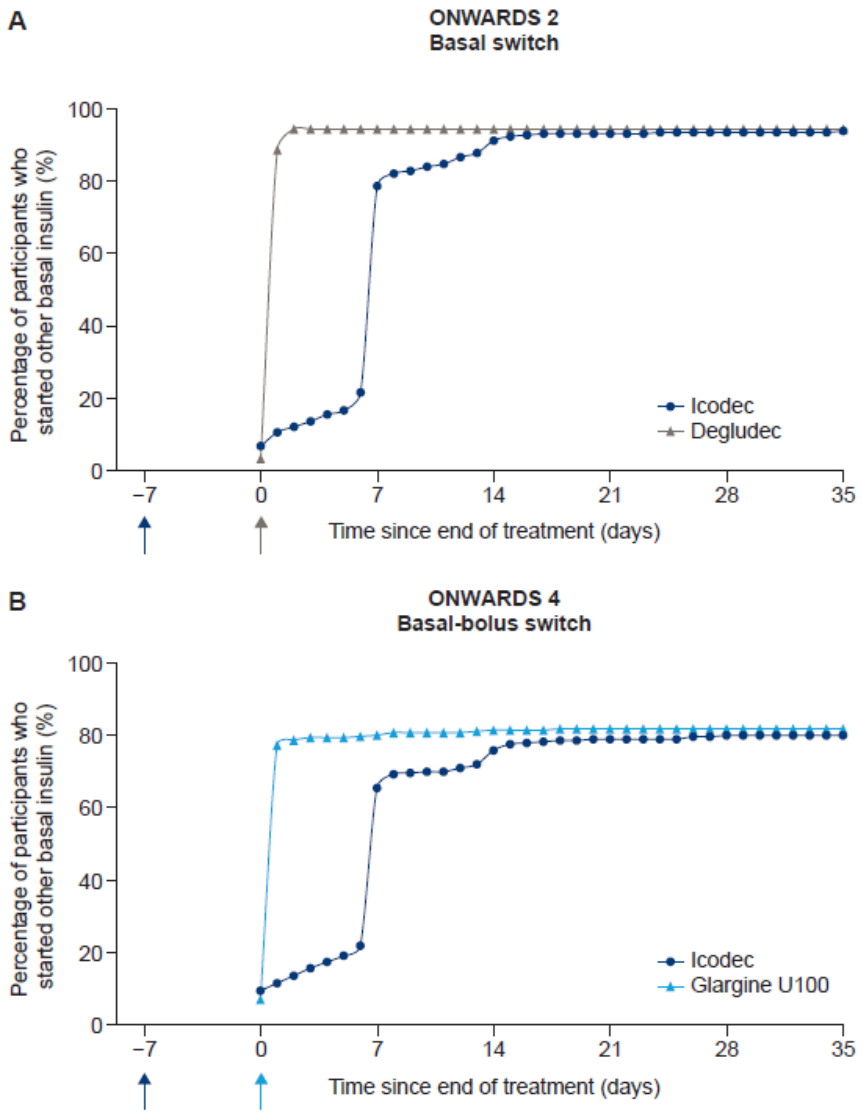
Supplementary Figure 4—Duration of overall CGM-derived hypoglycemic episodes (sensor glucose <3.9 mmol/L) by day during the switch periods of ONWARDS 2 (*A*) and ONWARDS 4 (*B*) and the end of treatment periods of ONWARDS 2 (*C*) and ONWARDS 4 (*D*). Plots show median ± IQR. *Day for the icodec arm represents the dosing day, with day of dose as day 1; day for the comparator arms represents the titration day, with the day of titration as day 1 (titration occurs once weekly). CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec; IQR, interquartile range.



