

Betting on Basal Insulin

*Improving the Odds for People
With Type 2 Diabetes*



*Official symposium of the 19th
International Conference on
Advanced Technologies &
Treatments for Diabetes.*

*This session is not included in main
Congress CME/CPD credit.*

Goals for Today

During this presentation, we will learn...

- **That basal insulin plays an important, evolving role in the management of T2DM**
- **That once-weekly basal insulins can be used effectively and safely in nearly all PwT2DM**
- **Why PwT2DM prefer once-weekly basal insulins to once-daily basal insulins**

The Rationale for Weekly Insulin in PwT2DM



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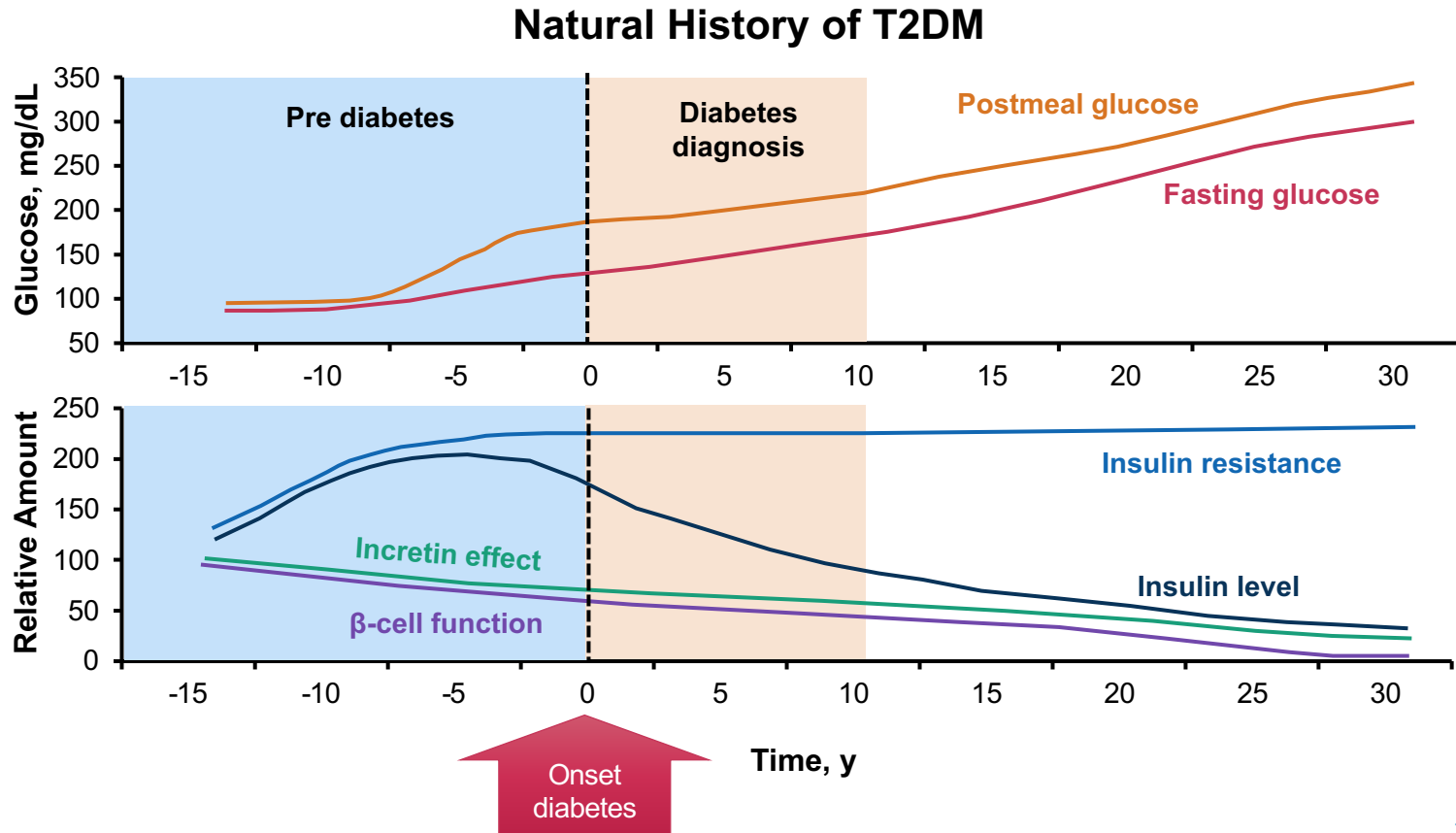
Recommendations for Basal Insulin Use in PwT2DM: ADA/EASD, Japan Diabetes Society, Chinese Diabetes Society¹⁻⁴



Because of its high glycemic efficacy, insulin can be considered in virtually any patient who is not at goal despite use of noninsulin agents or if noninsulin agents are not tolerated

ADA/EASD 2022	JDS 2024	CDS Primary Care 2025
<ul style="list-style-type: none">• Evidence of ongoing catabolism (weight loss, hypertriglyceridemia, ketosis)• Symptoms of hyperglycemia (ie, polyuria or polydipsia)• A1C >10% or blood glucose ≥ 300 mg/dL• Longer duration of T2DM and failure to reach glycemic target with oral agents• Once-daily, long-acting analogs preferred	<ul style="list-style-type: none">• Absolute indications<ul style="list-style-type: none">– insulin-dependent state– hyperglycemic coma (DKA, HHS)– severe hepatic disorder/renal impairment– severe infection or injury and surgery under general anesthesia– pregnancy if medical nutrition therapy insufficient– parenteral nutrition• Relative indications: FBG ≥ 250 mg/dL or RPG ≥ 350 mg/dL, oral meds insufficient, compromised nutritional status in lean patients, steroid treatment, glucotoxicity is actively eliminated	<ul style="list-style-type: none">• PwT2DM who do not reach glycemic goals after 3 mo of combined lifestyle change + oral medications• Short-term (2 wk to 3 mo) intensive insulin therapy or timely referral can be considered for newly diagnosed PwT2DM with A1C $\geq 9\%$ or FG ≥ 11.1 mmol/L (200 mg/dL) with significant hyperglycemic symptoms

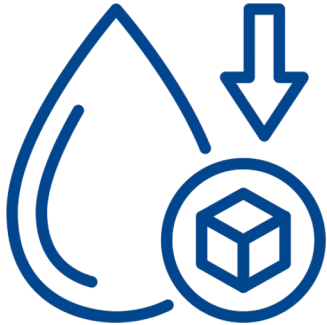
The Need for Insulin Therapy in T2DM Increases With Disease Duration and Loss of Beta-Cell Function¹



