Insulin Icodec: Once-Weekly Basal Insulin for Treatment of Adults with Diabetes Mellitus

Novo Nordisk

Endocrinologic and Metabolic Drugs Advisory Committee

May 24, 2024

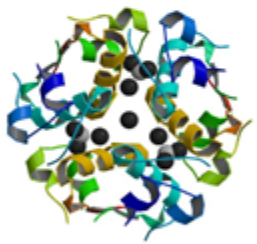
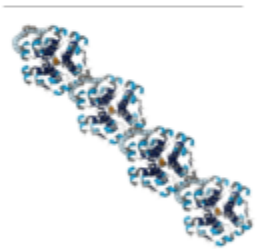
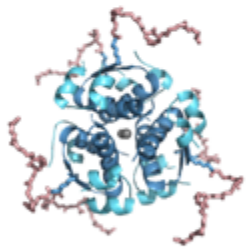
Introduction

Shawn Hoskin

Executive Director, Regulatory Affairs

Novo Nordisk

Insulin Icodec is the Continued Evolution of Insulin Therapy; Designed to Reduce Burden of Insulin Treatment

	NPH insulin	1st generation basal insulin analogs	Ultra long-acting basal insulin analogs	Once-weekly icodec
				
Half-life	5-10 hours	~0.5 day	~1 day	~1 week
Administration	Once daily / twice daily	Once daily / twice daily	Once daily	Once weekly

NPH = Neutral protamine Hagedorn

Insulin Icodec is Novel Long-Acting Insulin Designed to Cover Basal Insulin Requirements for a Full Week

- Fatty acid side chain prolongs duration of action
  - Strong, reversible albumin binding slows clearance
  - Insulin icodec slowly released from circulating and interstitial depot
- Stable glucose-lowering with weekly dosing
- PK/PD properties maintained across various patient factors
- Insulin icodec has a similar peak to trough ratio as with other daily basal insulins

PK/PD = Pharmacokinetics / pharmacodynamics

Worldwide Regulatory Status

Location	Approval Status	Indication
 **Canada**	**Approved** March 12, 2024	**Treatment of Adults with Diabetes Mellitus (T1D and T2D)**
 **Switzerland**	**Approved** March 7, 2024	
 **Europe**	**Recommended for Approval** March 21, 2024	

Six Randomized Controlled Studies Confirm Efficacy and Safety of Insulin Icodec Across Diverse Population

Type 2 Diabetes

ONWARDS 1 – 5

Augments safety data and adds to overall benefit-risk assessment of once-weekly insulin icodec

Presentation will focus on benefit-risk in T1D

Type 1 Diabetes

ONWARDS 6

Primary evidence of safety and efficacy of once-weekly insulin icodec in participants with T1D

ONWARDS 1-5 Supports Positive Benefit-Risk of Weekly Insulin Icodec in Adults with T2D

Efficacy (T2D)

- Non-inferior to daily basal insulin for change in HbA_{1c}
- HbA_{1c} reduction sustained for 52 weeks
- Glucose time in target range comparable to daily basal insulin

Safety (T2D)

- General safety profile similar to daily basal insulin
- Low absolute rate of level 2 or level 3 hypoglycemia
- No excess of level 3 hypoglycemic episodes

Weekly Insulin Icodec Can be Used Safely and Effectively in Adults with Type 1 Diabetes

Efficacy (T1D)

- Non-inferior to insulin degludec for change in HbA_{1c}
- HbA_{1c} reduction sustained through end of treatment
- CGM time in target range not clinically different from insulin degludec

Safety (T1D)

- General safety profile similar to insulin degludec
- Higher risk of hypoglycemia compared to insulin degludec

Hypoglycemic Episodes with Insulin Icodec in T1D Manageable, Consistent with Daily Insulin Degludec

- Management of hypoglycemic episodes same with insulin icodec and insulin degludec
- Duration of hypoglycemia not different from insulin degludec
- No participant characteristics predict for difference in relative hypoglycemia risk with insulin icodec
- Informed healthcare professionals can mitigate hypoglycemia risk
  - Knowledge of risk factors and insulin icodec PD aids treatment individualization
  - Limitation of use in adults with increased hypoglycemia risk

PD = Pharmacodynamics

Insulin Icodec Pen Injector

- U-700 formulation
- Pre-filled insulin pen injector with 10 U increments
- In insulin naïve patients, starting dose of 70 U weekly, equivalent to 10 U daily
- Weekly injection volume equivalent to daily injection volume

Unmet Need	**Ildiko Lingvay, MD, MPH, MSCS** Professor of Medicine Department of Internal Medicine/Endocrinology UT Southwestern Medical Center, Dallas, TX
ONWARDS Development Program and Insulin Icodec Dosing	**Stephen Gough, MD, FRCP** Global Chief Medical Officer, Senior Vice President Novo Nordisk
General Safety	**Roman Cailleteau, MD** Senior Medical Director Novo Nordisk
Efficacy and Hypoglycemia (T2D)	**Roman Cailleteau, MD**
Efficacy and Hypoglycemia (T1D)	**Stephen Gough, MD, FRCP**
Clinical Perspective	**Ildiko Lingvay, MD, MPH, MSCS**
Conclusion	**Stephen Gough, MD, FRCP**

Additional Novo Nordisk Experts

Kamilla Begtrup, MSc

Senior Statistical Director
Novo Nordisk

Erica Nishimura, PhD

Scientific Vice President
Novo Nordisk

Unmet Need for Basal Insulin Treatment

Ildiko Lingvay, MD, MPH, MSCS

Professor of Medicine

Department of Internal Medicine/Endocrinology

UT Southwestern Medical Center, Dallas, TX

Insulin has an Important Role in the Treatment of People with Diabetes

Insulin Therapy

T1D

Necessary and life-saving intervention

100%

T1D population requires insulin

Used by approximately

~1.7 Million

T2D

Among most effective glucose lowering interventions

~33%

T2D population treated with insulin

~7.4 Million

people in the US[1,2]

1. National Diabetes Statistics Report | Diabetes | CDC; 2. https://usafacts.org/articles/a-cap-on-insulin-costs-benefits-millions-of-americans-with-diabetes/

Insulin Remains One of the Most Burdensome and Feared Diabetes Treatments

Limitations

- Fear of injections
- Additional barriers imposed by complexity and inconvenience of injection
- Impact on quality of life

Consequences

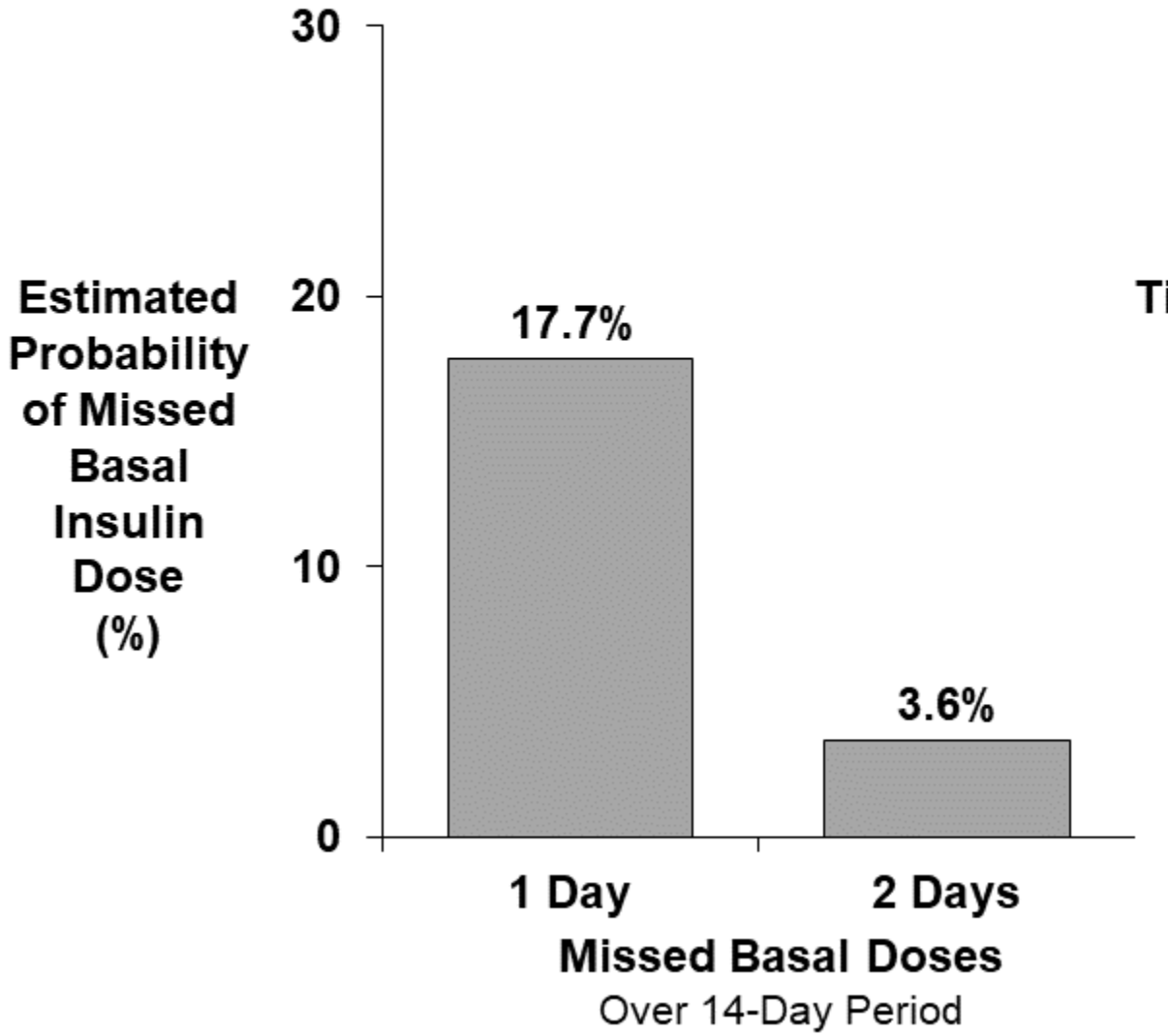
- Delays in insulin initiation in T2D
- Poor adherence in T1D and T2D

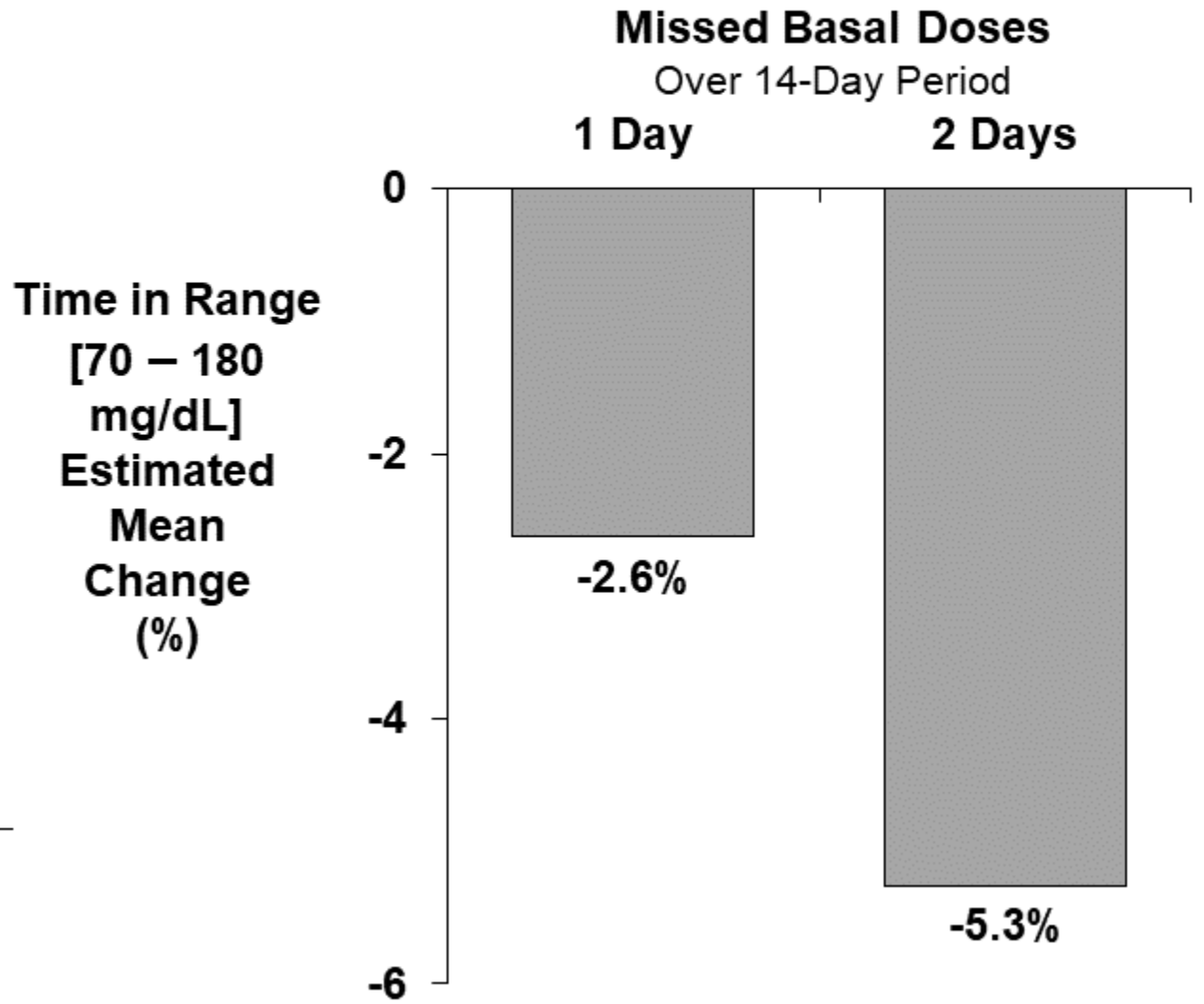
Insulin Adherence is Universally Suboptimal, with Common Patient-Reported Barriers

	Type 1 Diabetes		Type 2 Diabetes	
Rates of non-adherence[1-4]	53 - 88%		53 - 80%	
Common Barriers[5]	Low Adherence	Medium/High Adherence	Low Adherence	Medium/High Adherence
Forgetfulness	19.5%	4.7%	40.5%	3.3%
Time consuming	19.4%	5.1%	20.3%	9.3%
Embarrassing	8.3%	0.5%	12.3%	0.5%

1. Boonpattharatthiti, et al. Research in Social and Administrative Pharmacy, 2024; 2. Eby, et al. J Manag Care Spec Pharm, 2020;
3. Perez-Nieves, et al. Diabetes Ther, 2018; 4. Riaz, et al. Pak J Med Sci, 2014;
5. Farsaei, et al. PC Diabetes, 2014

Consequences of Low Insulin Adherence
1. *Glycemic Control*





Ekberg, et al. J Diabetes Science Technology, 2024

Consequences of Low Insulin Adherence
2. *Healthcare Utilization*

N = 21,363	Nonadherent (PDC < 80%) Mean (95% CI)	Adherent (PDC ≥ 80%) Mean (95% CI)
Diabetes-related resource utilization		
Number of hospitalizations	**0.64** (0.63, 0.65)	**0.53** (0.52, 0.54)
Hospital length of stay	**3.68** (3.61, 3.76)	**2.91** (2.83, 2.99)
Number of ER visits	**1.21** (1.19, 1.22)	**1.00** (0.98, 1.02)
All-cause resource utilization		
Number of hospitalizations	**0.89** (0.87, 0.90)	**0.73** (0.71, 0.74)
Hospital length of stay	**5.40** (5.29, 5.52)	**4.33** (4.20, 4.45)
Number of ER visits	**2.46** (2.43, 2.50)	**2.05** (2.01, 2.09)

Data from US-based Truven Health MarketScan Research Databases

Perez-Nieves, et al. Diabetes Ther, 2018;
PDC = Proportion of Days Covered
N = Total number of patients included in the study