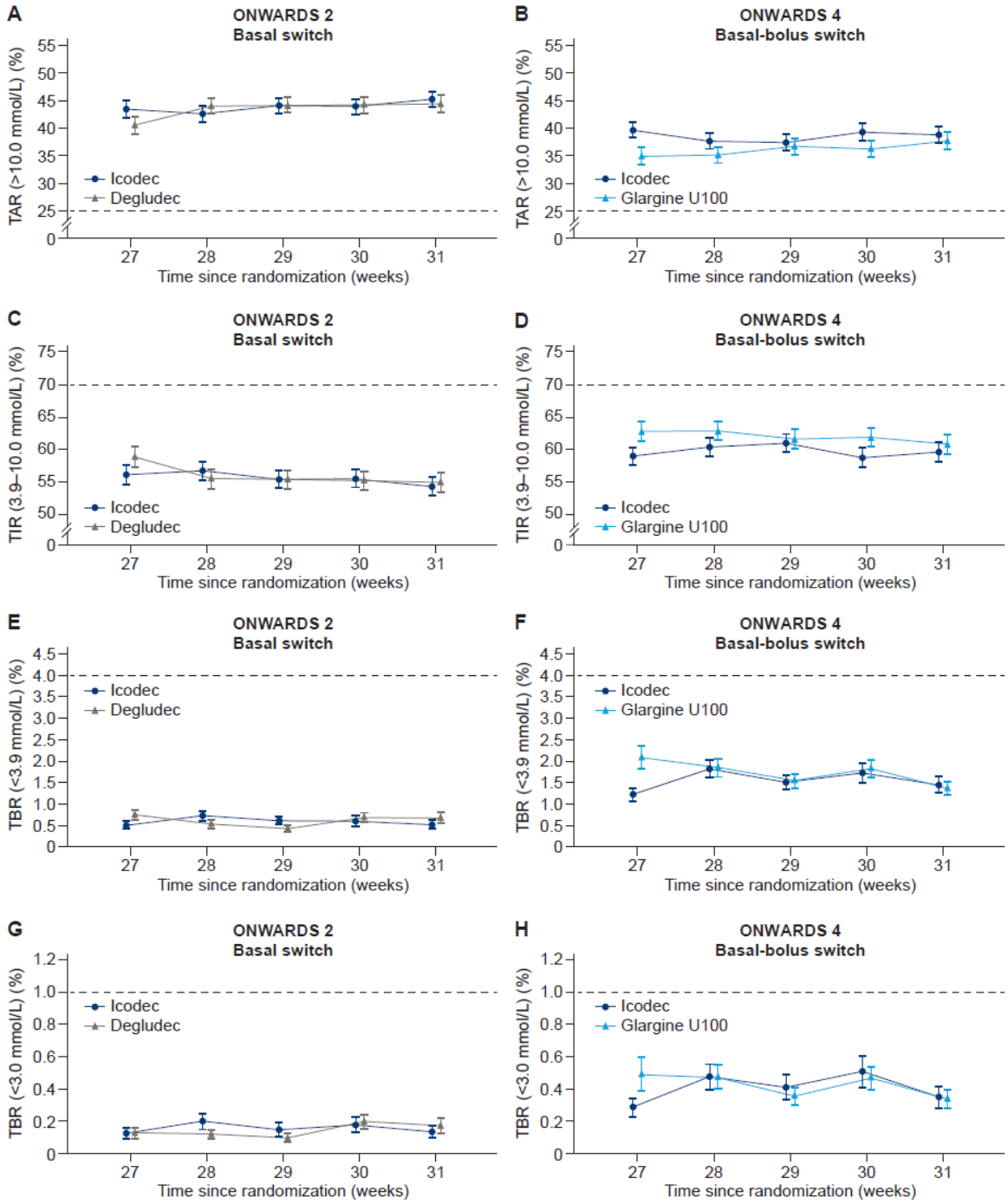
Supplementary Figure 5—Estimated frequency of participants achieving combined triple CGM targets during the end of treatment periods of ONWARDS 2 (*A*) and ONWARDS 4 (*B*). Statistical analysis based on multiple imputed data. EOR is icodec / degludec (ONWARDS 2); icodec / glargine U100 (ONWARDS 4). Statistical model was adjusted for geographic region and use of personal CGM or isCGM device. CGM, continuous glucose monitoring; degludec, insulin degludec; EOR, estimated odds ratio; glargine U100, insulin glargine U100; icodec, insulin icodec; isCGM, intermittently scanned CGM; TAR, time above range; TBR, time below range; TIR, time in range.