1. Kendall DM et al. *Am J Med.* 2009;122:S37-S50.

Barriers to Treatment Intensification With Insulin Therapy¹

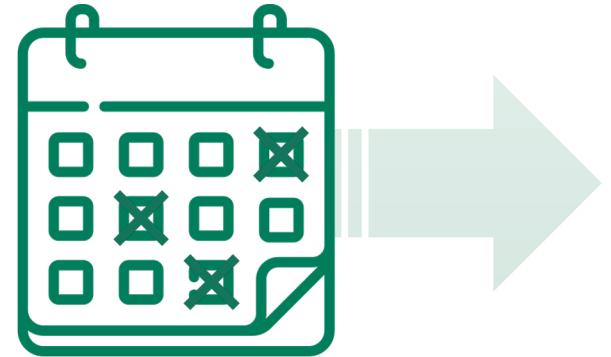
Hypoglycemia






Complexity



Poor treatment adherence



Nonadherence to Basal Insulin Therapy Is Common Among PwT2DM

Geographic Region	Nonadherence or Missed Doses	Key Findings	Data Source
Multinational cohort¹ 	<ul style="list-style-type: none">17.6% missed ≥ 1 basal dose over 14 days	<ul style="list-style-type: none">Missing 2 basal or 4 bolus insulin doses over 14 days was associated with a clinically relevant decrease of $>5\%$ in TIR	N = 31,195 smart pen and CGM users
United States² 	<ul style="list-style-type: none">42% adherent (eg, PDC $\geq 80\%$) at 12 mo57% persistent at 12 mo	<ul style="list-style-type: none">Higher persistence and adherence associated with lower healthcare utilization and medical costs	Large claims-based cohort study, 2016-2018, N = 64,953
Western Europe^{3,a} 	<ul style="list-style-type: none">56% adherent at 12 mo66% persistent at 12 mo	<ul style="list-style-type: none">Persistence stagnates over timeNew strategies to reduce treatment complexity, dosing frequency, improve safety profile, and better patient education and communication recommended	Systematic review of claims/patient cohorts, 2012-2022, N = 13 publications

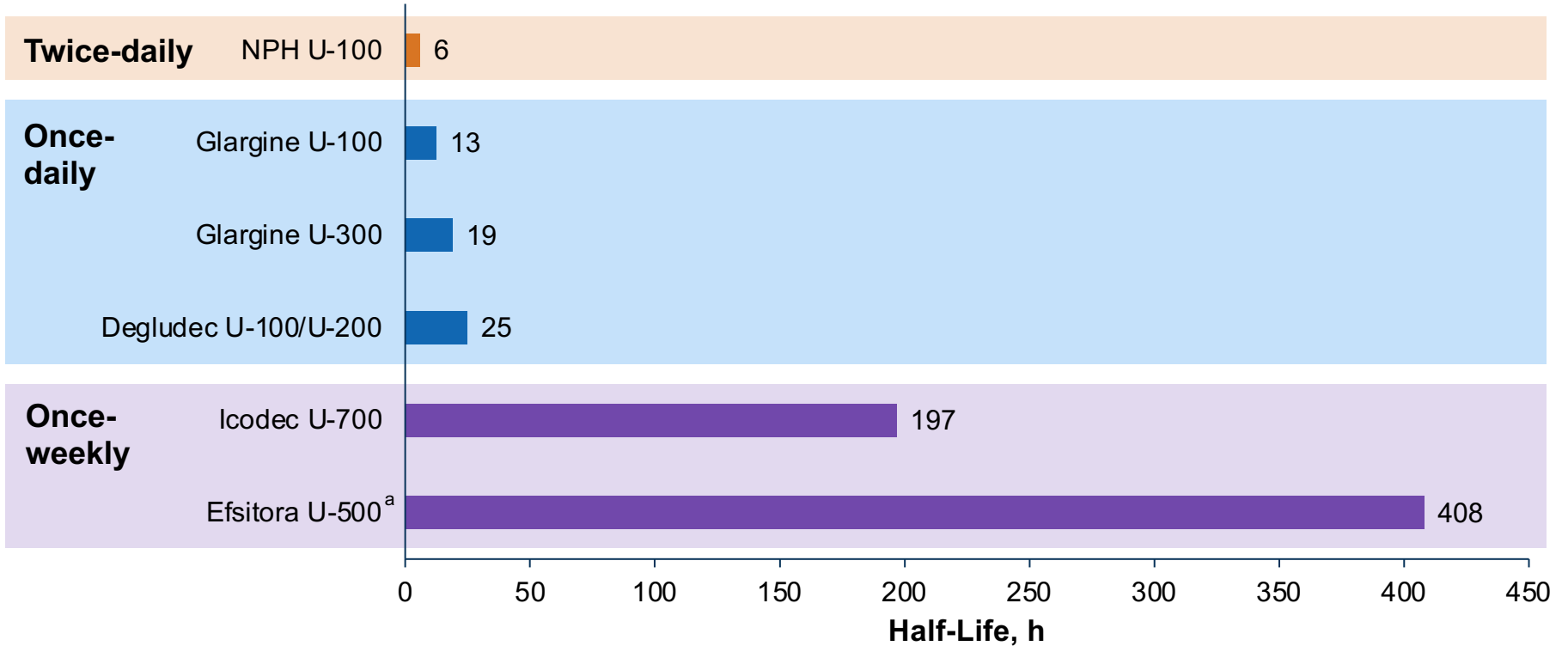
^a United Kingdom, France, Spain, Switzerland, the Netherlands, Ireland, Austria, Portugal, Denmark, Norway, Sweden, Finland, Italy, Germany, Iceland, Belgium.
1. Danne TPA et al. *Diabetes Care*. 2024;47:995-1003. 2. Aroda VR et al. *BMJ Open Diabetes Res Care*. 2024;12:e003825. 3. Gimeno EJ et al. *Diabetes Ther*. 2024;15:1047-1067.

Intermediate-, Long-, and Ultralong-Acting Daily Basal Insulin Formulations¹⁻¹¹

Duration of Action	Insulin	Concentration	Administration Frequency	Rx Needed?	Generic or Biosimilar Available?
Intermediate-acting	NPH	U-100	1-2 daily	US: No Canada: No EU: Yes	Yes
	RHI	U-500	1-3 daily	Yes	No
Long-acting	Glargine	U-100	1-2 daily	Yes	Yes
Ultralong acting	Glargine	U-300	1 daily	Yes	No
	Degludec	U-100	1 daily	Yes	No
	Degludec	U-200	1 daily	Yes	No

- Humulin N (insulin isophane human) https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/018781s193lbl.pdf.
- Novolin N (insulin isophane human) https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/019959s085lbl.pdf.
- Humulin R U-500 (insulin human) <https://uspl.lilly.com/humulinru500/humulinru500.html#pi>.
- Lantus (insulin glargine) https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021081s078s079lbl.pdf.
- Toujeo U-300 (insulin glargine) https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206538Orig1s017Lbl.pdf.
- Tresiba (insulin degludec) https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203314s018s020lbl.pdf.
- <https://www.goodrx.com/classes/insulins/insulin-types-how-to-use>.
- Rosenstock J et al. *Endocr Rev.* 2024;45:379-413.
- <https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/awiqli-en-product-monograph-12-march-2024.pdf>.
- https://www.ema.europa.eu/en/documents/product-information/awiqli-epar-product-information_en.pdf.
- Niskanen L et al. *J Diabetes Ther.* 2024;16:e13491.

