CGM-based metrics and CGM-derived hypoglycemia duration with once-weekly insulin icodec versus once-daily insulin glargine U100 in insulin-naive T2D: ONWARDS 1 post hoc analyses

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Aim

- To investigate the effect of treatment with once-weekly (OW) insulin icodec (icodec) versus once-daily (OD) insulin glargine U100 (glargine U100) in insulin-naive individuals with type 2 diabetes (T2D) using continuous glucosemonitoring (CGM)-based metrics and CGM-derived hypoglycemia duration via *post hoc* analyses of CGM data recorded during ONWARDS 1, a phase 3a clinical trial (NCT04460885).

Introduction

- In ONWARDS 1, icodec significantly improved glycated hemoglobin (A1C) and time spent in glycemic range compared with glargine U100.
- Combined clinically significant or severe hypoglycemia rates (based on self-measured blood glucose) remained below one event per patient-year of exposure in both arms.
- From baseline to the end of follow-up, there was one episode of severe hypoglycemia with icodec and seven episodes with glargine U100.
- ONWARDS 1 assessed the long-term safety of icodec[1] and it is of interest to further characterize the safety profile of icodec using CGM-based metrics from this trial.
- CGM-based metrics (e.g., time spent in, above or below glycemic range [TIR, TAR and TBR, respectively]) and CGM-derived duration of hypoglycemic episodes collected at predefined periods throughout the time during which OW treatments are received may provide a more comprehensive picture than self-measured blood glucose.

Methods

Study design and treatment

- CGM data were analyzed from ONWARDS 1, a 78-week, randomized, open-label, treat-to-target phase 3a trial in adults (age: ≥ 18 years) with T2D who were insulin-naive.
  - Participants with inadequately controlled T2D (n = 984) were randomized (1:1) to OW icodec or OD glargine U100.
- Double-blinded CGM (Dexcom G6) data were obtained at treatment initiation (weeks 0–4), mid-trial (weeks 22–26) and at the end of the main and extension phases (weeks 48–52 and 74–78, respectively).
- Starting dosage was 70 U/week for icodec and 10 U/day for glargine U100. Treatments were titrated weekly based on pre-breakfast self-measured blood glucose values.

Analyses

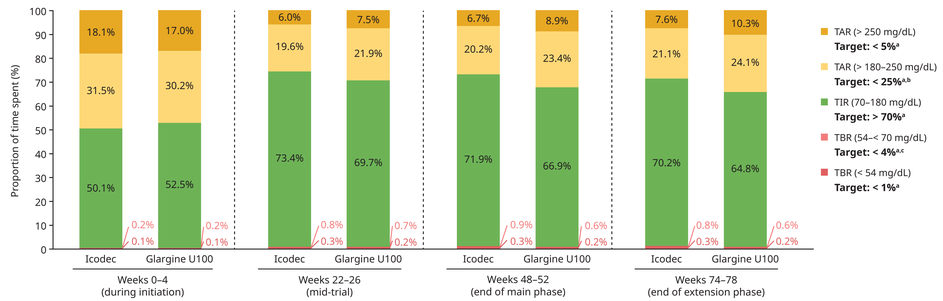
- CGM data were analyzed to assess TIR, TAR and TBR (as defined by the International Consensus on time in range[2]), the proportion of participants achieving the recommended CGM targets[2] and the duration of hypoglycemic episodes with OW icodec compared with OD glargine U100.
  - TIR, TAR (> 180 mg/dL) and TBR (< 54 mg/dL) at weeks 48–52 were prespecified trial endpoints. Furthermore, TIR was a confirmatory secondary endpoint, with the analysis adjusted for multiplicity.
- CGM-derived hypoglycemic epidsodes were defined as below.[2]
  - Sensor glucose value below 70 mg/dL for at least 15 consecutive minutes; considered resolved when sensor glucose returned to at least 70 mg/dL for at least 15 minutes.
  - Sensor glucose value below 54 mg/dL for at least 15 consecutive minutes.
- Median duration of CGM-derived overall hypoglycemic episodes below 70 mg/dL and the percentage of such episodes with time spent below 54 mg/dL were assessed.