Low Insulin Adherence is the Most Common Cause of Recurrent DKA

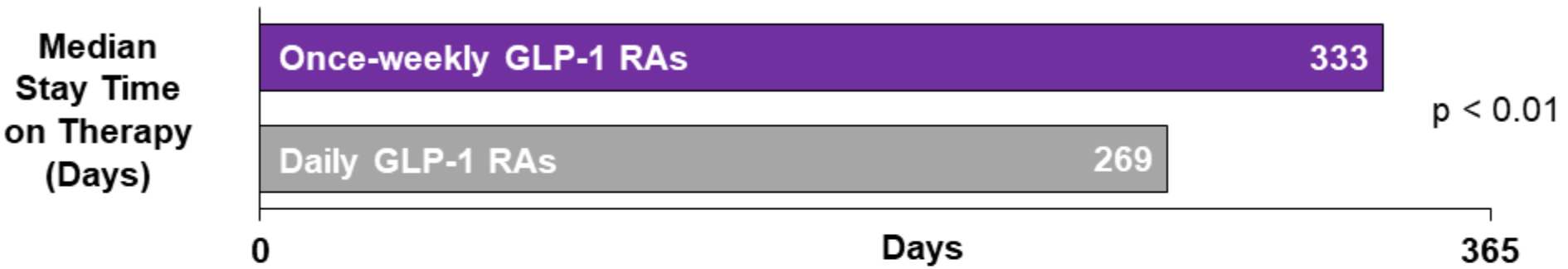
	Multivariate Analysis	
	Odds Ratio (95% CI)	**p-value**
Poor adherence to insulin therapy	**26.29** (1.78, 388.5)	**0.02**
Psychiatric illness	**2.72** (0.94, 7.89)	**0.06**
Alcohol abuse and/or illicit drug use	**1.63** (0.56, 4.69)	**0.37**
A1C	**1.20** (0.93, 1.55)	**0.16**
Macrovascular complications	**0.98** (0.20, 4.82)	**0.98**
Precipitating factor for DKA episode	**0.97** (0.35, 2.68)	**0.95**
Sex (men)	**0.91** (0.29, 2.82)	**0.87**
Insulin regimen (pump)	**0.21** (0.01, 9.17)	**0.42**
Neurocognitive disorder	**0.14** (0.01, 3.53)	**0.23**

Del Degan, et al. Canadian Journal of Diabetes, 2019

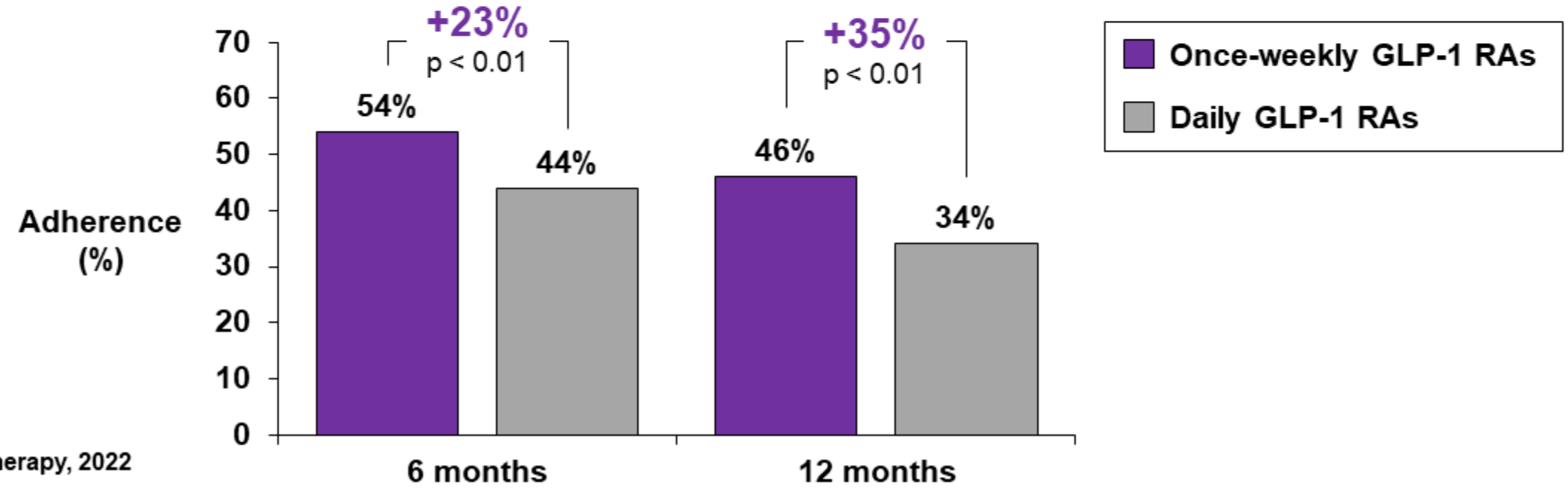
CI = Confidence Interval; DKA = Diabetic Ketoacidosis; Odds Ratio represents group with recurrent DKA versus isolated event of DKA

Once-Weekly Medication Dosing Improves Adherence and Persistence in People with Diabetes

Higher Persistence



Higher Adherence



Polonsky, et al. Diabetes Therapy, 2022
RA = Receptor Agonist

Once-Weekly Insulin Icodec Would Provide an Important Option for Diabetes Management

A once weekly insulin has the potential to:

- Reduce barriers to insulin initiation
- Minimize treatment burden
- Improve quality of life
- Increase treatment adherence and persistence

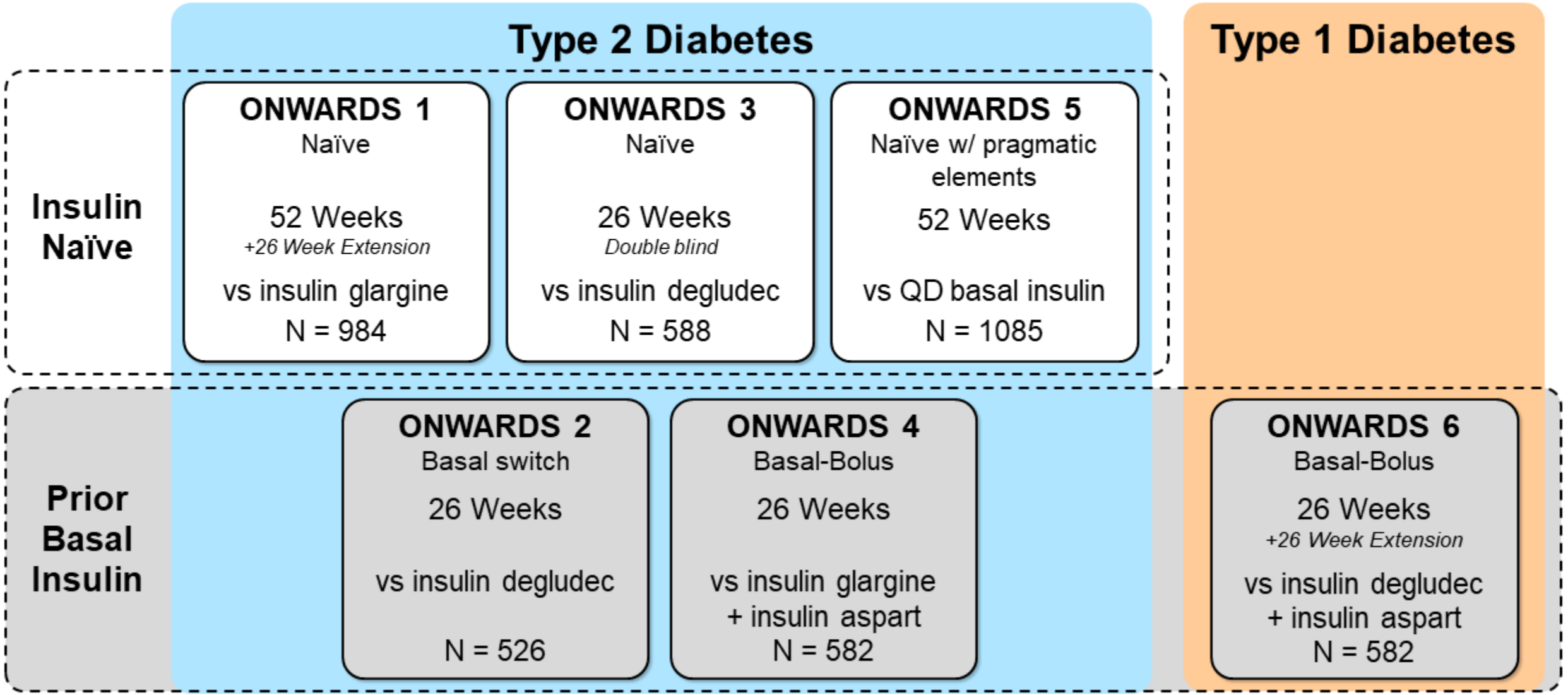
ONWARDS Development Program and Icodec Dosing

Stephen Gough, MD, FRCP

Global Chief Medical Officer, Senior Vice President

Novo Nordisk

Six Phase 3 Randomized, Controlled Trials Support Insulin Icodec Efficacy and Safety



QD = Once Daily; N = Number of Randomized Participants

Weekly Insulin Icodec Dosing Initiation in ONWARDS Studies Based on Baseline Characteristics

	Type 2 Diabetes	Type 1 Diabetes	
Insulin Naïve	**Single Starting Dose** 70 U		
Prior Basal Insulin	**Single Starting Dose** 1.5 x Daily Basal Insulin Dose x 7 **Second Dose** Daily Basal Insulin Dose x 7	***HbA_{1c} < 8%, glargine U300 or twice daily basal insulin*** **Single Starting Dose** 1.5 x Daily Basal Insulin Dose x 7	***HbA_{1c} ≥ 8%*** **Single Starting Dose** 2 x Daily Basal Insulin Dose x 7
		Second Dose Daily Basal Insulin Dose x 7	

Self-Monitored Blood Glucose (SMBG) Guided Weekly Insulin Icodec Dose Adjustments

Type 2 Diabetes
Insulin Icodec Titration Algorithm

	mg/dL	Dose Adjustment (U/week)
Lowest SMBG value	< 80	-20
Mean SMBG values	80 - 130	0
	> 130	+20

Type 1 Diabetes
Insulin Icodec Titration Algorithm

	mg/dL	Dose Adjustment (U/week)
Lowest SMBG value	< 80	-20
	80 - 130	0
	> 130	+20

Based on three pre-breakfast SMBG values measured two days prior and on day of titration

ONWARDS Studies Included Key Prespecified Assessments

Primary Efficacy Measure

- Change in HbA_{1c}

Secondary Efficacy Measures

- Change in fasting plasma glucose (FPG)
- Time in glucose range (70-180 mg/dL)
- Time spent with glucose < 54 mg/dL
- Time spent with glucose > 180 mg/dL

Continuous Glucose Monitoring (CGM) Data Augmented Traditional Efficacy and Safety Assessments

- CGM data provide accurate glucose values and trends throughout day and night
- ONWARDS 1, 2 and 4 (T2D)
  - CGM assessed during last 4 weeks of planned treatment
  - Participants and investigators blinded
- ONWARDS 6 (T1D)
  - CGM assessed throughout entire trial
  - Participants and investigators not blinded

Hypoglycemia Carefully Assessed in ONWARDS Trials

- Frequency
- Duration
- Management of hypoglycemic episodes
- Timing of hypoglycemia in relationship to dosing
- Hypoglycemia during dose initiation or titration
- Investigation of risk factors associated with hypoglycemia

Classification of Hypoglycemic Episodes in ONWARDS Trials

Level	Hypoglycemia	Glycemia criteria	Description
Level 1	**Alert value**	< 70 mg/dL and ≥ 54 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Level 2	**Clinically significant**	< 54 mg/dL	Sufficiently low to indicate serious, clinically important hypoglycemia
Level 3	**Severe**	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

- Pre-specified analyses for combined level 2 and level 3 hypoglycemic episodes

ADA, Diabetes Care, 2024

Post-hoc CGM-Based Analysis of Clinically Significant (Level 2) Hypoglycemic Episodes

- CGM-based method well-established in current clinical guidelines and regulatory guidance[1,2,3]
- CGM provides objective assessment of hypoglycemic episodes
  - Based on 5-minute interval glucose values
  - Not impacted by measurement frequency and self-reporting as required with SMBG-based approach
- Same CGM device used across ONWARDS studies

1. Battelino T, et. al., Lancet Diabetes & Endocrinology, 2023
2. European Medicines Agency. Guidance on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, 2023
3. FDA. Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products. Draft Guidance, 2023

Participants Enrolled Representative of a Broad Diabetes Population as Seen in Clinical Practice

		T2D (ONWARDS 1-5)		T1D (ONWARDS 6)	
		Icodec N = 1880	Daily Basal N = 1878	Icodec N = 290	Degludec N = 292
Age	Mean Years (SD)	59 (10)	60 (10)	44 (14)	44 (14)
	≥ 65 years	34%	35%	8%	7%
Sex	Male	59%	56%	57%	59%
Race	White	71%	69%	79%	75%
	Asian	22%	24%	18%	25%
	Black or African American	4%	4%	3%	1%
Region	Europe	42%	40%	47%	48%
	North America	31%	31%	37%	29%
	Asia	19%	21%	17%	23%

- ≥ 94% randomized to insulin icodec completed treatment in main trial period

Baseline Diabetes Characteristics Well-Balanced Across Treatment Groups and Populations

	T2D (ONWARDS 1-5)		T1D (ONWARDS 6)	
	Icodec N = 1880	Daily Basal N = 1878	Icodec N = 290	Degludec N = 292
BMI (kg/m^2), mean	**30.7**	**30.6**	**26.8**	**26.2**
Renal function (eGFR mL/min/1.73m^2), mean	**86.1**	**85.5**	**98.5**	**97.0**
Normal (≥ 90)	**49%**	**50%**	**68%**	**65%**
Mild impairment (≥ 60 - < 90)	**40%**	**37%**	**30%**	**32%**
Moderate impairment (≥ 30 - < 60)	**11%**	**12%**	**2%**	**3%**
Severe impairment (< 30)	**< 1%**	**< 1%**	**-**	**-**
HbA_{1c} (%), mean	**8.6**	**8.5**	**7.6**	**7.6**
< 8% (< 64 mmol/mol)	**37%**	**38%**	**64%**	**65%**
≥ 8% (≥ 64 mmol/mol)	**63%**	**62%**	**36%**	**35%**
History of cardiovascular disease	**27%**	**28%**	**8%**	**9%**
Duration of diabetes ≥ 10 years (%)	**63%**	**62%**	**74%**	**72%**

Safety of Once-Weekly Injection of Insulin Icodec

Roman Cailleteau, MD

Senior Medical Director

Novo Nordisk

ONWARDS 1-6: > 2100 Participants Exposed to Insulin Icodec During Phase 3 Development Program

	Total (ONWARDS 1-6)		T1D (ONWARDS 6)		T2D (ONWARDS 1-5)	
	N	Patient-Years	N	Patient-Years	N	Patient-Years
Total Exposure	2170	2119	290	300	1880	1819

- General safety data includes extension parts of ONWARDS 1 and ONWARDS 6

Overall Safety Profile of Insulin Icodec Similar to Well-Established Profile of Daily Basal Insulin

- No unexpected findings or unacceptable risks identified
- Majority of events non-serious, mild, and resolved
- Similar proportion of participants with T1D receiving insulin icodec and insulin degludec experienced:
  - AEs
  - Non-hypoglycemia related SAEs
  - AEs leading to discontinuation