Weekly Insulins Have a Much Longer Half-Life Compared With Daily Insulins¹⁻²



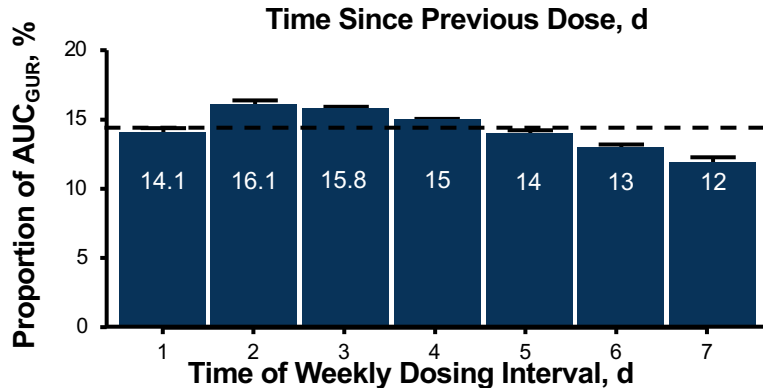
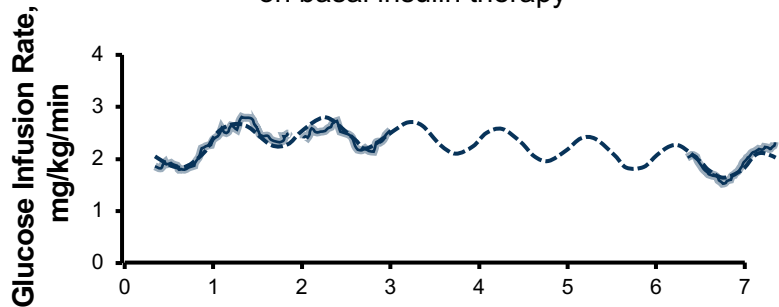
^a Investigational agent.

1. Rosenstock J et al. *Endocr Rev.* 2024;45:379-413. 2. Almoud EN et al. *Front Endocrinol (Lausanne).* 2024;14:1285147.

Pharmacodynamics of Once-Weekly Insulins

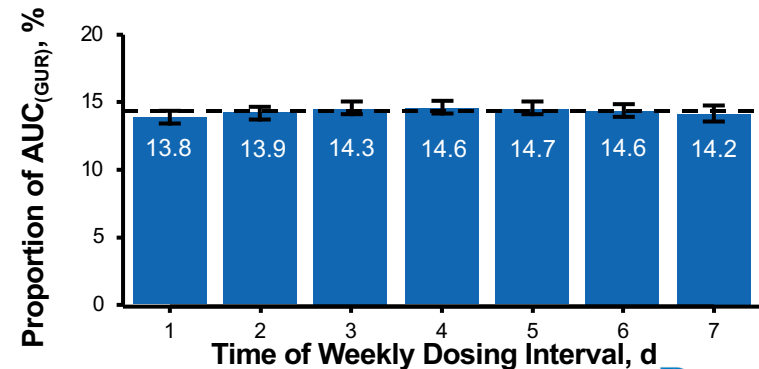
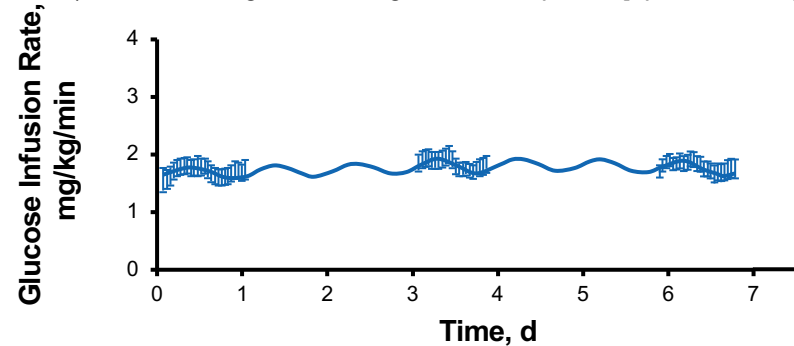
Icodec¹: half life ~8 days

Study conducted in 45 participants with T2DM on basal insulin therapy



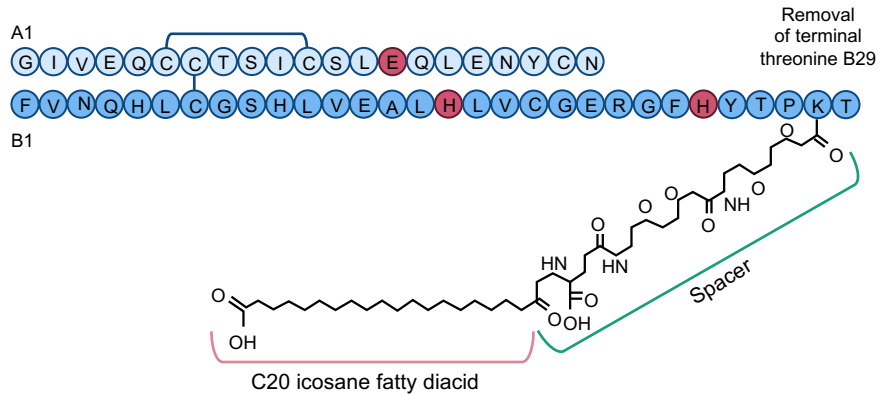
Efsitora²: half-life ~18 days

Study conducted in 53 participants with T2DM, basal naïve (initiated on degludec during the lead-in period [up to 4 weeks])



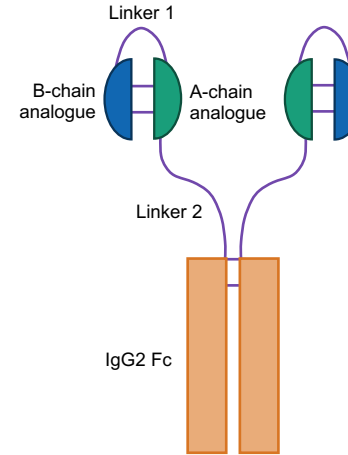
Molecular Features of Icodec and Efsitora¹

Icodec



- Covalently bound to C20 icosane fatty diacid
- Strong, reversible binding to albumin


Efsitora



- Single-chain insulin molecule bound to IgG2 Fc domain
- Homodimer, molecular mass 64.1 kDa


Clinician Perspectives on Once-Weekly Basal Insulin

Endocrinologist




There will be major stacking of insulin and thus prolonged hypoglycemia. Impossible to manage.

Diabetes Educator/Dietician



With so much insulin on board, people will gain a lot of weight.

Primary Care Physician



Oh, this is nice! So, we can now give insulin the same way we give GLP-1 receptor agonists!

Patient Perspectives on Once-Weekly Basal Insulin

Insulin-Naïve Person With Diabetes

Why do you ask me whether I would like to administer one injection a day or one injection a week?

Person With Diabetes Using MDI for 5 Years

You need to keep giving me the once-weekly insulin.

HCP

But what is the difference if you need to give mealtime insulin anyway?

Every injection I can avoid is a plus. What a relief that I did not have to give my basal insulin every day.