Results

TIR, TAR, TBR

- At weeks 22–26, 48–52 and 74–78, the recommended target of more than 70% mean TIR was met with icodec; there was a significant difference in TIR in favor of icodec versus glargine U100 (**Figure 1**).
- TIR, TAR and TBR did not differ significantly between arms at weeks 0–4.
- Compared with weeks 0–4, TAR was lower at all other time points in both treatment arms and was significantly different in favor of icodec versus glargine U100.
- There was no significant difference between treatment arms in TBR below 54 mg/dL. There was a significant difference in favor of glargine U100 in TBR below 70 mg/dL at weeks 48–52 and 74–78, but mean TBR below 70 mg/dL and TBR below 54 mg/dL remained well below the recommended targets of below 4% and below 1%,[2] respectively, at all time points in both arms, reflecting low hypoglycemia risk.
- More participants achieved the triple composite endpoint of TIR above 70%, TAR below 25%, and TBR (below 70 mg/dL) below 4% at weeks 22–26, 48–52 and 74–78 with icodec versus glargine U100 (**Figure 2**).

Figure 1: Time spent in, above or below the target glycemic range of 70–180 mg/dL during treatment initiation (weeks 0–4), mid-trial (weeks 22–26) and at the end of the main (weeks 48–52) and extension (74–78) phases



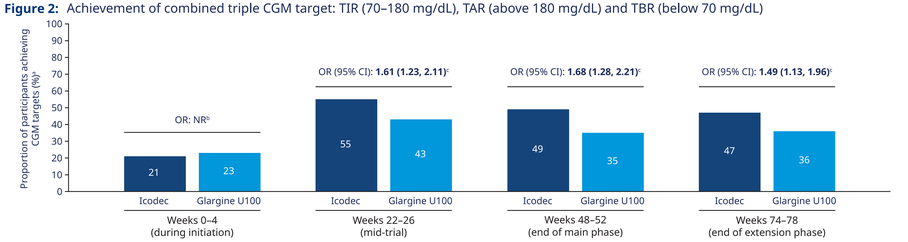
		Weeks 0–4 (during initiation)	Weeks 22–26 (mid trial)	Weeks 48–52 (end of main phase)	Weeks 74–78 (end of extension phase)
ETD (95% CI)	$TAR_{>180\ mg/dL}$	2.34 (−1.09, 5.77)[d]	**−3.69 (−6.03, −1.34)**[d]	**−4.58 (−6.99, −2.17)**[d]	**−4.65 (−7.20, −2.10)**[d]
	$TIR_{70–180\ mg/dL}$	−2.39 (−5.79, 1.02)[d]	**3.57 (1.27, 5.87)**[d]	**4.27 (1.92, 6.62)**[d,e]	**4.41 (1.92, 6.90)**[d]
ETR (95% CI)	$TBR_{<70\ mg/dL}$	1.20 (0.85, 1.70)[f]	1.10 (0.89, 1.38)[f]	**1.48 (1.19, 1.84)**[f]	**1.34 (1.07, 1.68)**[f]
	$TBR_{<54\ mg/dL}$	1.27 (0.81, 1.97)[f]	1.16 (0.86, 1.55)[f]	1.27 (0.94, 1.71)[f]	1.20 (0.89, 1.61)[f]

Data based on the full analysis set. Bold text indicates a statistically significant difference in favor of icodec (TIR and TAR) or glargine U100 (TBR < 70 mg/dL)
[a]CGM recommended targets are based on international guidelines.[2,3] [b]Includes percentage of values above 250 mg/dL. [c]Includes percentage of values below 54 mg/dL. [d]ANOVA model, with region and randomized treatment as fixed factors. [e]Confirmatory endpoint. [f]Negative binomial model using the number of recorded measurements below range, with a log-link function and the logarithm of the total number of recorded measurements as an offset. Region and randomized treatment were included as fixed factors
ANOVA, analysis of variance; CGM, continuous glucose monitoring; CI, confidence interval; ETD, estimated treatment difference (icodec – glargine U100); ETR, estimated treatment ratio (icodec/glargine U100); glargine U100, insulin glargine U100; icodec, insulin icodec; TAR, time above range; TBR, time below range; TIR, time in range