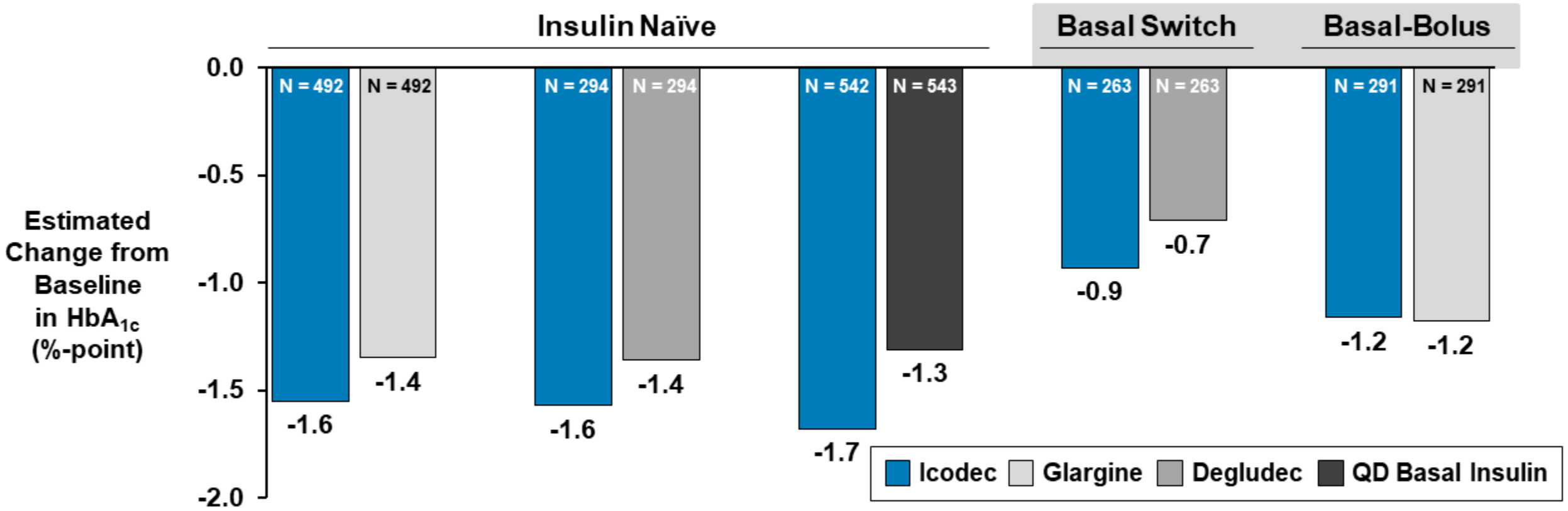
Efficacy and Hypoglycemia in Participants with Type 2 Diabetes

Roman Cailleteau, MD

Senior Medical Director

Novo Nordisk

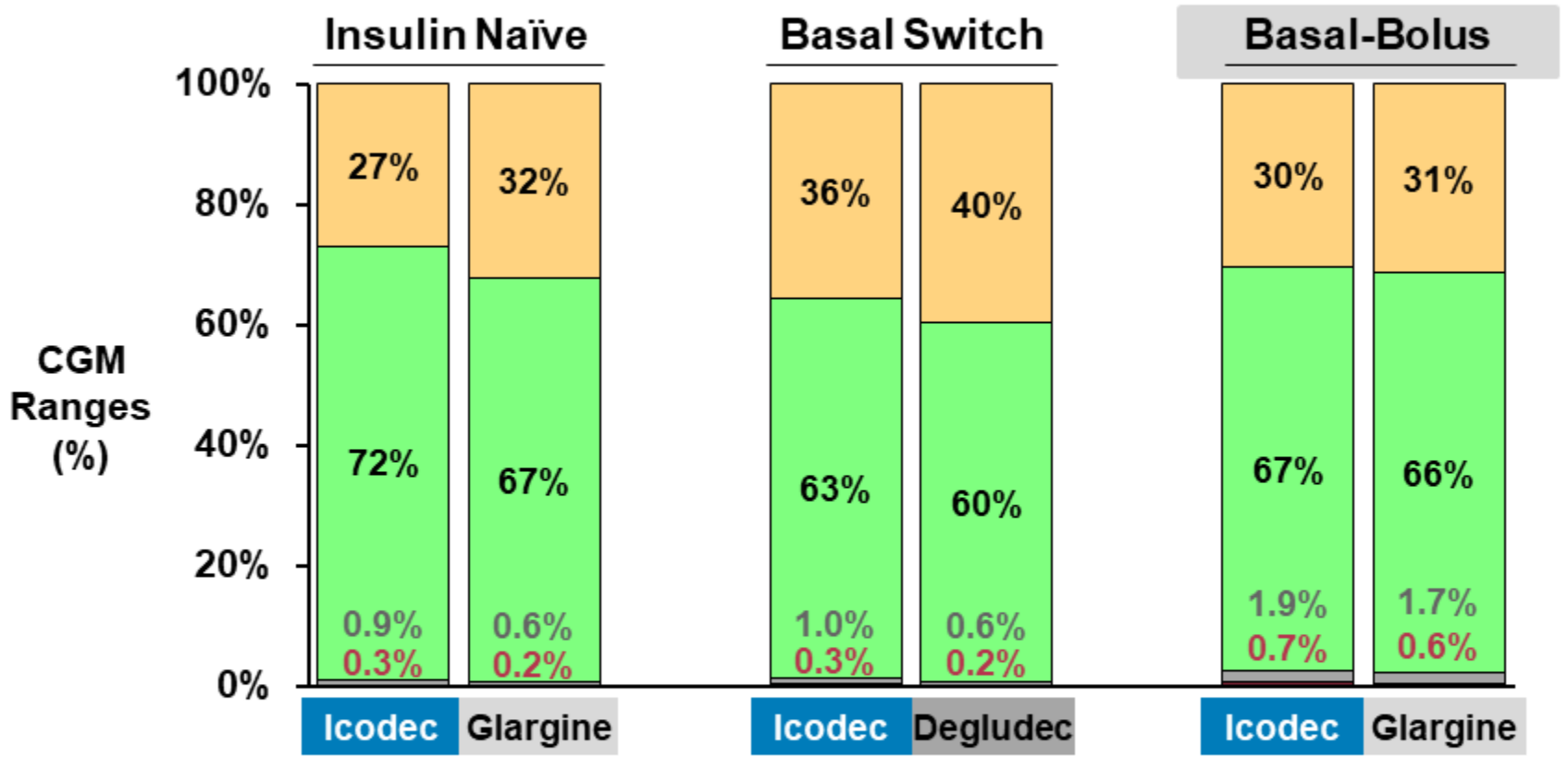
T2D: Weekly Insulin Icodec Non-Inferior to Daily Basal Insulin for Change in HbA_{1c} in All Studies



T2D Studies	ONWARDS 1	ONWARDS 3	ONWARDS 5*	ONWARDS 2	ONWARDS 4
Baseline HbA_{1c} (%)	8.47	8.52	8.92	8.13	8.30
Difference [95% CI]	**-0.19** [-0.36, -0.03]	**-0.21** [-0.34, -0.08]	**-0.38** [-0.66, -0.09]	**-0.22** [-0.37, -0.08]	**0.02** [-0.11, 0.15]
p-value Non-Inferiority	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
p-value Superiority	0.0210	0.0016	0.0092	0.0028	NA

*ONWARDS 5 participants receiving insulin icodec used an electronic dosing guide to assist with insulin icodec titration

T2D: Insulin Icodec had Better or Comparable Time in Target Glucose Range using CGM



T2D Studies	ONWARDS 1 (Weeks 48-52)	ONWARDS 2 (Weeks 22-26)	ONWARDS 4 (Weeks 22-26)
ETD_{TIR} [95% CI]	4.27%-point [1.92, 6.62]	2.41%-point [-0.84, 5.65]	0.29%-point [-2.52, 3.09]
p-value	0.0004		

Consensus Guidelines	Target Time in Range[1, 2]
TAR > 180 mg/dL	< 25%
TIR 70 – 180 mg/dL	> 70%
TBR 54 – 69 mg/dL	< 4%
TBR < 54 mg/dL	< 1%

TBR = Time below range. TIR = Time in range. TAR = Time above range. ETD = Estimated treatment difference

1. Battelino, Diabetes Care, 2019
2. Battelino, Lancet Diabetes & Endocrinology, 2022

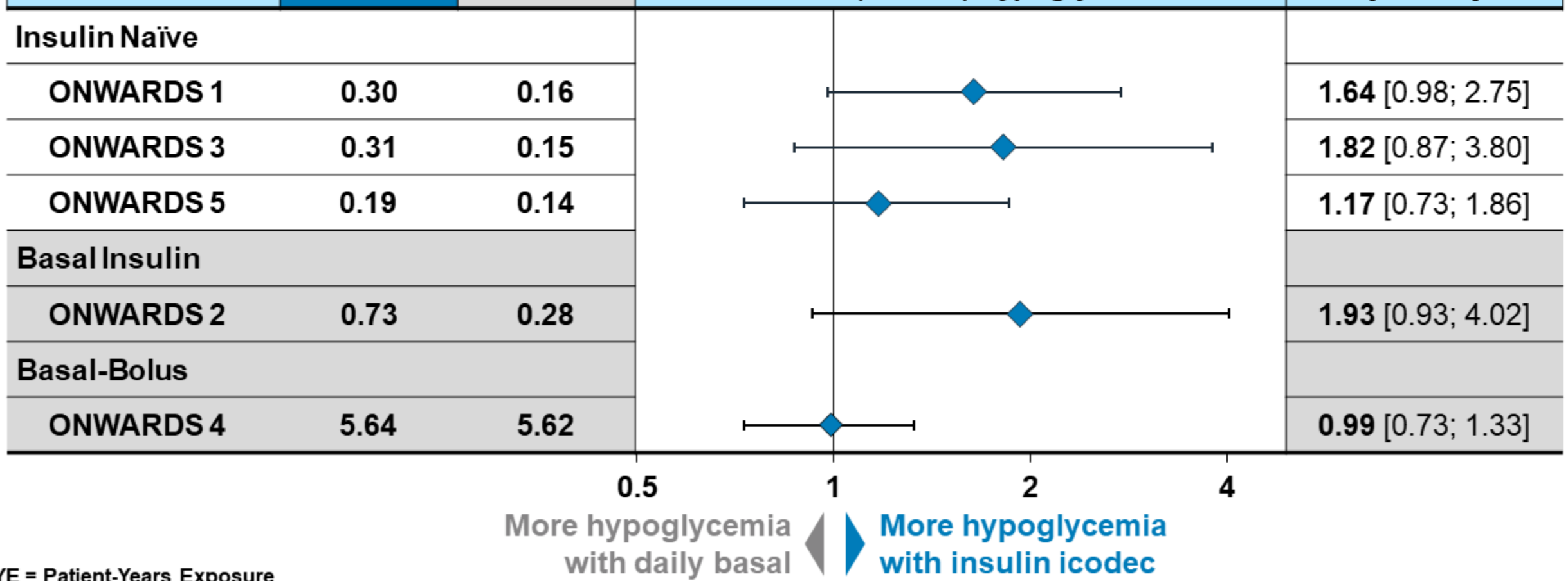
ONWARDS 1-5: Hypoglycemia Episodes in Participants with T2D

T2D: Proportion of Participants with Hypoglycemia

	Insulin Naïve						Basal Switch		Basal-Bolus	
	ONWARDS 1		ONWARDS 3		ONWARDS 5		ONWARDS 2		ONWARDS 4	
	Insulin Icodec N = 492	Daily Basal N = 492	Insulin Icodec N = 293	Daily Basal N = 294	Insulin Icodec N = 542	Daily Basal N = 538	Insulin Icodec N = 262	Daily Basal N = 263	Insulin Icodec N = 291	Daily Basal N = 291
Level 2 or 3	9.8%	10.6%	8.9%	6.1%	11.8%	8.4%	14.1%	7.2%	51.5%	55.7%
Level 2	9.8%	10.0%	8.9%	5.8%	11.8%	7.8%	14.1%	7.2%	50.9%	55.0%
Level 3	0.2%	0.6%	0	0.7%	0	0.7%	0	0.4%	1.4%	0.7%

T2D: Level 2 (Clinically Significant) or Level 3 (Severe) Hypoglycemic Event Rate

T2D	Episodes / 1 PYE: Insulin Icodec	Episodes / 1 PYE: Daily Basal	Level 2 (Clinically Significant) or Level 3 (Severe) Hypoglycemia	Estimated Rate Ratio [95% CI]
Insulin Naïve				
ONWARDS 1	0.30	0.16		**1.64** [0.98; 2.75]
ONWARDS 3	0.31	0.15		**1.82** [0.87; 3.80]
ONWARDS 5	0.19	0.14		**1.17** [0.73; 1.86]
Basal Insulin				
ONWARDS 2	0.73	0.28		**1.93** [0.93; 4.02]
Basal-Bolus				
ONWARDS 4	5.64	5.62		**0.99** [0.73; 1.33]



PYE = Patient-Years Exposure

Weekly Insulin Icodec Provides Safe and Effective Glycemic Control in People with Type 2 Diabetes

Efficacy

- Non-inferior to daily basal insulin for change in HbA_{1c}
- Glucose time in target range comparable to daily basal insulin
- HbA_{1c} reduction sustained 52 weeks

Hypoglycemia

- Low absolute rate of level 2 or level 3 episodes
- No excess of level 3 episodes with insulin icodec
- Management of episodes same as with daily basal insulin
- Titration algorithm allows for safe and efficacious dosing