Phase 3 Clinical Trial Programs for Icodec and Efsitora

Insulin-Naïve T2DM				Insulin-Experienced T2DM		T1DM
Icodec¹⁻⁶	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
Design	Basal initiation	Double-blind, double-dummy	Icodec + titration app	Basal switch	BBT switch	BBT switch
N	984	588	1,085	526	582	582
Efsitora⁷⁻¹¹	QWINT-1		QWINT-2	QWINT-3	QWINT-4	QWINT-5
Design	Fixed-dose titration		Free titration	Switch from basal	Replace basal in MDI	Replace basal in MDI
N	795		928	986	730	692

1. Rosenstock J et al. *N Engl J Med.* 2023;389:297-308. 2. Lingvay I et al. *JAMA.* 2023;330:228-237. 3. Bajaj HS et al. *Ann Intern Med.* 2023;176:1476-1485. 4. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol.* 2023;11:414-425. 5. Mathieu C et al. *Lancet.* 2023;401:1929-1940. 6. Russell-Jones D et al. *Lancet.* 2023;402:1636-1647. 7. Rosenstock J et al. *N Engl J Med.* 2025;393:325-335. 8. Wysham C et al. *N Engl J Med.* 2024;391:2201-2211. 9. Philis-Tsimikas A et al. *Lancet.* 2025;405:2279-2289. 10. Blevins T et al. *Lancet.* 2025;405:2290-2301. 11. Bergenstal RM et al. *Lancet.* 2024;404:1132-1142.

The Insulin-Naïve Patient

Integrating Once-Weekly Insulin for Individualized T2DM Care



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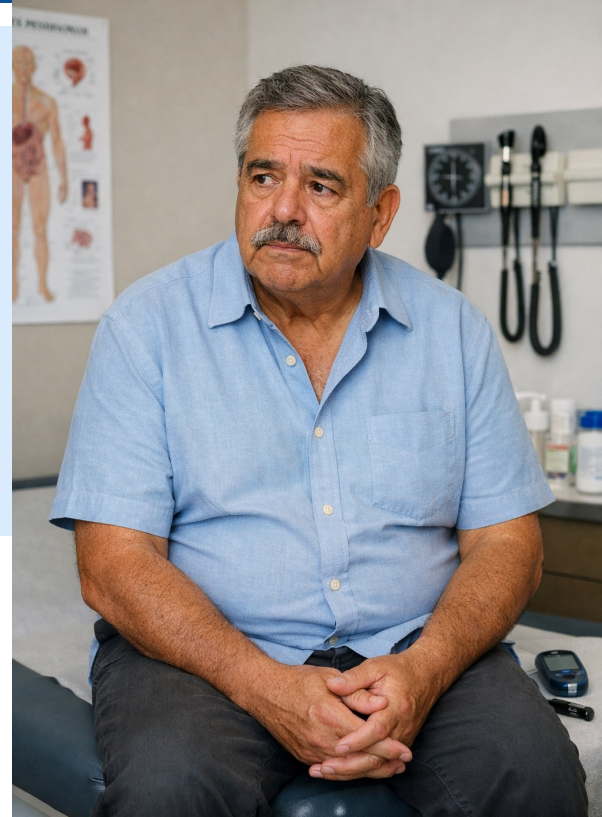
Case Study:

José, a Spanish Man Aged 66 Years

- **Medical history:** T2DM, 12 years
- **A1C:** 7.9% (63 mmol/mol)
- **Weight:** 90 kg
- **BMI:** 31 kg/m²
- **eGFR:** 60 mL/min/1.73 m²;
UACR: 27 mg/g (3 mg/mmol)
- **Current medications** (all at maximally tolerated doses)
 - Metformin 1,000 mg twice daily
 - Tirzepatide 10 mg once weekly
 - Empagliflozin 25 mg once daily

Patient Notes

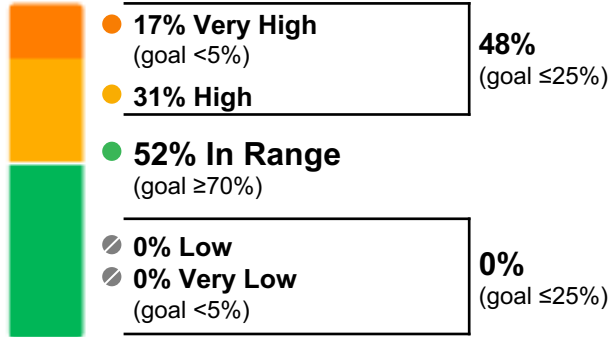
- Retired, lives with wife
- Worried that insulin will cause weight gain and hypoglycemia
- Would like to simplify treatment regimen



AI-generated patient image

Ambulatory Glucose Profile: José, a Spanish Man Aged 66 Years

Time in Ranges



Glucose Metrics

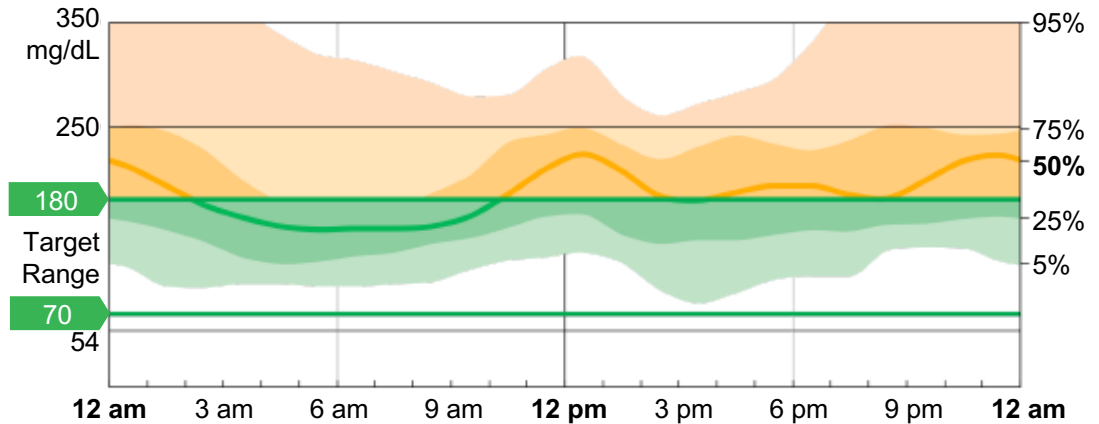
Average Glucose
(goal <154 mg/dL) **191 mg/dL**

GMI (goal <7%) **7.9%**

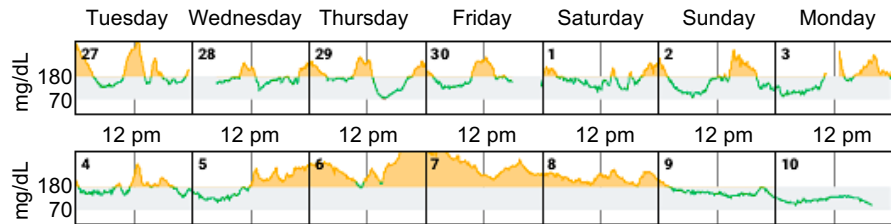
Coefficient of Variation
(goal <35%) **33.6%**