CGM-derived hypoglycemic episodes

- The median duration of CGM-derived hypoglycemic episodes (< 70 mg/dL) was comparable for icodec and glargine U100 during all time periods (**Table**).
- Most CGM-derived hypoglycemic episodes (< 70 mg/dL) had no period spent below 54 mg/dL at all or that lasted more than 15 minutes (**Table**).
- There were no substantial differences between icodec and glargine U100 in the percentage of hypoglycemic episodes with time spent below 54 mg/dL for at least 15 minutes, irrespective of time period (**Table**).

Figure 2: Achievement of combined triple CGM target: TIR (70–180 mg/dL), TAR (above 180 mg/dL) and TBR (below 70 mg/dL)



Data based on the full analysis set. Bold text indicates a statistically significant difference in favor of icodec
[a]CGM targets: TIR (70–180 mg/dL) above 70%, TAR (above 180 mg/dL) below 25% and TBR (below 70 mg/dL) below 4%. [b]OR for weeks 0–4 was not calculated because icodec was not at steady state. [c]The binary response was analyzed using a binary logistic regression model (logit link) with treatment and region as fixed factors
CGM, continuous glucose monitoring; CI, confidence interval; glargine U100, insulin glargine U100; icodec, insulin icodec; NR, not reported; OR, odds ratio (icodec/glargine U100); TAR, time above range; TBR, time below range; TIR, time in range

Table: CGM-derived duration and classification of hypoglycemia episodes across all time points

	Weeks 0–4 (during initiation)		Weeks 22–26 (mid-trial)		Weeks 48–52 (end of main phase)		Weeks 74–78 (end of extension phase)	
	Icodec	**Glargine U100**	**Icodec**	**Glargine U100**	**Icodec**	**Glargine U100**	**Icodec**	**Glargine U100**
Duration of hypoglycemia episode (< 70 mg/dL), median (IQR)	35 (20, 65) min	35 (20, 60) min	35 (20, 65) min	35 (20, 70) min	35 (20, 70) min	35 (20, 70) min	35 (20, 70) min	35 (20, 70) min
Classification of CGM-based overall hypoglycemic episodes (< 70 mg/dL) by time < 54 mg/dL								
Percentage of hypoglycemic episodes (< 70 mg/dL) with no time spent < 54 mg/dL	63%	65%	63%	64%	70%	65%	62%	62%
Percentage of hypoglycemic episodes (< 70 mg/dL) with < 15 consecutive minutes spent < 54 mg/dL	11%	11%	12%	12%	9%	12%	12%	13%
Percentage of hypoglycemic episodes (< 70 mg/dL) with ≥ 15 consecutive minutes spent < 54 mg/dL	26%	24%	25%	24%	21%	23%	27%	25%

Data based on the full analysis set
CGM, continuous glucose monitoring; glargine U100, insulin glargine U100; icodec, insulin icodec; IQR, interquartile range

Conclusion

- In adults with T2D who were previously insulin-naive:
  - there was a significant difference in TIR and TAR at weeks 22–26, 48–52 and 74–78 in favor of icodec versus glargine U100. Although there was a significant difference in favor of glargine U100 for TBR below 70 mg/dL at weeks 48–52 and 74–78, TBR Below 54 mg/dL, representing clinically significant hypoglycemia, was comparable between treatment arms
  - TBR below 70 mg/dL and TBR below 54 mg/dL remained well below the recommended targets of below 4% and below 1%, respectively
  - CGM–derived hypoglycemia duration during all specified time points was comparable with icodec versus glargine U100
  - the majority of CGM-derived hypoglycemic episodes had minimal (< 15 minutes) or no time spent below 54 mg/dL for both treatment arms. Observed percentage of CGM-derived hypoglycemic episodes with time spent below 54 mg/dL during a hypoglycemic episode was comparable between treatment arms across all specified time points
  - more participants achieved the triple composite endpoint of TIR above 70%, TAR below 25% and TBR (below 70 mg/dL) below 4% at weeks 22–26, 48–52 and 74–78 with icodec versus glargine U100.

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