Efficacy and Hypoglycemia in Participants with Type 1 Diabetes

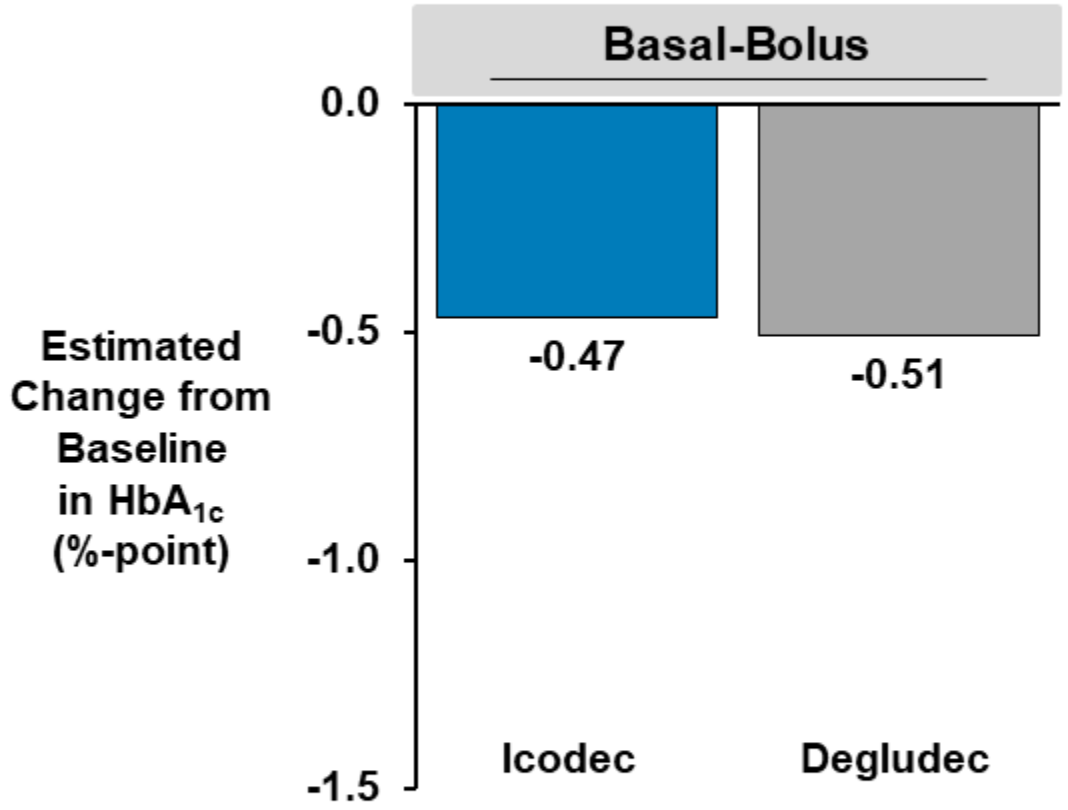
Stephen Gough, MD, FRCP

Global Chief Medical Officer, Senior Vice President

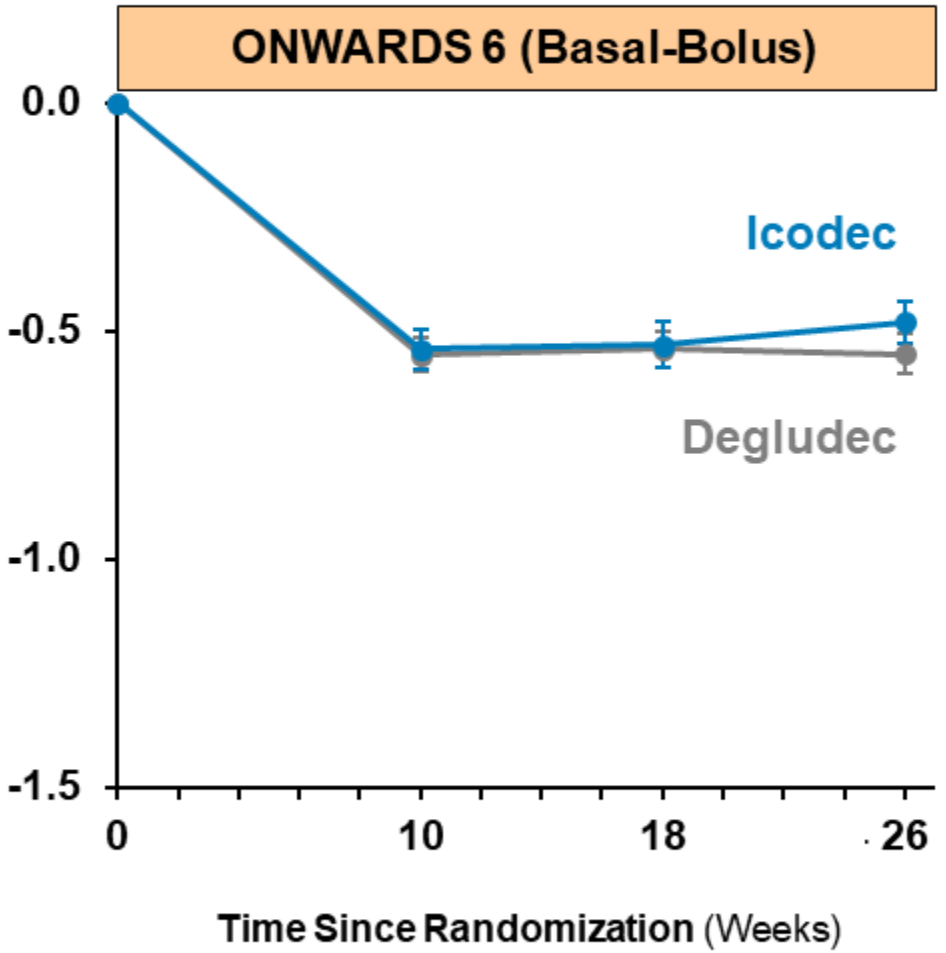
Novo Nordisk

ONWARDS 6: Efficacy Results in Participants with T1D

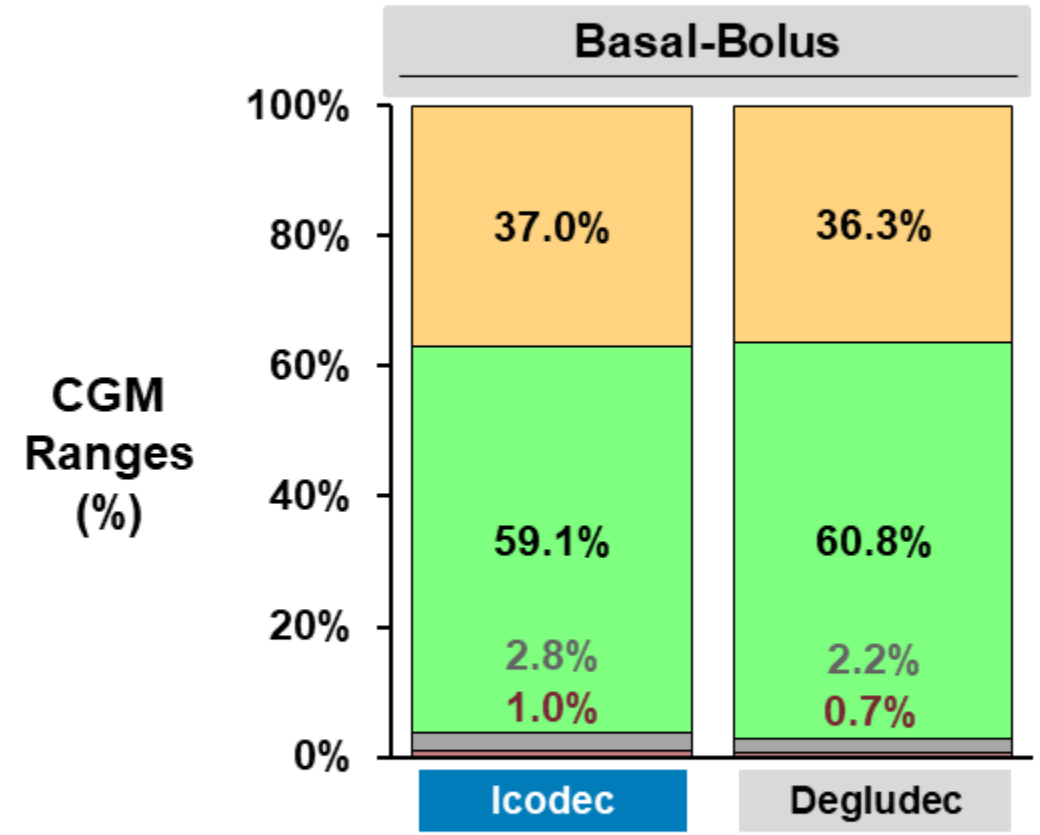
T1D: Weekly Insulin Icodec Achieved Non-Inferiority to Daily Insulin Degludec



T1D Study	ONWARDS 6
Baseline HbA_{1c} (%)	7.6
Difference [95% CI]	0.05 [-0.13, 0.23]
p-value Non-Inferiority	0.0065



T1D: Time in Target Glucose Range using CGM Comparable Between Treatment Groups



T1D Study	ONWARDS 6 (Week 22-26)
ETD_{TIR} [95% CI]	-2.00%-point [-4.38;0.38]

TAR > 180 mg/dL

TIR 70 – 180 mg/dL

TBR 54 – 69 mg/dL

TBR < 54 mg/dL

Consensus Guidelines

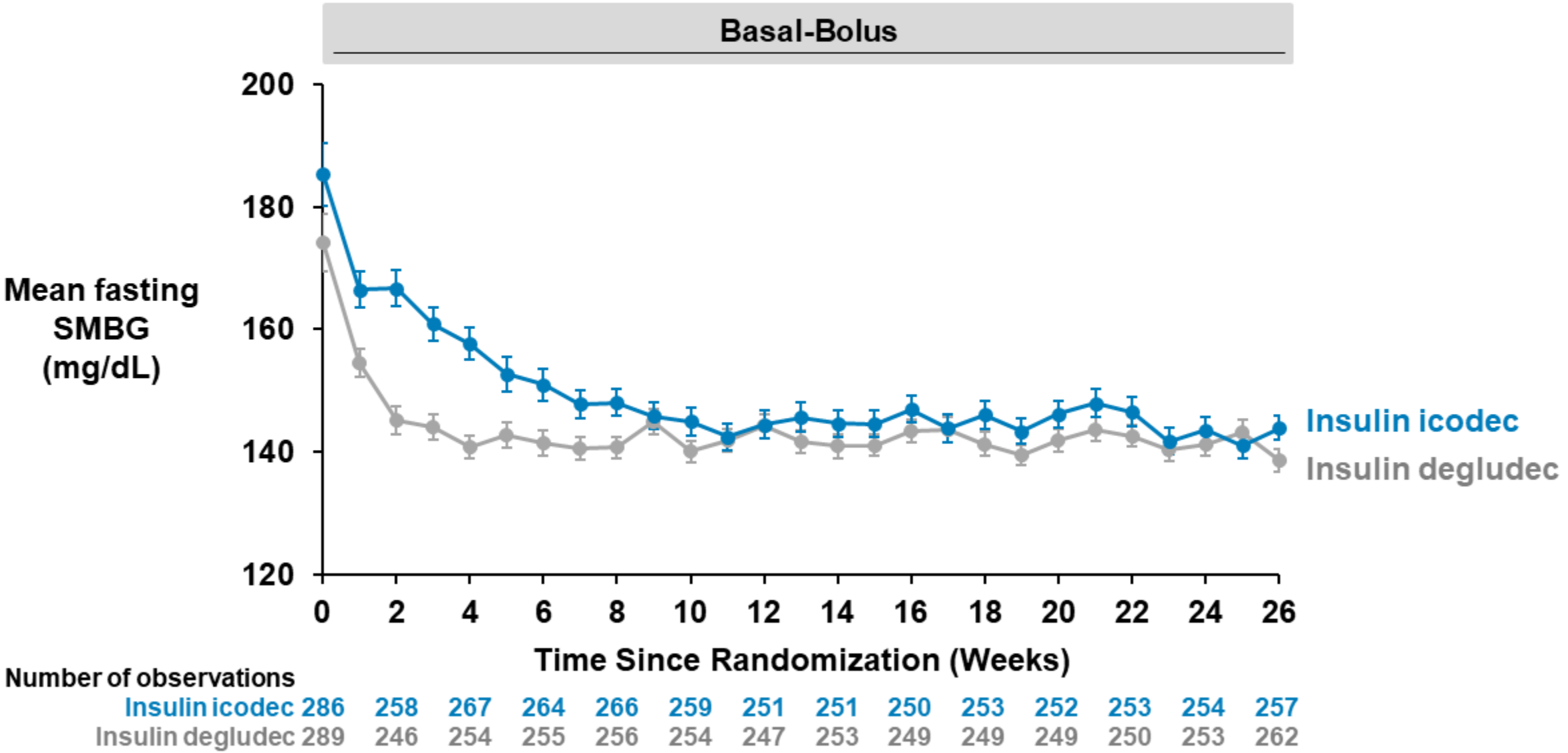
Target Time in Range[1, 2]

TAR	< 25%
TIR	> 70%
TBR 54 – 69 mg/dL	< 4%
TBR < 54 mg/dL	< 1%

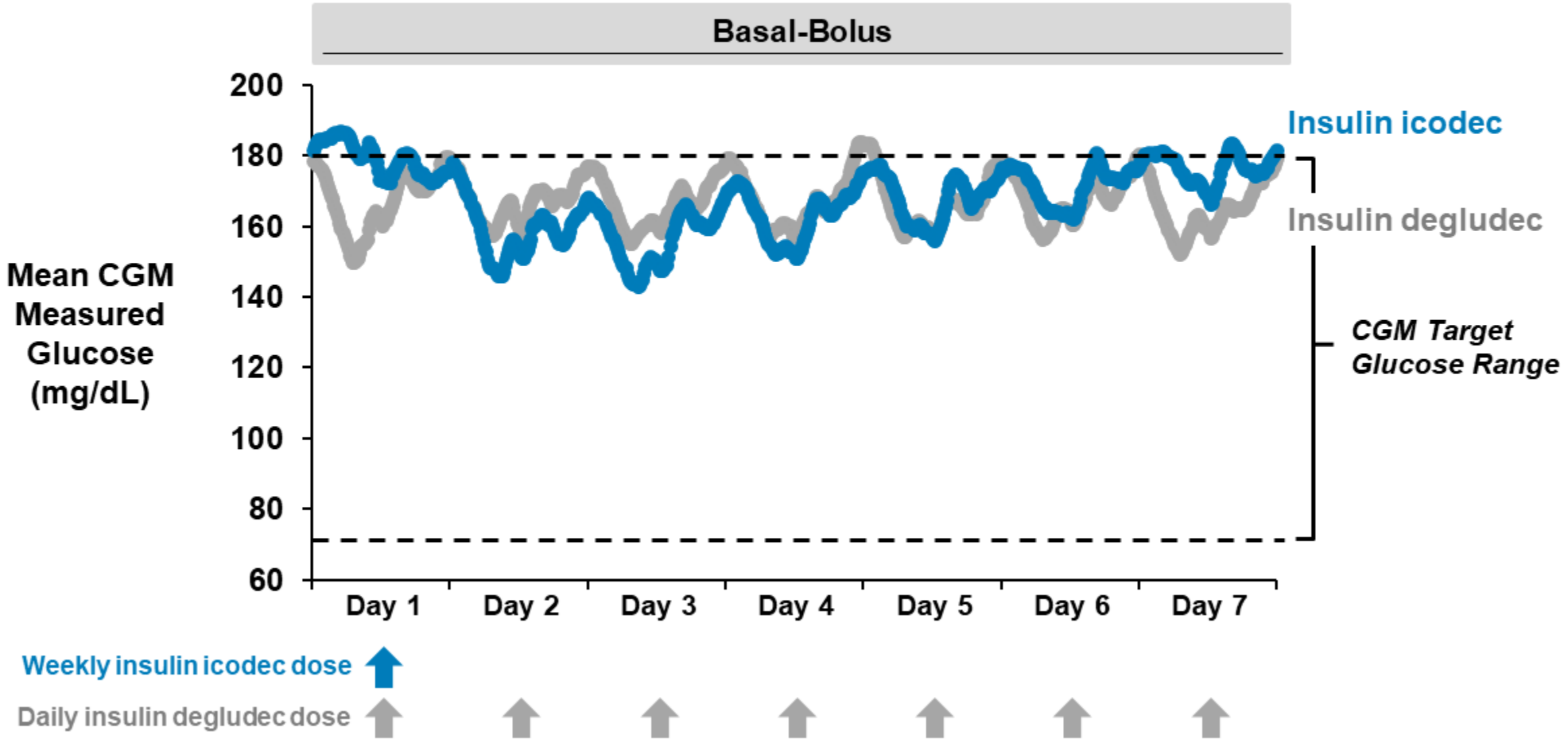
TBR = Time below range. TIR = Time in range. TAR = Time above range. ETD = Estimated treatment difference

1. Battelino, Diabetes Care, 2019
2. Battelino, Lancet Diabetes & Endocrinology, 2022

T1D: Change in Fasting SMBG Demonstrates Insulin Icodec Dosing Algorithm is Effective



T1D: Fluctuations in CGM Measured Glucose Over the Week



Mean CGM within a week summarized for week 22-26

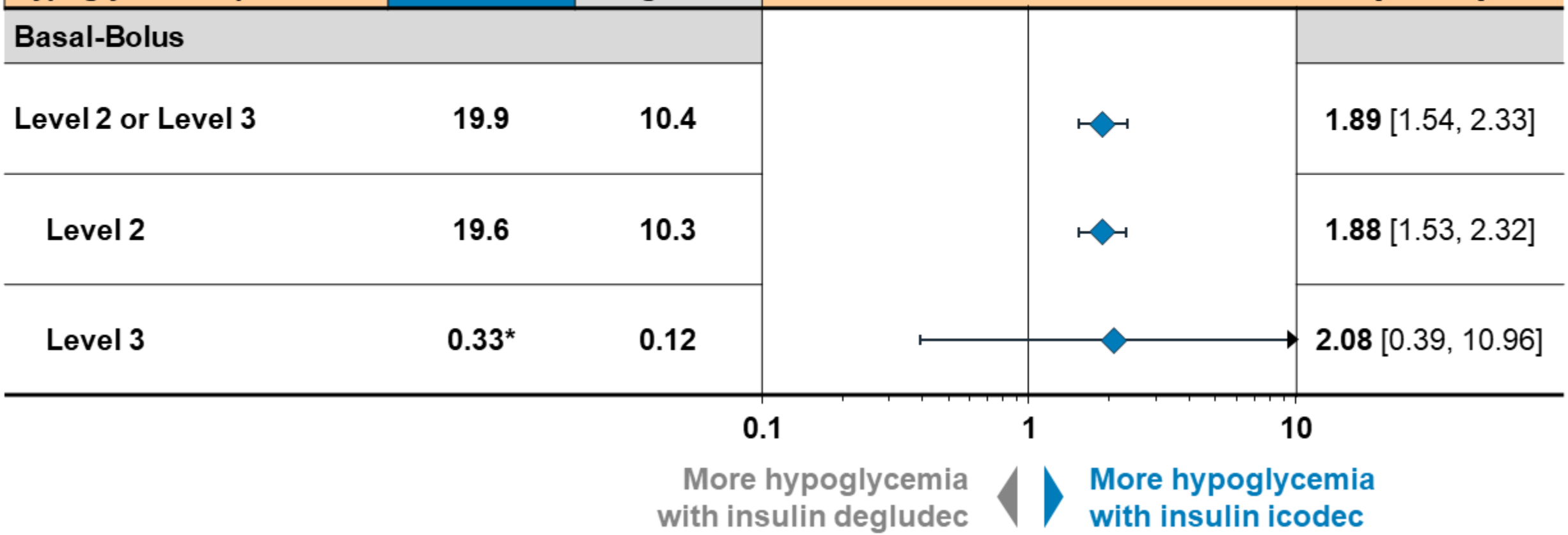
ONWARDS 6: Hypoglycemia Episodes in Participants with T1D