Time CGM Active **95.8%**

Ambulatory Glucose Profile



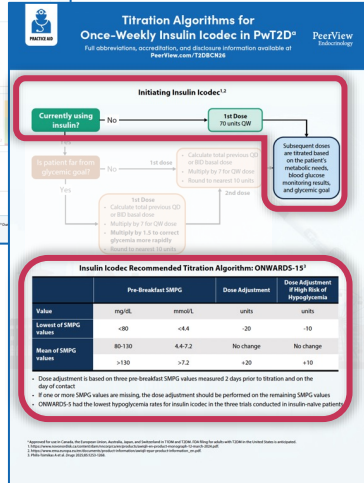
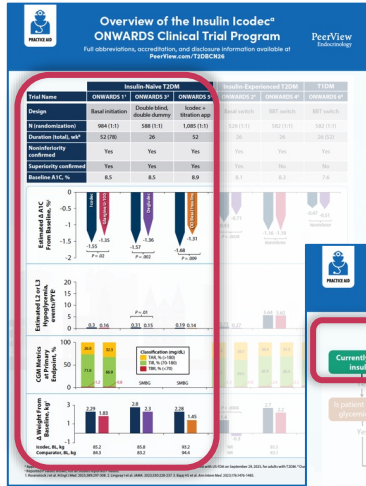
Daily Glucose Profile



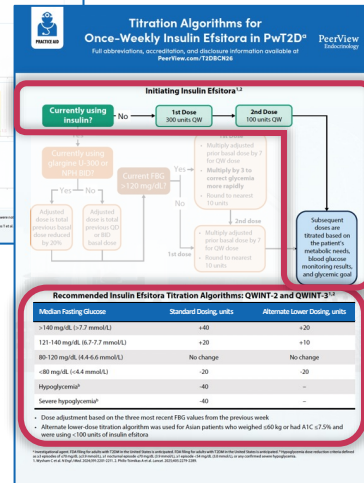
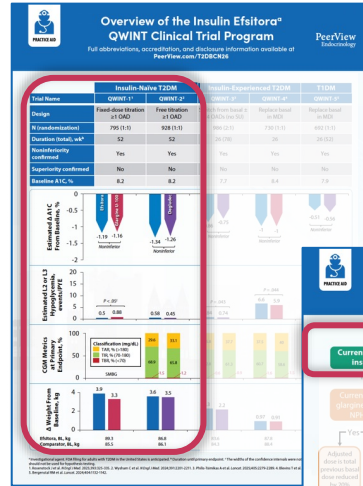
What are your recommendations for José?

Practice Aids Are Available to Assist in Your Practice

Insulin Icodec



Insulin Efsitora



Scan to download!



Once-Weekly Basal Insulin Has Similar or Superior Efficacy as Once-Daily Basal Insulin in Insulin-Naïve PwT2DM

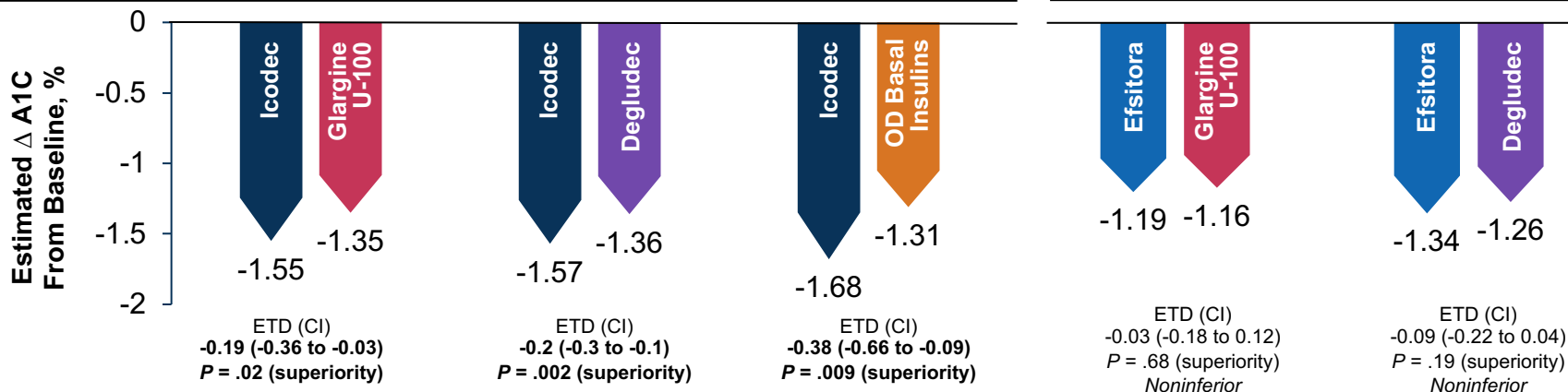
Icodec

Efsitora^a

Insulin-Naïve T2DM

Insulin-Naïve T2DM

Trial Name	ONWARDS 1 ¹	ONWARDS 3 ²	ONWARDS 5 ³	QWINT-1 ⁴	QWINT-2 ⁵
Design	Basal initiation	Double-blind, double-dummy	Icodec + titration app	Fixed-dose titration	Free titration
Baseline A1C, %	8.5	8.5	8.9	8.2	8.2



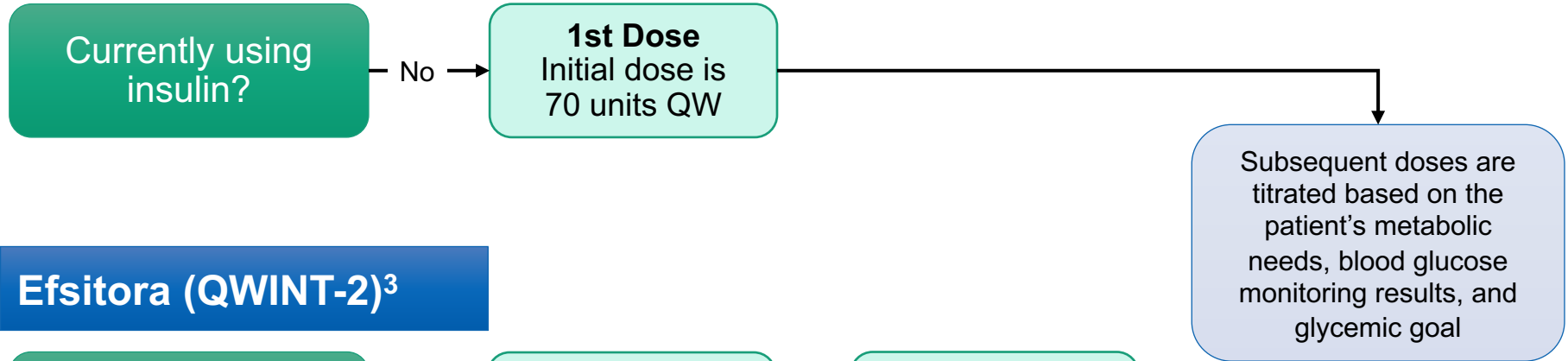
^a Investigational agent.

1. Rosenstock J et al. *N Engl J Med.* 2023;389:297-308. 2. Lingvay I et al. *JAMA.* 2023;330:228-237. 3. Bajaj HS et al. *Ann Intern Med.* 2023;176:1476-1485.