TAR (>13.9 mmol/L) TARGET: <5%
TAR (10.1–13.9 mmol/L) TARGET: <25%*
TIR (3.9–10.0 mmol/L) TARGET: >70%
TBR (3.0–3.8 mmol/L) TARGET: <4%†
TBR (<3.0 mmol/L) TARGET: <1%
End of treatment
A
ONWARDS 2
Basal switch
Percentage of time (%)
100
80
60
40
20
0
13.2 26.1 59.3 0.8 0.5
14.6 27.6 56.6 0.7 0.5
10.1 23.5 63.4 2.0 0.9
13.7 25.9 58.8 1.0 0.6
9.7 23.2 65.1 1.5 0.4
13.7 26.2 59.4 0.6 0.2
9.9 23.3 65.5 1.1 0.2
13.1 26.5 59.9 0.5 0.1
10.6 24.6 64.0 0.7 0.1
12.7 26.6 60.2 0.4 0.1
10.9 25.9 62.6 0.5 0.1
13.0 26.5 60.0 0.4 0.1
11.3 26.0 62.2 0.4 0.1
12.1 26.9 60.5 0.4 0.1
Icodec Degludec
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
B
ONWARDS 4
Basal-bolus switch
Percentage of time (%)
100
80
60
40
20
0
10.3 22.9 64.4 1.4 1.0
8.8 22.5 65.4 2.0 1.3
7.5 20.6 67.3 3.0 1.6
8.9 22.2 65.4 2.3 1.3
7.8 20.0 68.5 2.7 0.9
9.0 22.3 66.5 1.7 0.5
7.6 21.2 68.5 2.1 0.6
8.6 23.6 66.1 1.4 0.4
8.5 22.5 67.3 1.4 0.3
8.7 23.5 66.3 1.2 0.3
9.1 23.5 65.8 1.3 0.3
8.4 23.2 66.6 1.4 0.4
8.9 23.2 66.1 1.4 0.4
8.4 22.2 67.5 1.6 0.3
Icodec Glargine U100
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7

Supplementary Figure 6—Mean CGM-based metrics by day during the end of treatment periods of ONWARDS 2 (*A*) and ONWARDS 4 (*B*). *Target includes TAR >13.9 mmol/L. †Target includes TBR <3.0 mmol/L. Data are shown by day. Day for the icodec arm represents the dosing day, with day of dose as day 1; day for the comparator arms represents the titration day, with the day of titration as day 1. CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec; TAR, time above range; TBR, time below range; TIR, time in range.



Supplementary Figure 7—Percentage of participants starting daily basal insulin after end of treatment (during the follow-up periods) in ONWARDS 2 (*A*) and ONWARDS 4 (*B*). Data are the percentage of participants who started daily basal insulin after ending trial treatment relative to participants in the full analysis set. Dark blue (icodec), gray (degludec), and light blue (glargine U100) arrows indicate the time of last randomized insulin injection. CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec.



Supplementary Figure 8—Percentage of CGM-based TAR in ONWARDS 2 (*A*) and ONWARDS 4 (*B*), TIR in ONWARDS 2 (*C*) and ONWARDS 4 (*D*), TBR (<3.9 mmol/L) in ONWARDS 2 (*E*) and ONWARDS 4 (*F*), and TBR (<3.0 mmol/L) in ONWARDS 2 (*G*) and ONWARDS 4 (*H*) by week during the follow-up period. Plots show mean ± standard error (error bars). Percentage of time spent is defined as 100

times the number of recorded measurements in a given range, divided by the number of recorded measurements. Dashed lines indicate recommended glycemic targets (2). CGM, continuous glucose monitoring; degludec, insulin degludec; glargine U100, insulin glargine U100; icodec, insulin icodec; TAR, time above range; TBR, time below range; TIR, time in range.

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1. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640

2. Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinol 2023;11:42–57