T1D: Proportion of Participants with Hypoglycemia

ONWARDS 6	Insulin Icodec N = 290	Insulin Degludec N = 292
Level 1	99%	98%
Level 2	85%	76%
Level 3	3%	3%

T1D: Level 3 (Severe) or Level 2 (Clinically Significant) Hypoglycemic Event Rate

ONWARDS 6 Hypoglycemia Episodes	Episodes / 1 PYE		Estimated Rate Ratio [95% CI]
	Insulin Icodec	Insulin Degludec	
Basal-Bolus			
Level 2 or Level 3	19.9	10.4	**1.89** [1.54, 2.33]
Level 2	19.6	10.3	**1.88** [1.53, 2.32]
Level 3	0.33*	0.12	**2.08** [0.39, 10.96]



PYE = Patient years of exposure

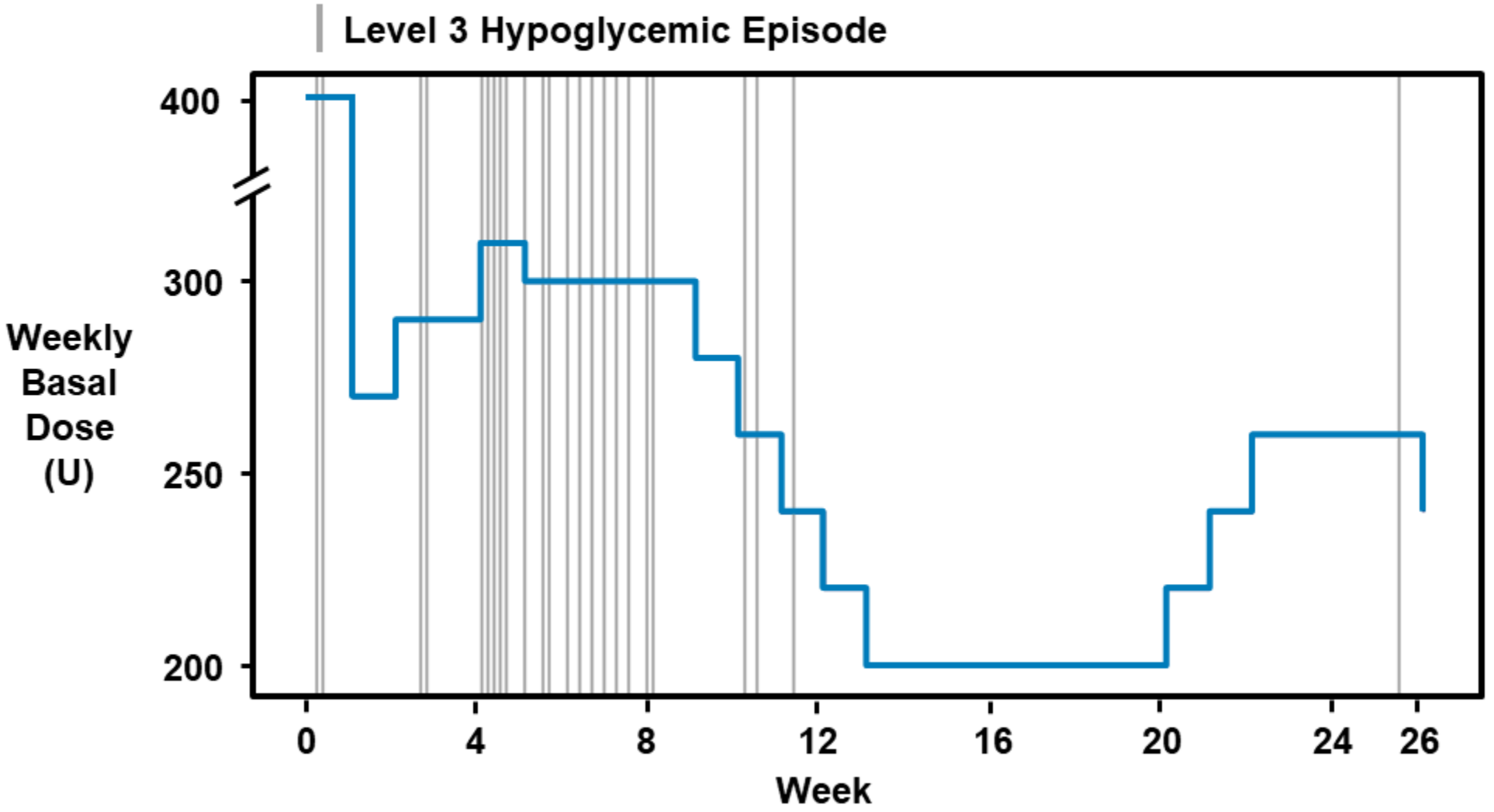
* Includes single participant who experienced 33 of 47 (70%) total level 3 hypoglycemic episodes

T1D: Recurrent Level 3 (Severe) Hypoglycemic Episodes

ONWARDS 6	Insulin Icodec N = 290	Insulin Degludec N = 292
Level 3, % (n)		
No Episodes	**96.9%** (281)	**96.9%** (283)
1 – 2 Episodes	**2.1%** (6)	**2.4%** (7)
3 – 4 Episodes	**0.7%** (2)	**0.3%** (1)
≥ 5 Episodes	**0.3%** (1)*	**0.3%** (1)

*Single participant experienced 33 of 47 (70%) total level 3 hypoglycemic episodes

T1D: Weekly Insulin Icodec Dose in Participant with 33 Level 3 Hypoglycemic Episodes



Female

26 years old

Diabetes duration: 5.7 years

Baseline HbA_{1c}: 6.7%

Lifestyle change: 5% weight loss

Glycemic Variability: %CV = 40.3%

- Participant also had 5 level 2 hypoglycemic episodes

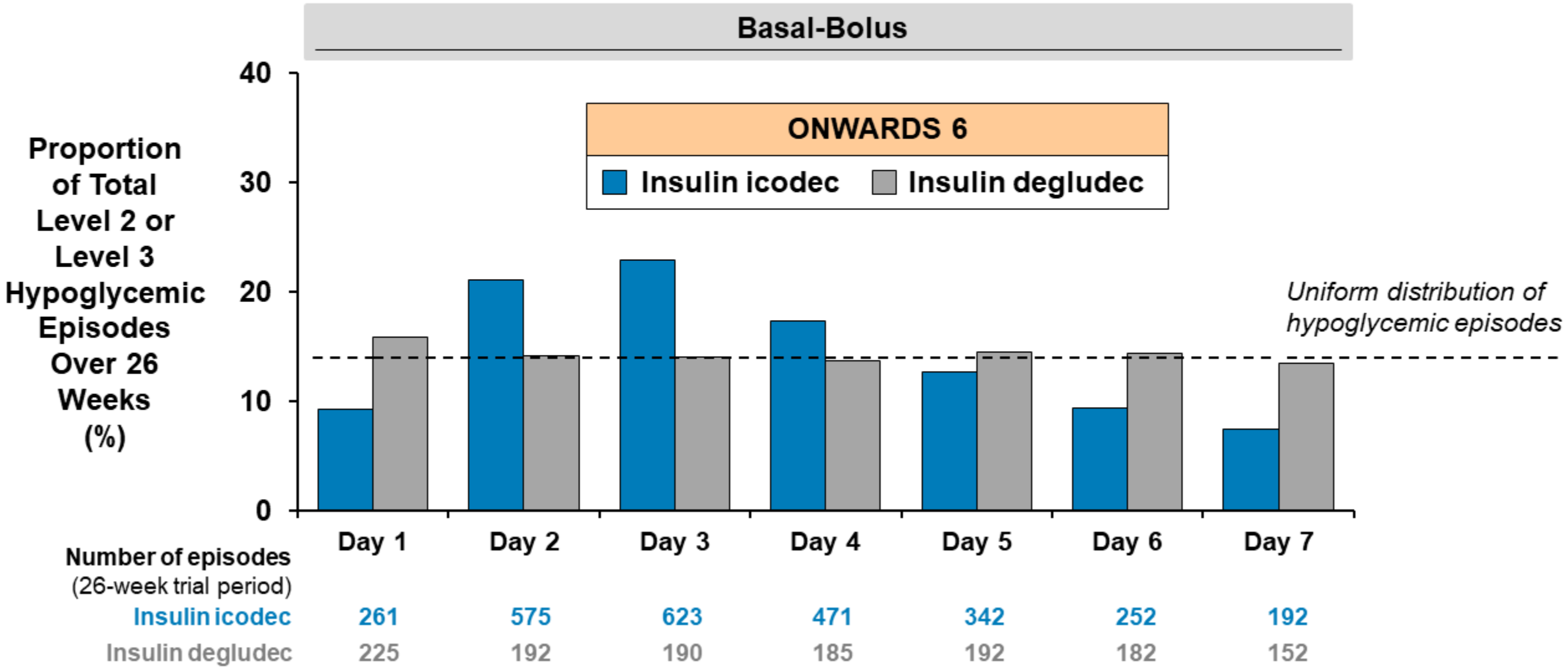
T1D: Management of Severe Hypoglycemic Episodes was Similar with Insulin Icodec and Insulin Degludec

ONWARDS 6		Insulin Icodec			Insulin Degludec		
		N	Episodes	% of Episodes	N	Episodes	% of Episodes
Severe (level 3) episodes		9	47	100%	9	17	100%
Medical Assistance	Yes	6	8	17%	3	3	18%
	Yes in Clinic/ER/Hospital	4	5	11%	2	2	12%
Treatments received	Eat or drink only	6	39	83%	7	13	76%
	Glucagon	2	3	6%	0		
	IV glucose	4	5	11%	2	2	12%

- Same instructions for management of hypoglycemic episodes provided to all participants

The same participant could be reported in more than one category if different episodes from the same participant fell in different categories.

T1D: Higher Proportion of Level 2 or Level 3 Hypoglycemic Episodes on Day 2-4 as Predicted by PD



Number of episodes (26-week trial period)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Insulin icodec	261	575	623	471	342	252	192
Insulin degludec	225	192	190	185	192	182	152

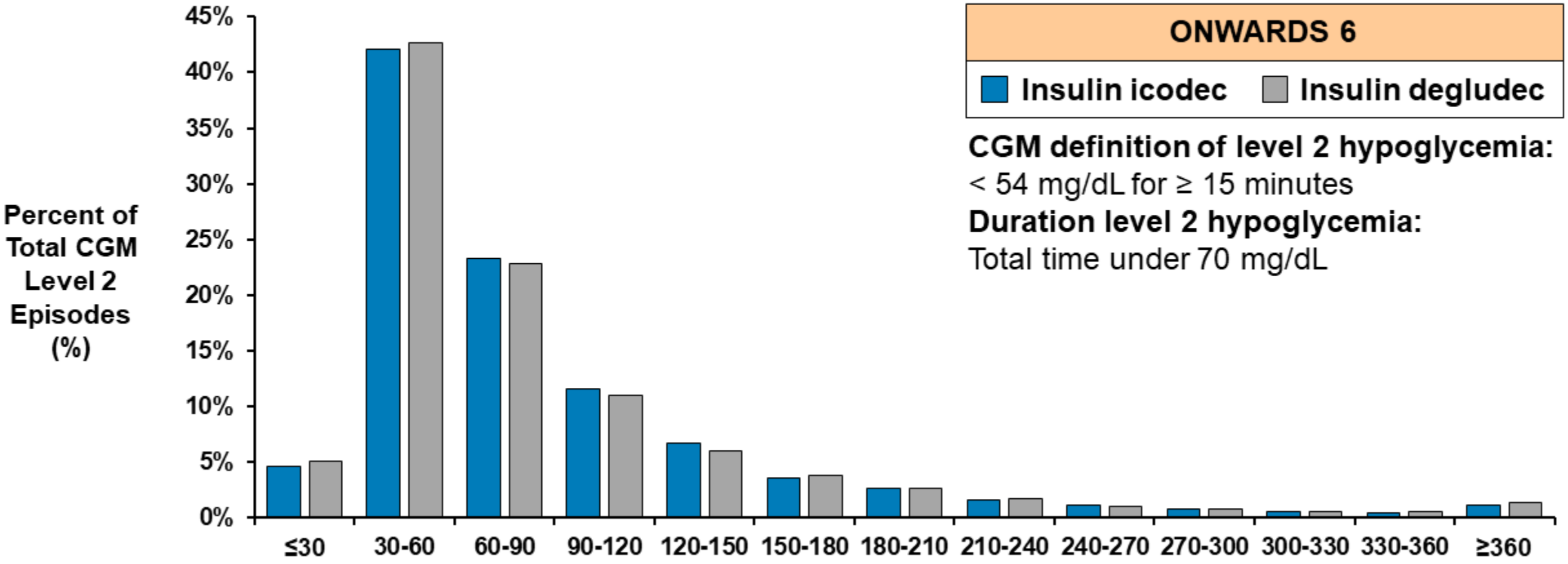
PD = Pharmacodynamics

T1D: Reassuring Rate Ratio of Level 2 (Clinically Significant) Hypoglycemic Episodes Based on CGM

ONWARDS 6	Episodes / 1 PYE		Estimated Rate Ratio [95% CI]
	Insulin Icodec	Insulin Degludec	
Basal-Bolus			
Self-monitored blood glucose (SMBG)	19.6	10.3	**1.88** [1.53, 2.32]
Continuous glucose monitoring (CGM)	105.6	74.6	**1.38** [1.17, 1.62]

PYE = Patient years of exposure

T1D: Data Show Comparable Duration of CGM Level 2 Hypoglycemia with Insulin Icodec and Insulin Degludec