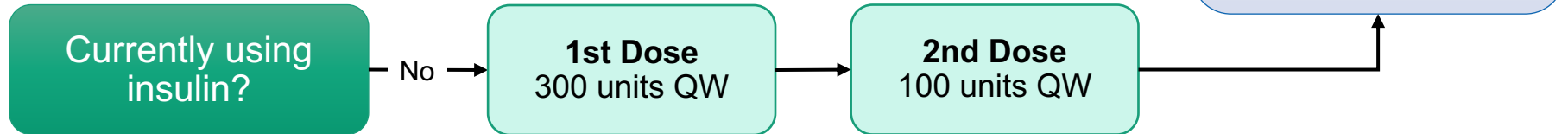
4. Rosenstock J et al. *N Engl J Med.* 2025;393:325-335. 5. Wysham C et al. *N Engl J Med.* 2024;391:2201-2211.

Once-Weekly Insulin Doses Are 7x Once-Daily Doses

Icodec (European and Canadian Prescribing Information)^{1,2}



Efsitora (QWINT-2)³

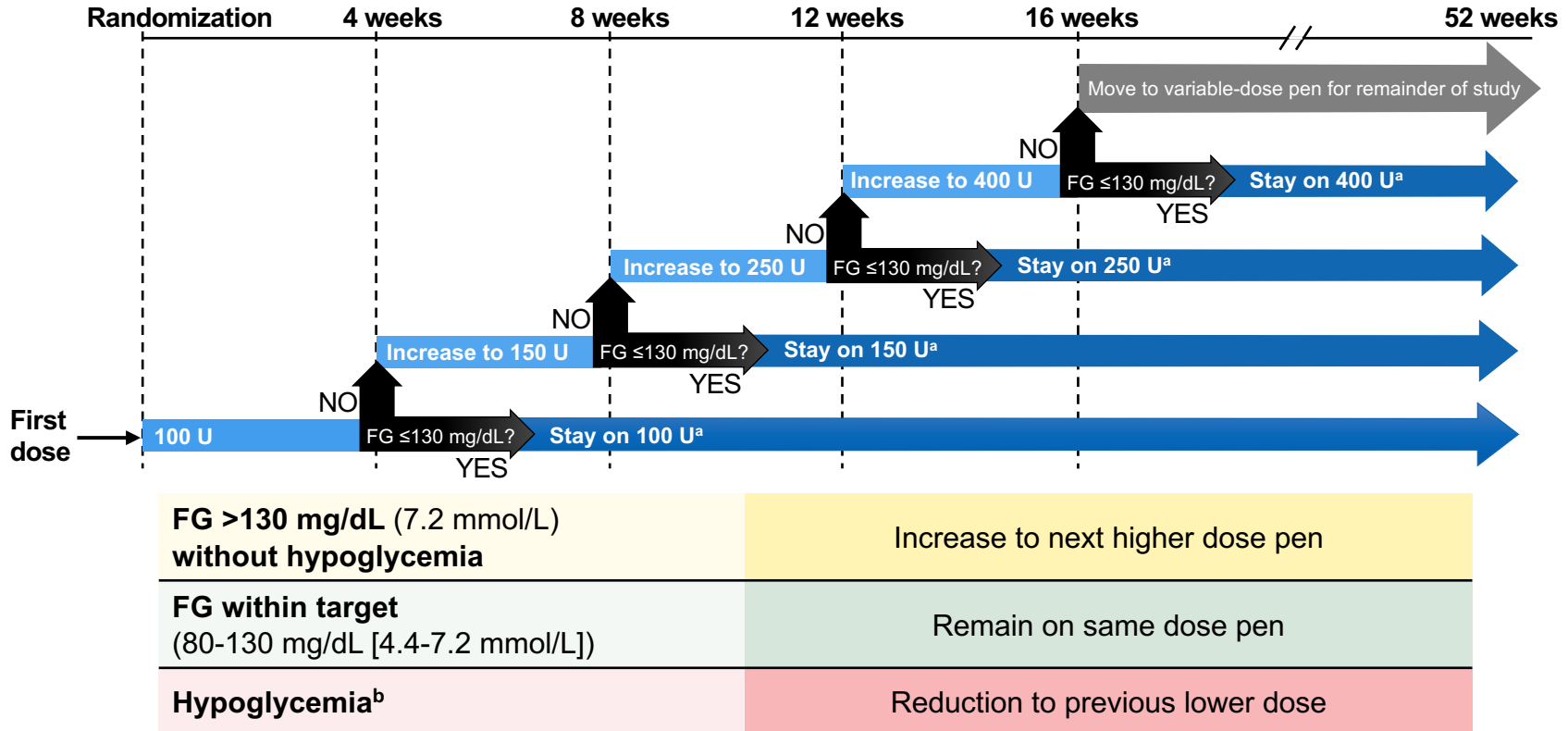


1. <https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/awiqli-en-product-monograph-12-march-2024.pdf>.

2. https://www.ema.europa.eu/en/documents/product-information/awiqli-epar-product-information_en.pdf.

3. Wysham C et al. *N Engl J Med*. 2024;391:2201-2211.

Fixed Dosing of Efsitora in QWINT-1¹



^a Until fasting glucose assessment that requires an increase to the next dose level. ^b ≥3 hypoglycemic events ≤70 mg/dL (3.9 mmol/L), ≥1 hypoglycemic event <54 mg/dL (3.0 mmol/L), ≥1 nocturnal hypoglycemic event ≤70 mg/dL, or any severe hypoglycemic event in the preceding 7 days. If hypoglycemia was observed, dose reductions could occur at any time.

1. Rosenstock J et al. *N Engl J Med.* 2025;393:325-335.

Icodec Titration Protocol: ONWARDS 1-5^{1,2}

- Dose adjustment is based on three pre-breakfast SMPG values measured 2 days prior to titration and on the day of contact
- If one or more SMPG values are missing, the dose adjustment should be performed on the remaining SMPG values

	Pre-Breakfast SMPG		Standard Dose Adjustment	Dose Adjustment if High Risk of Hypoglycemia
Value	mg/dL	mmol/L	units	units
Lowest of SMPG Values	<80	<4.4	-20	-10
Mean of SMPG Values	80-130	4.4-7.2	No change	No change
	>130	>7.2	+20	+10

- ONWARDS-5 used app-based dosing and had the lowest hypoglycemia rates for icodec in the 3 trials conducted in insulin-naïve patients

Insulin Efsitora Titration Protocol: QWINT-2 and QWINT-3^{1,2}

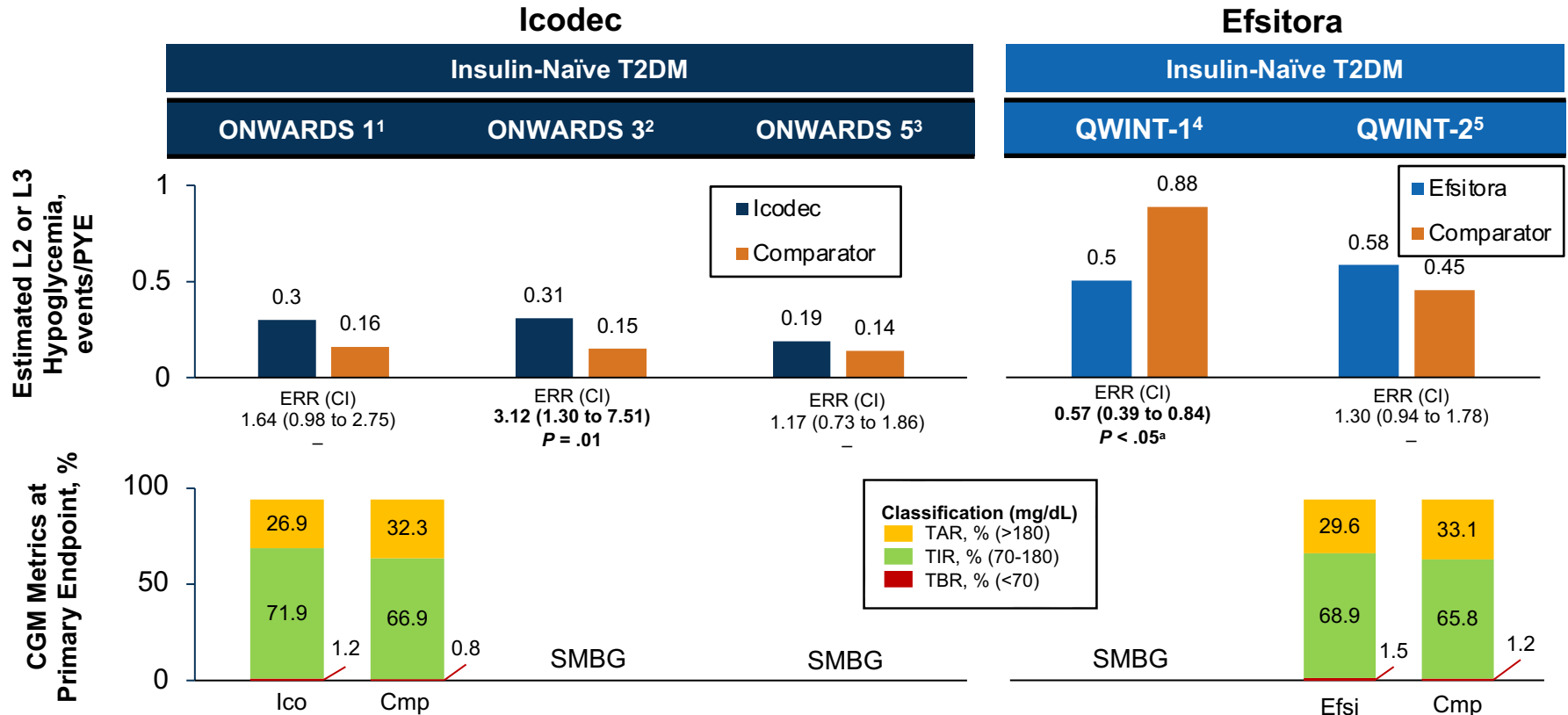
- Dose adjustment based on the three most recent FBG values from the previous week
- Alternate lower-dose titration algorithm was used for Asian patients who weighed ≤ 60 kg or had A1C $\leq 7.5\%$ and were using < 100 units of insulin efsitora

Median Fasting Glucose	Standard Dosing, units	Alternate Lower Dosing, units
>140 mg/dL (>7.7 mmol/L)	+40	+20
121-140 mg/dL (6.7-7.7 mmol/L)	+20	+10
80-120 mg/dL (4.4-6.6 mmol/L)	No change	No change
<80 mg/dL (<4.4 mmol/L)	-20	-20
Hypoglycemia ^a	-40	–
Severe hypoglycemia ^a	-40	–

^a Hypoglycemia dose reduction criteria defined as ≥ 3 episodes of ≤ 70 mg/dL (≤ 3.9 mmol/L), ≥ 1 nocturnal episode ≤ 70 mg/dL (3.9 mmol/L), ≥ 1 episode < 54 mg/dL (3.0 mmol/L), or any confirmed severe hypoglycemia.

1. Wysham C et al. *N Engl J Med.* 2024;391:2201-2211. 2. Philis-Tsimikas A et al. *Lancet.* 2025;405:2279-2289.

Hypoglycemia Incidence for Once-Weekly Insulins Is Generally Similar to Once-Daily Insulins

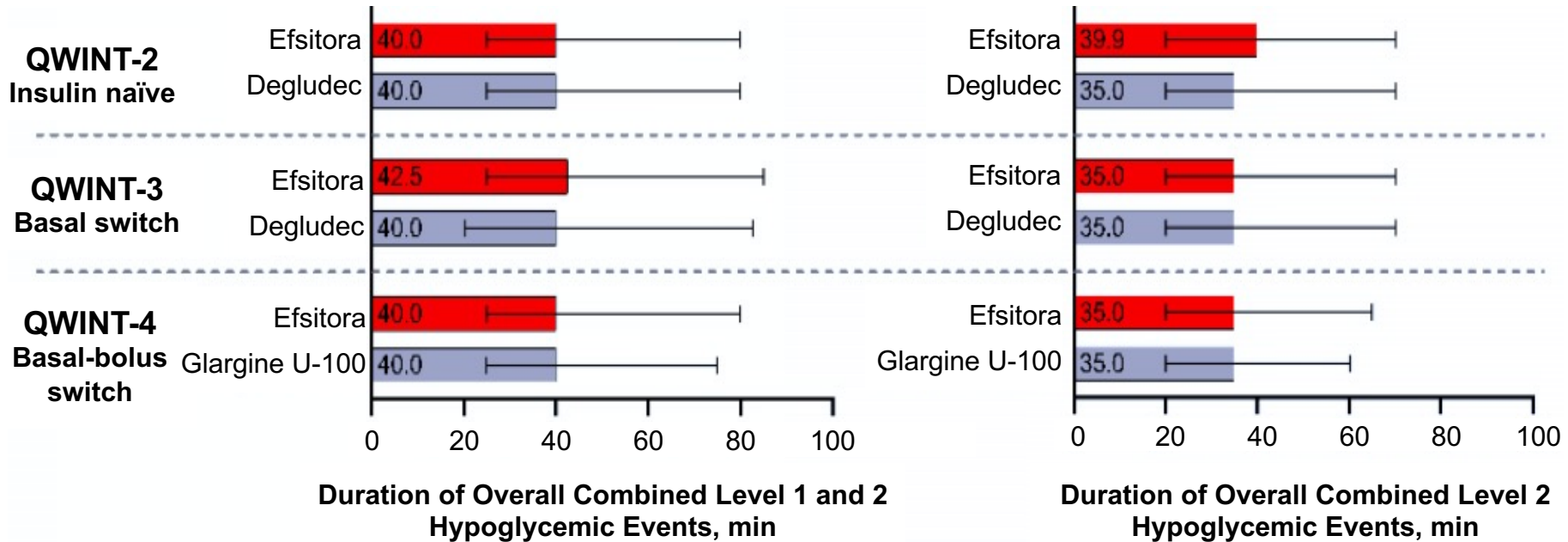


^a Not adjusted for multiplicity; not for hypothesis testing.

1. Rosenstock J et al. *N Engl J Med.* 2023;389:297-308. 2. Lingvay I et al. *JAMA.* 2023;330:228-237. 3. Bajaj HS et al. *Ann Intern Med.* 2023;176:1476-1485.