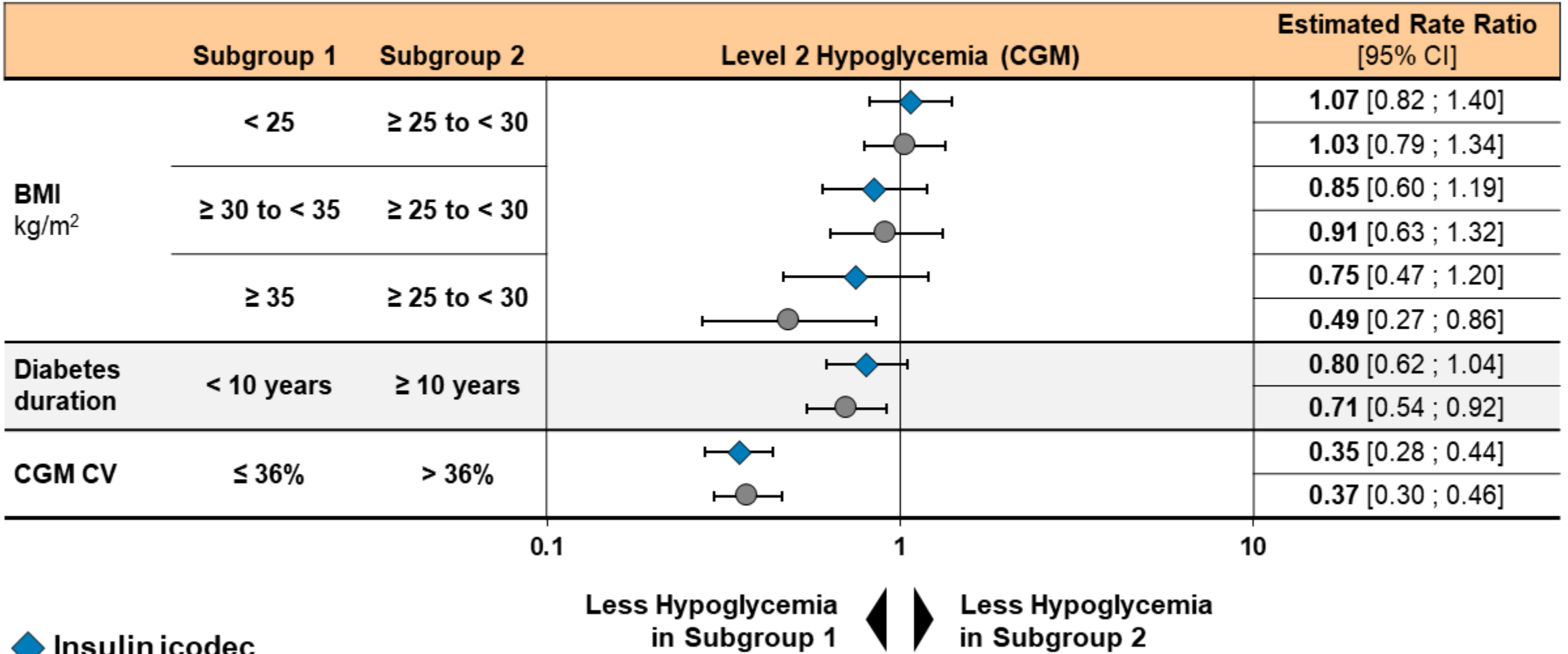


Number of episodes (26-week trial period)	≤30	30-60	60-90	90-120	120-150	150-180	180-210	210-240	240-270	270-300	300-330	330-360	≥360
Insulin icodec	639	5840	3227	1612	923	499	364	214	159	106	75	62	163
Insulin degludec	511	4246	2278	1100	599	374	259	165	105	80	50	59	139

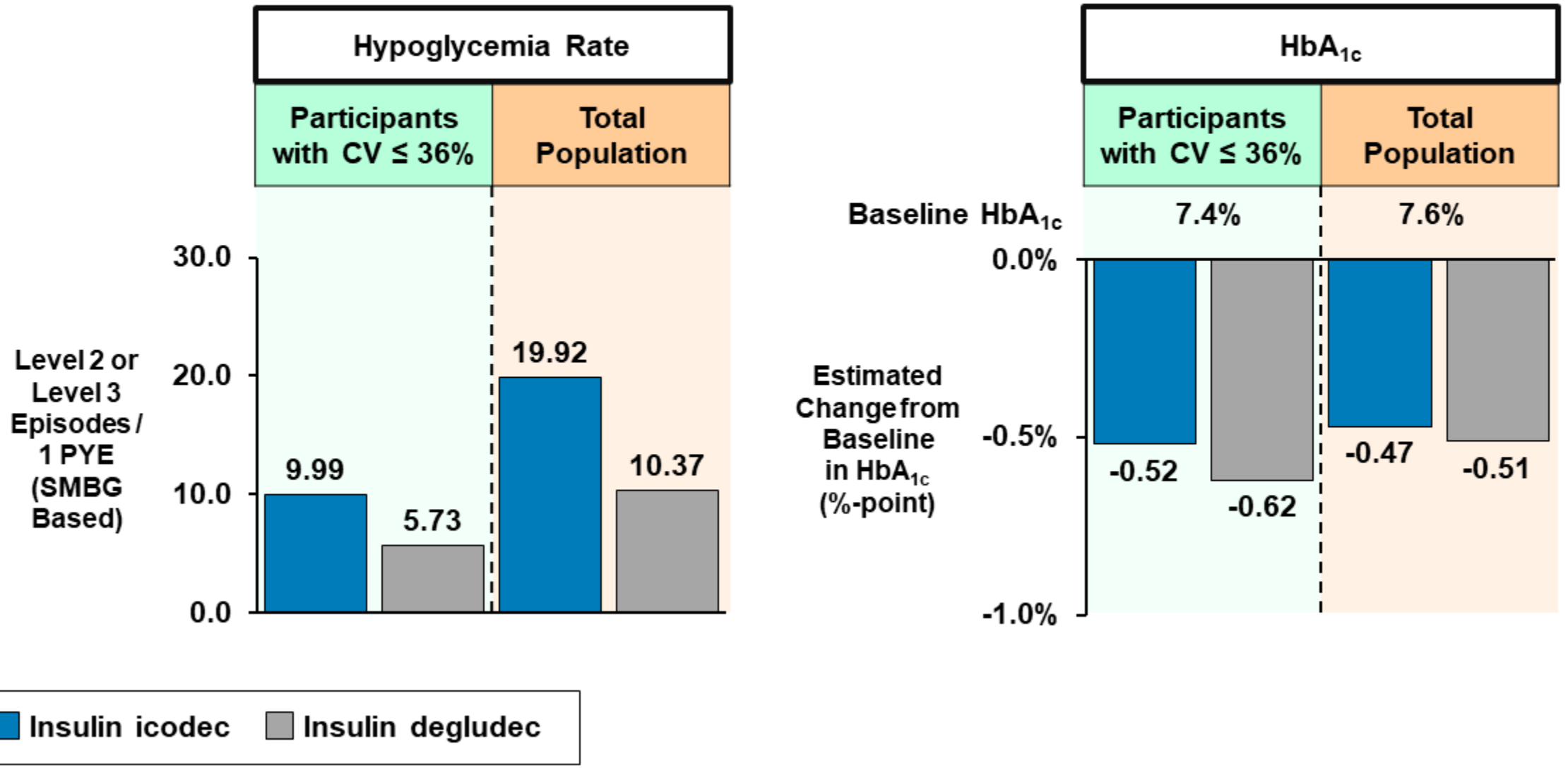
T1D: No Participant Characteristics Predict for Difference in Relative Hypoglycemia Risk with Insulin Icodec

- Comprehensive assessment evaluated characteristics that might identify participants with lower hypoglycemia risk
- Considered role of participant characteristics in individualizing treatment
- No subgroups identified with differential benefit-risk profile for insulin icodec

T1D: Characteristics Associated with Reduced Hypoglycemia Risk Consistent with Other Insulins



T1D: Lower Hypoglycemia Rates and Maintained Efficacy for Participants with Low Glycemic Variability



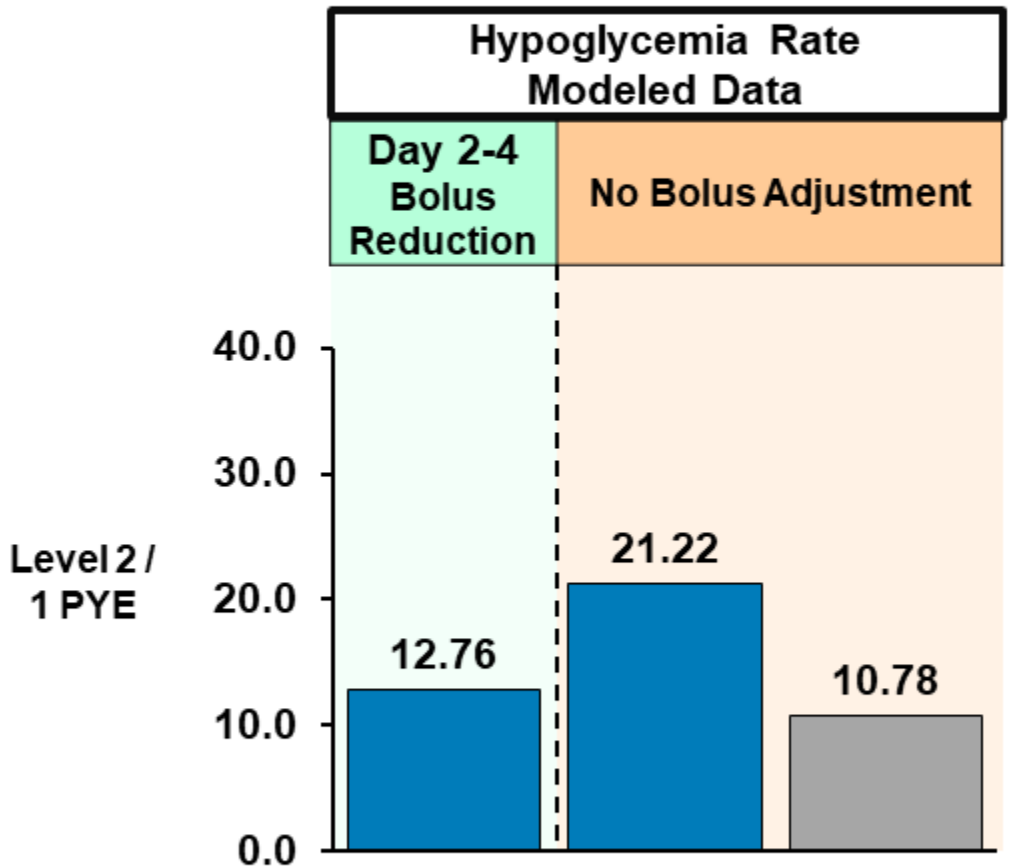
PYE = patient years exposure

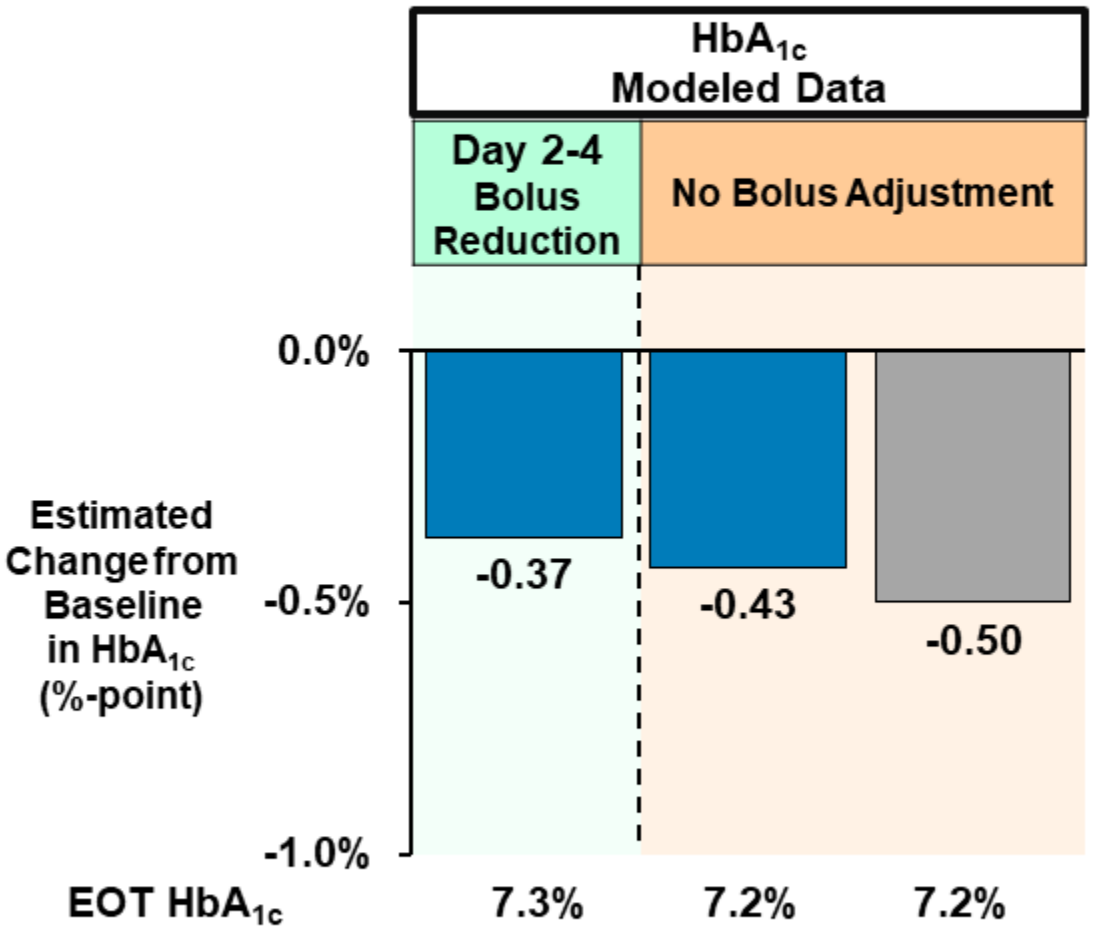
T1D: Modeling Explored as Opportunity to Inform Further Individualization of Dosing Regimen

- ONWARDS 6 established dosing regimen can be used safely and effectively
- PD profile of insulin icodec suggests bolus adjustment may optimize benefit-risk for some people
- Modeling used to estimate effects of bolus insulin adjustment
  - Contributes to participant and healthcare professional education

PD = Pharmacodynamics

T1D: Lower Predicted Hypoglycemia Rates when Bolus Insulin Adjusted to PD Profile (Modeled Data)





Insulin icodec Insulin degludec

Model predictions of HbA_{1c}, HbA_{1c} change-from-baseline, level 2 hypoglycemia rate per PYE, for alternative titration approaches with bolus insulin compared to titration approach used in ONWARDS 6. Insulin icodec titrated as in ONWARDS 6. Results based on 100 repeated simulations per scenario. N = 290 insulin icodec. N = 292 insulin degludec. PYE: Patient years of exposure. EOT: End of treatment.

PD = Pharmacodynamics

Hypoglycemia Risk Factors Not Unique to Insulin Icodec but May Guide Treatment Individualization

- Risk factors same for weekly insulin icodec and daily insulin degludec
- Knowledge of risk factors and insulin icodec PD profile aids treatment individualization
- Potential actions that may lower hypoglycemia rates
  - Apply insights from CGM variability
  - Adjust bolus insulin dose if needed

PD = Pharmacodynamics

T1D: Positive Benefit-Risk with Weekly Insulin Icodec, Providing Safe and Effective Glycemic Control

Efficacy

- Non-inferior to insulin degludec for change in HbA_{1c}
- HbA_{1c} reduction sustained through end of treatment
- CGM time in range not clinically different from insulin degludec

Hypoglycemia

- Higher rate of level 2 or level 3 episodes with insulin icodec
- Duration and management similar to that of insulin degludec
- Recognized risk factors and insulin icodec PD impact risk of hypoglycemia
  - Known strategies can be applied for insulin icodec to mitigate risk of hypoglycemia

PD = Pharmacodynamics

Clinical Perspective

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Professor of Medicine

Department of Internal Medicine/Endocrinology

UT Southwestern Medical Center, Dallas, TX

Insulin Icodec in Type 2 Diabetes – Favorable Benefit-Risk Balance

- Expected improvement in glucose levels
- No difference in level 3 hypoglycemia
- Small imbalance in level 2 hypoglycemia
  - One extra level 2 hypoglycemia episode every 6 years or longer in treatment naïve population
- No safety findings

Insulin Icodec in Type 1 Diabetes – Hypoglycemia Mitigation

Higher rate of hypoglycemia compared to insulin degludec

Hypoglycemia Prevention

- Risk factors → patient selection
  - Example: glycemic variability
- Timing → anticipatory treatment adjustments
  - Example: bolus insulin reduction on days 2-4 after injection

Hypoglycemia Management

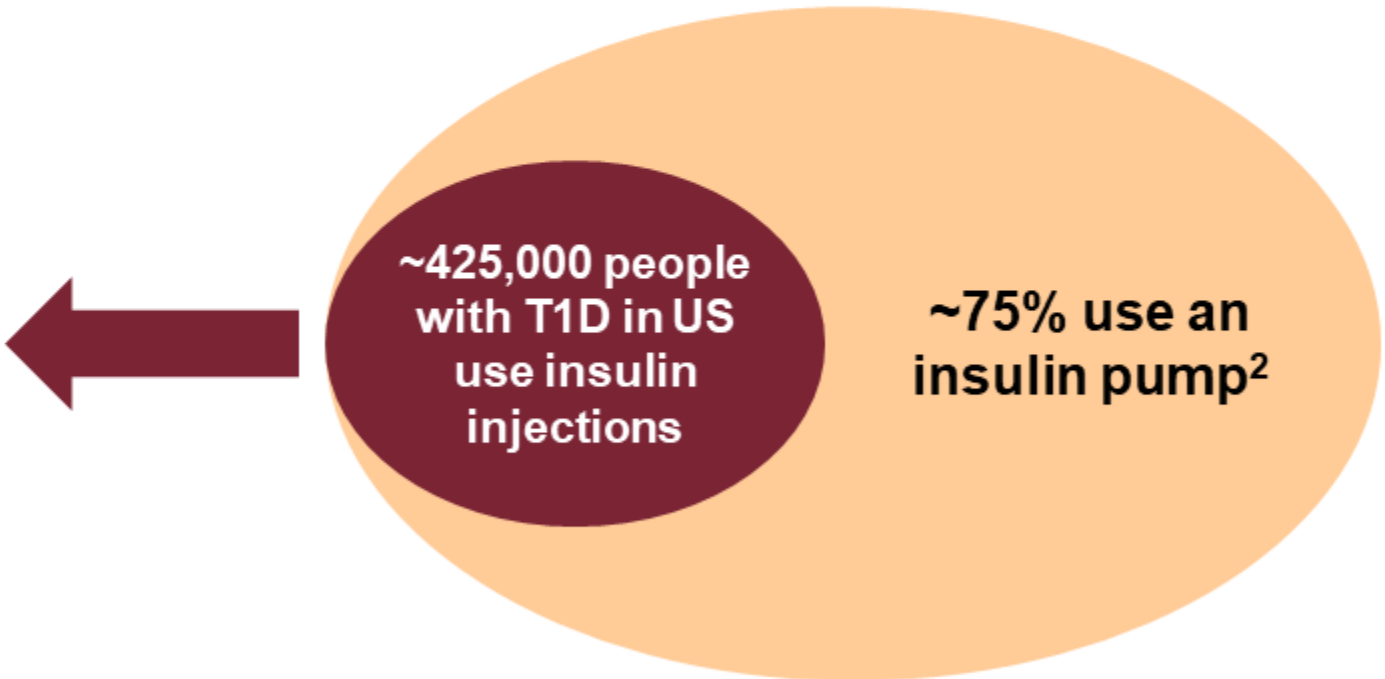
- Same duration
- Same treatment
- Individualized treatment adjustments
  - Example: CGM guided

Insulin Icodec in Type 1 Diabetes – Patient Selection

Unique populations who might benefit from weekly insulin

- Low therapy adherence
- Recurrent DKA
- Rely on caregivers
- Living in care facility
- Find insulin burdensome
- Unpredictable daily schedules
- Young adults
- Shift workers

~1.7 Million
people with Type 1 Diabetes in the US[1]

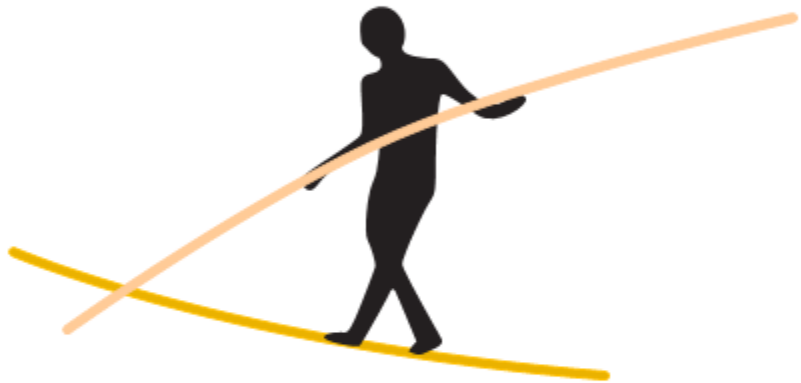


1. National Diabetes Statistics Report | Diabetes | CDC; 2. Type 1 Diabetes Exchange https://t1dexchange.org; estimate from 2017-2020

Insulin Icodec in Type 1 Diabetes – Balancing Benefits and Risks

Treatment Individualization

↑ adherence
↑ convenience
↓ treatment burden



↑ hypoglycemia

Examples of treatment adjustments made to mitigate hypoglycemia:

- Alter titration frequency or increments
- Decrease insulin dose
- Relax glycemic target
- Split insulin dose
- Alter daily bolus insulin coverage
- Switching to different insulin

Insulin Icodec: Clinician Perspective

Ideal for MOST People with Type 2 Diabetes

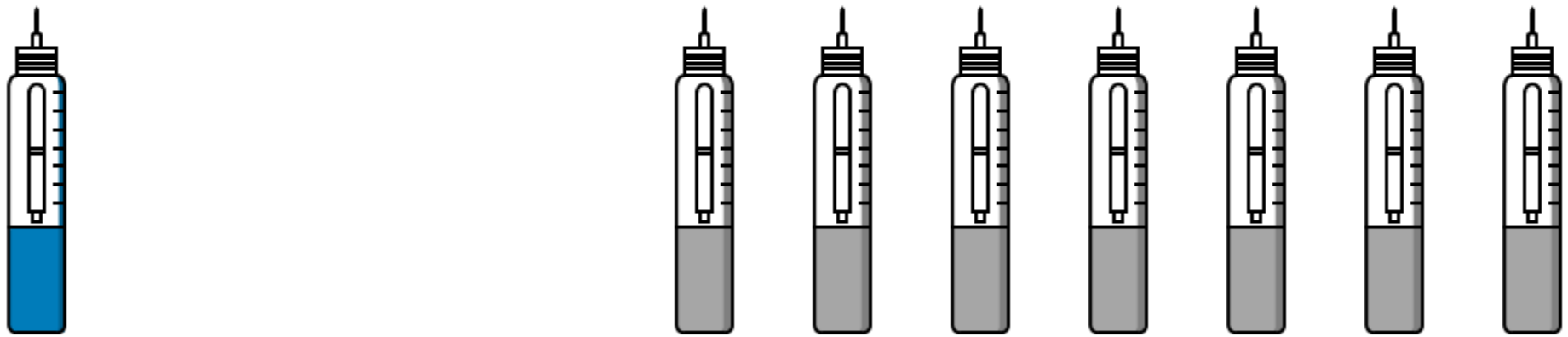
- People requiring basal insulin

Ideal for SOME People with Type 1 Diabetes

- People using basal insulin injections
- Without high risk for hypoglycemia

Insulin Icodec Reduces Treatment Burden

Once-weekly Insulin Icodec VS **Daily Basal Insulin**



✓ **313 fewer injections a year**

Conclusion

Stephen Gough, MD, FRCP

Global Chief Medical Officer, Senior Vice President

Novo Nordisk

T2D: Benefits of Once-Weekly Insulin Icodec Outweigh Potential Risks

	T2D (ONWARDS 1-5)
Once-weekly insulin icodec non-inferior to daily basal insulin for change in HbA_{1c}	✓
Reductions in HbA_{1c} and glucose sustained within target ranges	✓
Safety profile similar to well-established profile of daily basal insulin	✓
Low absolute event rates of hypoglycemic episodes	✓

T1D: Once-Weekly Insulin Icodec is Effective and Can be Safely Used

	T1D (ONWARDS 6)
Once-weekly insulin icodec non-inferior to insulin degludec for change in HbA_{1c}	✓
Reductions in HbA_{1c} and glucose sustained within target ranges	✓
General safety profile similar to insulin degludec	✓
Higher hypoglycemia risk is manageable and can be mitigated	✓

Hypoglycemia Risk Mitigated and Managed as with Current Insulin Products

Frequency	▪ Higher rate of level 2 or level 3 episodes with insulin icodec ▪ Same proportion of participants with level 3 episodes in both groups
Duration	▪ Duration of hypoglycemia similar to that of insulin degludec
Management	▪ Management of episodes same with insulin icodec and insulin degludec
Subgroups	▪ No identifiable subgroup at differential relative hypoglycemia risk with insulin icodec vs insulin degludec

T1D: Strategies to Lessen Hypoglycemia Risk and Enhance Benefit-Risk of Insulin Icodec

- Selection of individuals who could benefit from once-weekly insulin icodec
  - Limitation of use to exclude people with hypoglycemic unawareness or recurrent severe hypoglycemia
- Create awareness via label and support materials
  - Information on increased hypoglycemia risk during Days 2-4 to guide weekly bolus insulin dosing for some patients
  - Recommend CGM use to inform dose decisions
- Clinicians individualize care
- Collaborate with FDA based on Committees insights

Insulin icodec offers a valuable treatment option for people living with T1D

Insulin Icodec: Once-Weekly Basal Insulin for Treatment of Adults with Diabetes Mellitus

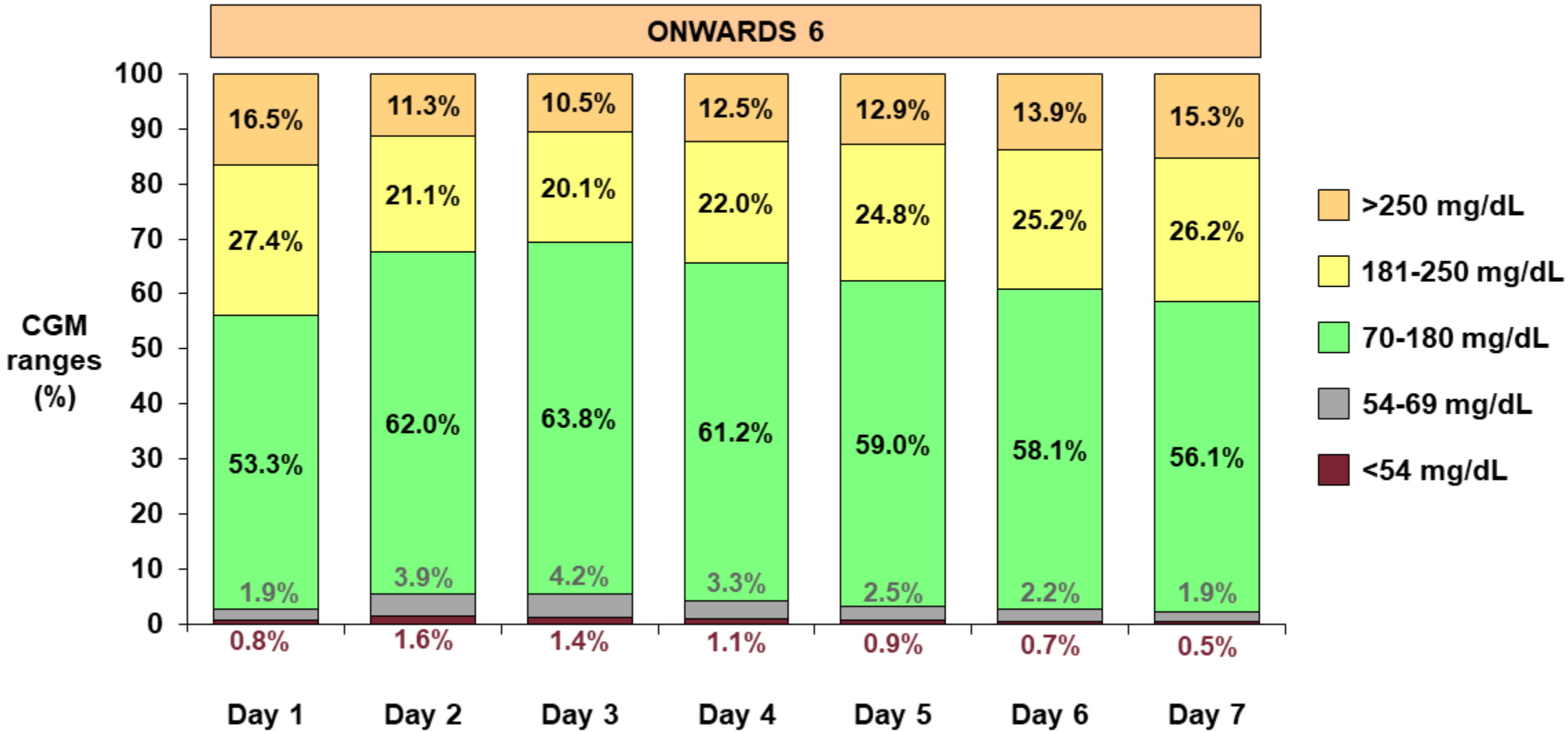
Novo Nordisk

Endocrinologic and Metabolic Drugs Advisory Committee

May 24, 2024

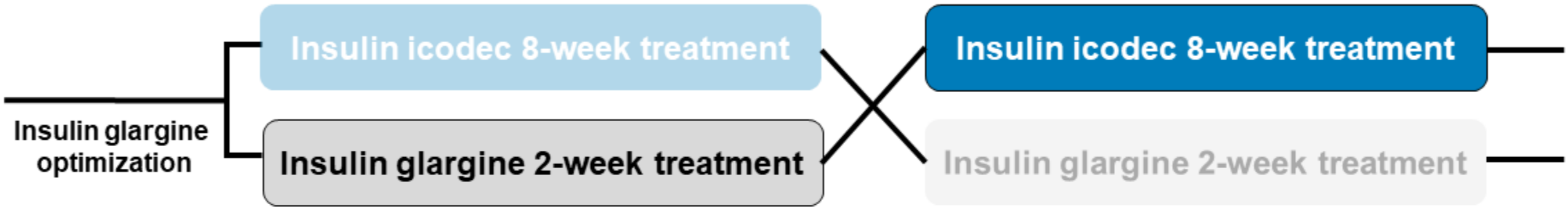
BACK-UP SLIDES SHOWN

T1D: Higher Time Below and Time in Range With Insulin Icodec on Days 2-4



Based on data from week 22 to week 26. CGM: Continuous glucose monitoring; T1D: Type 1 diabetes.

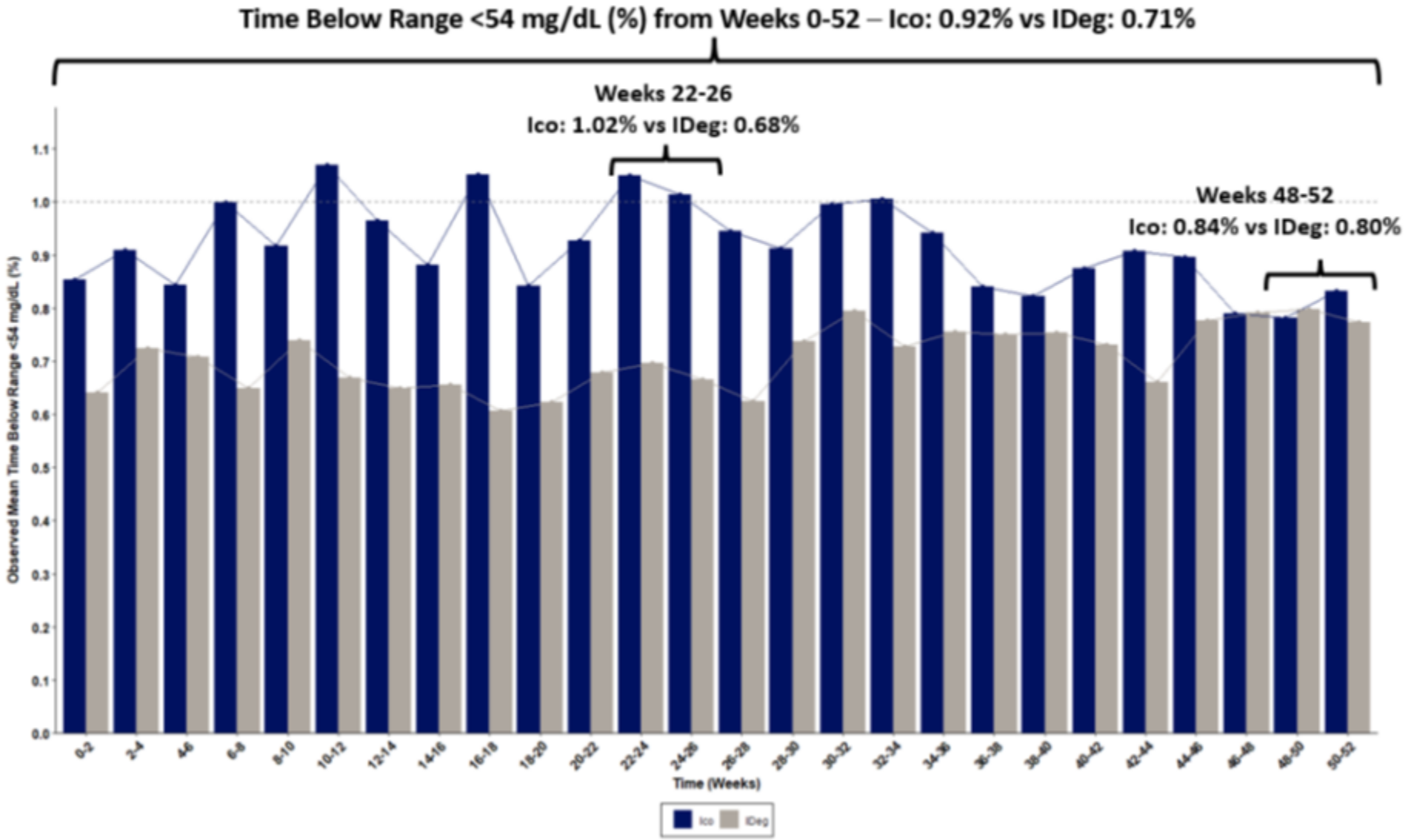
T1D: %CV was Stable Before and After Switch to Insulin Icodec (Phase 1 Trial)



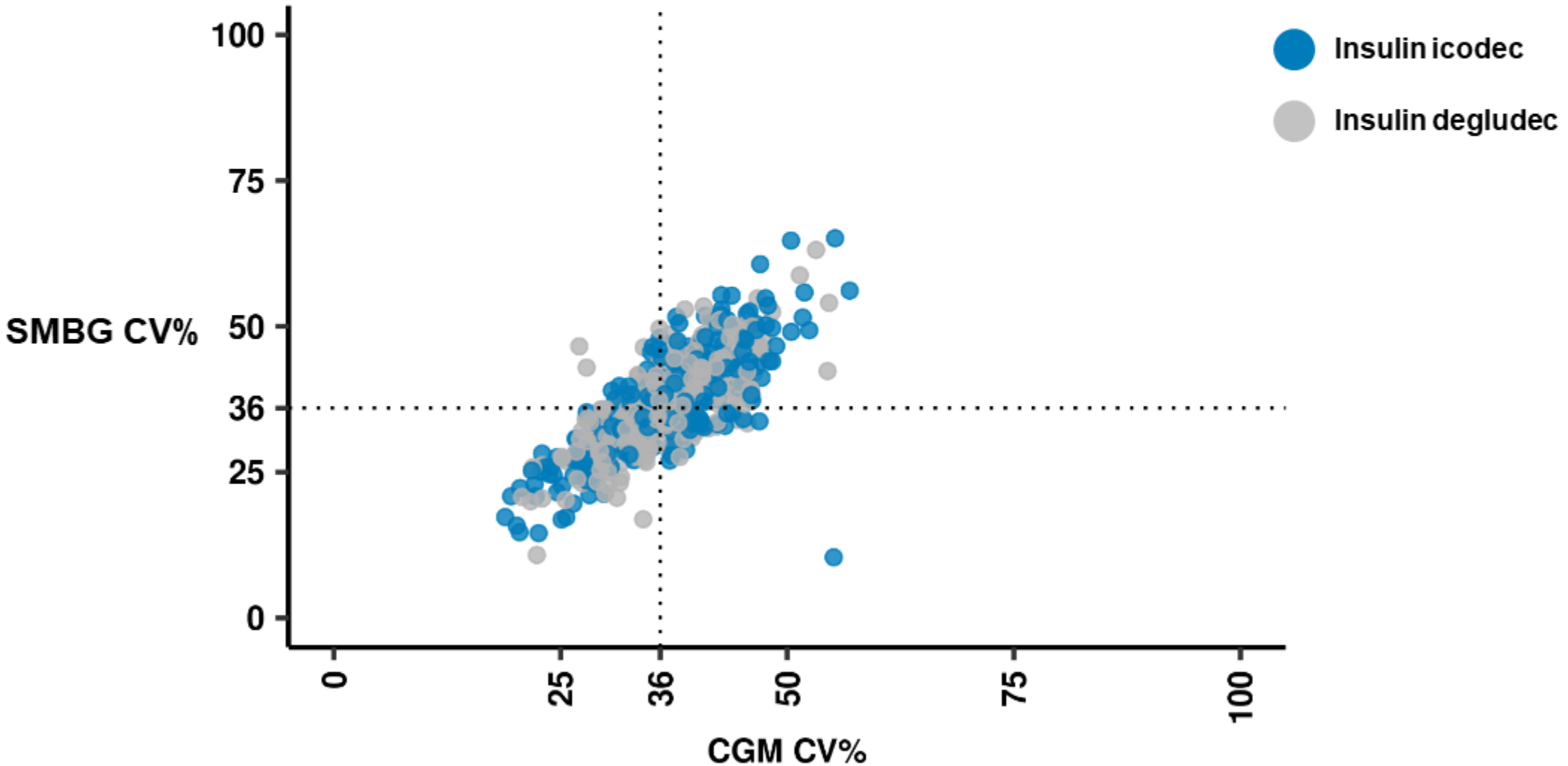
Trial 4225 (phase 1 dose response trial)	Insulin glargine		Insulin icodec (first 14 days)	
	N	Mean (SD)	N	Mean (SD)
CGM CV%	28	35.76 (4.23)	27	35.86 (4.27)

Study 4225. CGM CV% group for the first two weeks of glargine and icodec treatment, respectively (treatment arm B).
CGM: Continuous glucose monitoring; CV: Coefficient of variation; N: number of participants; SD: Standard deviation.

Figure 7. Time Below Range <54 mg/dL (%)—ONWARDS 6 (FAS)



T1D: Strong Correlation Between %CV-Grouping Based on CGM-Measured Glucose or 4-point SMBG



Main phase data. CV%: Coefficient of variation; CGM: Continuous glucose monitoring; SMBG: Self-measured blood glucose

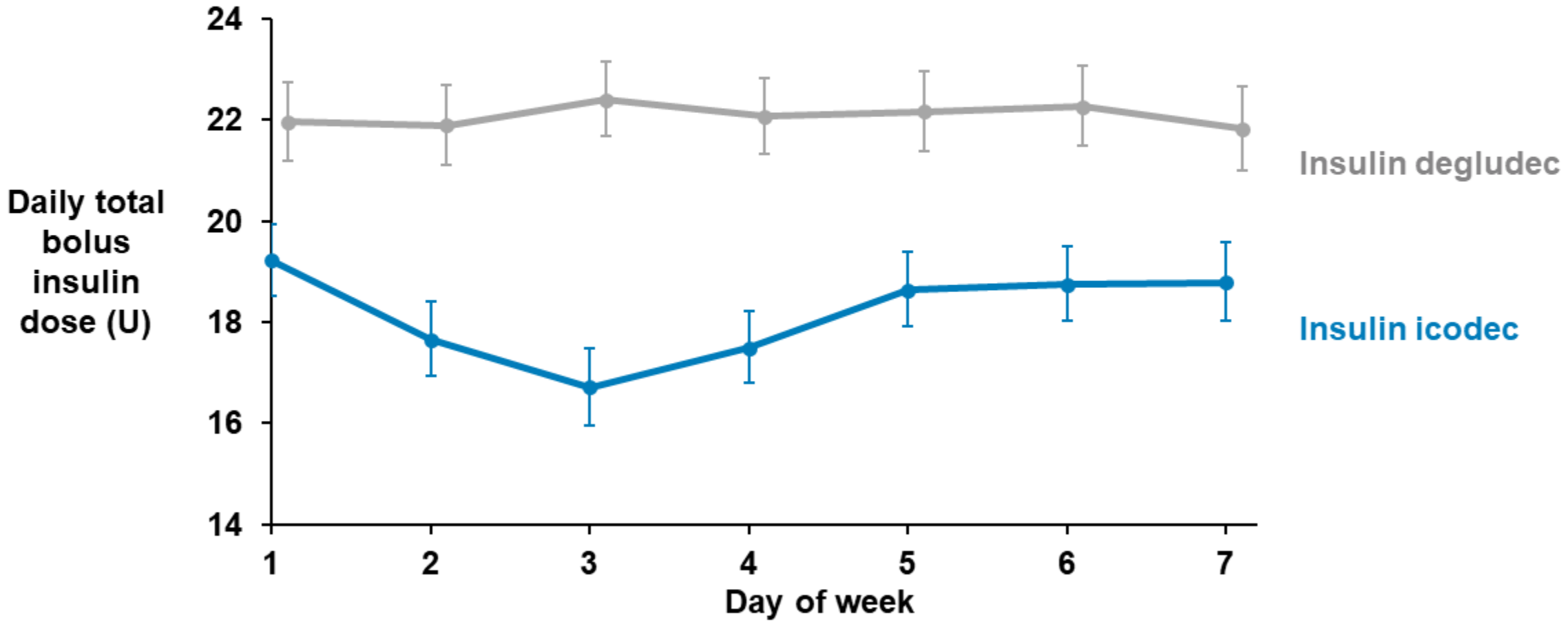
Reducing the Bolus Insulin Dose by 30% on Days 2-4 Reduces the Risk of Hypoglycemia

Simulation results with 30% reduction of bolus insulin dose on days 2-4

	ONWARDS 6	30% reduction
HbA_{1c} (%), mean (SD)	7.20 [7.16, 7.25]	7.26 [7.21, 7.31]
HbA_{1c} (%) change from baseline, mean (SD)	-0.43 [-0.47, -0.38]	-0.37 [-0.42, -0.32]
Weekly mean pre-breakfast SMBG (mg/dL)	154 [152, 157]	155 [152, 157]
Level 2 hypoglycemia (episodes PYE)	21.2 [19.3, 23.6]	12.8 [11.5, 14.4]
Basal insulin dose (U/week)	178 [175, 182]	179 [175, 183]
Bolus insulin dose (U/week)	128 [122, 132]	113 [108,117]

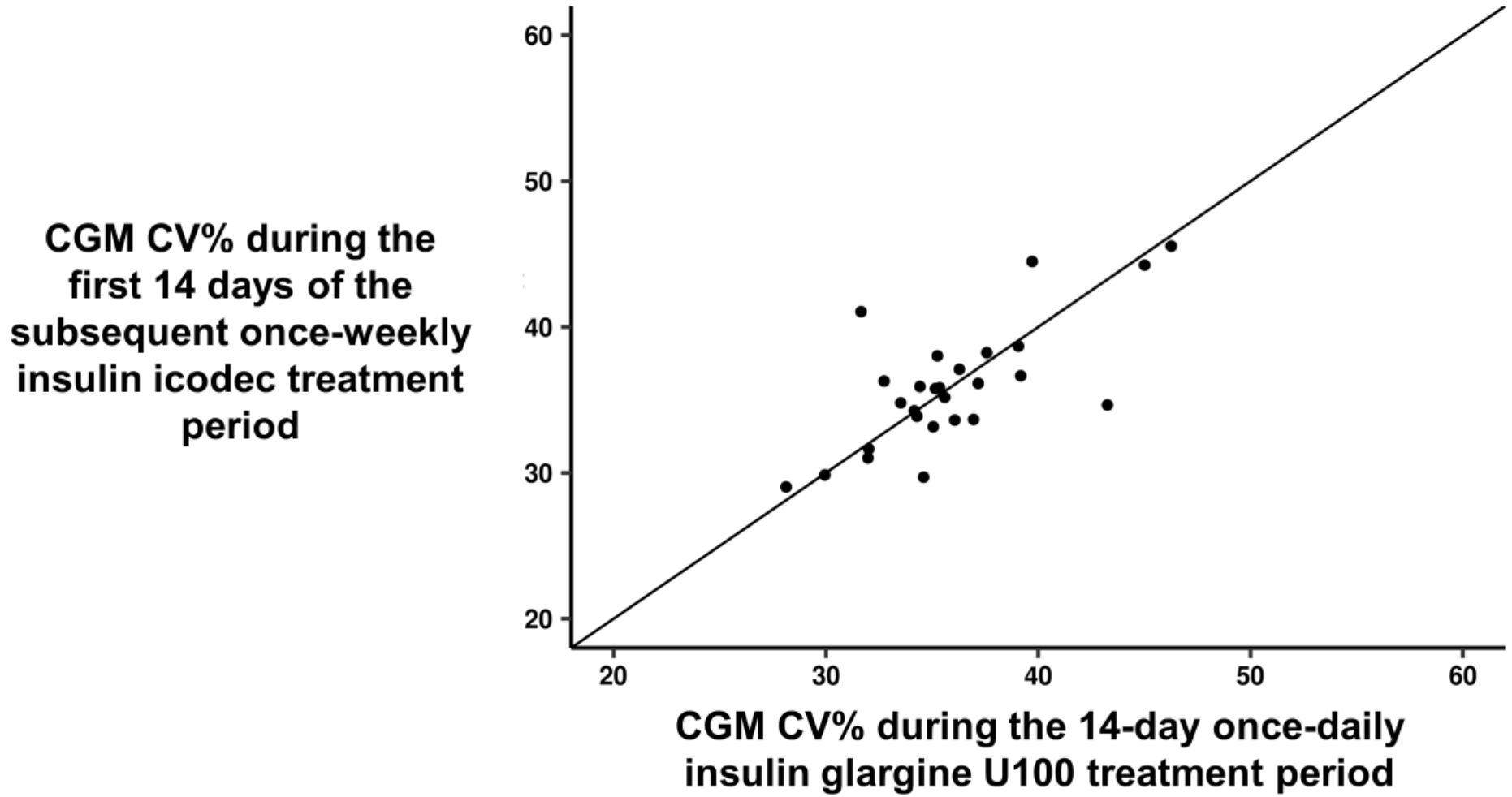
Model predictions of HbA_{1c}, HbA_{1c} change-from-baseline, weekly mean pre-breakfast SMPG, level 2 hypoglycemia rate per PYE, and basal (icodec) and bolus insulin dose (after 26 weeks) for alternative titration approaches with bolus insulin compared to the titration approach used in ONWARDS 6. Insulin icodec titrated as in ONWARDS 6. Results are based on 100 repeated simulations per scenario. N = 290. Geometric mean for basal and bolus insulin dose. SD: Standard deviation; SMBG: Self-measured blood glucose; PYE: Patient years of exposure (1 PYE = 365.25 days); U: Units. Numbers in square brackets indicate the 95% range of the (geometric) means across the 100 repeated simulations.

T1D: Small Reduction in Mean Bolus Insulin dose on Days 2-4 Observed with Insulin Icodec



Actual daily total bolus insulin dose across an insulin icodec titration interval summed up for last 2 weeks of planned treatment (week 24-26) in ONWARDS 6

T1D: Strong Correlation Between CGM CV% Pre-Insulin Icodec Exposure and Subsequent CV% for Insulin Icodec



CGM: continuous glucose monitoring; CV%: coefficient of variation in percent; N: number of participants; T1D: type 1 diabetes
Trial 4225: Participants with T1D (N=27) receiving 14 days of insulin glargine U100 treatment followed by 8 weeks of insulin icodec treatment at an individualized dose