4. Rosenstock J et al. *N Engl J Med.* 2025;393:325-335. 5. Wysham C et al. *N Engl J Med.* 2024;391:2201-2211.

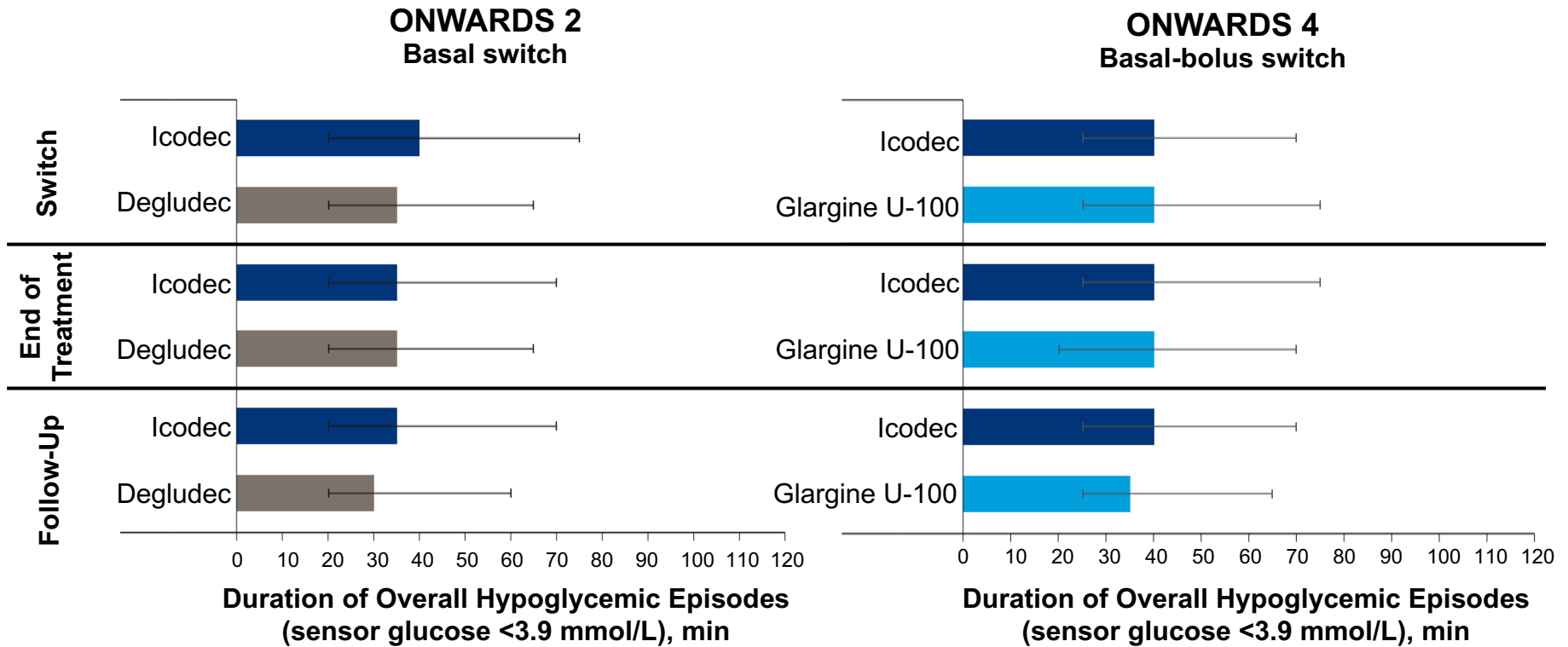
Duration of Hypoglycemic Events Was Similar for Efsitora and Comparators in QWINT-2, QWINT-3, and QWINT-4¹



Glucose <70 mg/dL (3.9 mmol/L)
with recovery to ≥70 mg/dL

Glucose <54 mg/dL (3.0 mmol/L)
with recovery to ≥54 mg/dL

Duration of Hypoglycemic Events Was Similar for Icodec and Comparators in ONWARDS 2 and 4¹

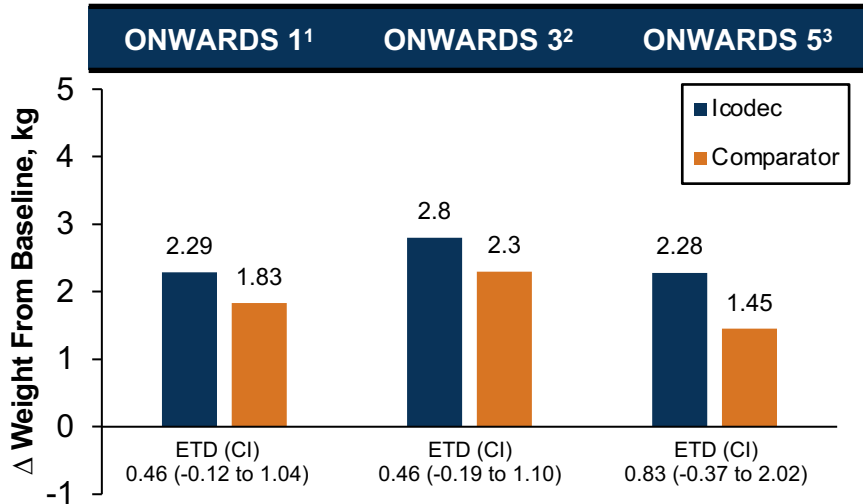


1. Bajaj HS et al. *Diabetes Care*. 2024;47:729-738.

Comparable Weight Gain With Once-Weekly Insulins and Once-Daily Insulins

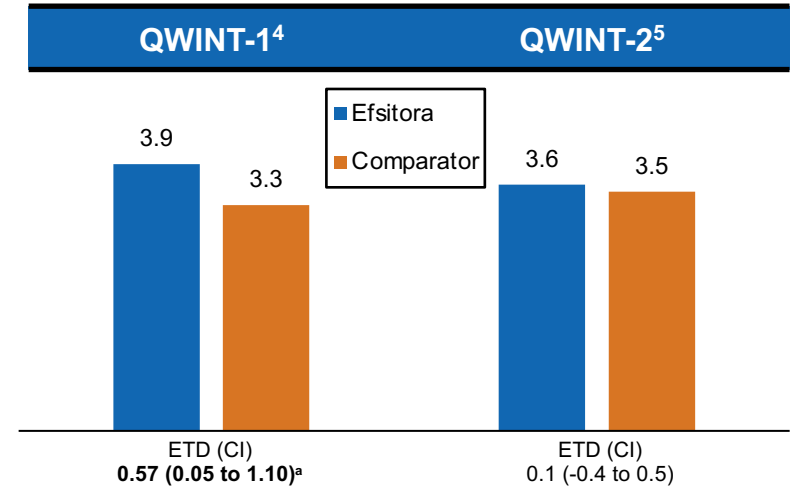
Icodec¹⁻³

Insulin-Naïve T2DM



Efsitora^{4,5}

Insulin-Naïve T2DM



Icodec, BL, kg	85.2	85.8	93.2
Cmp, BL, kg	84.3	83.2	94.4

Efsitora, BL, kg	89.3	86.8
Cmp, BL, kg	85.5	86.1

^a Not adjusted for multiplicity; not for hypothesis testing.

1. Rosenstock J et al. *N Engl J Med.* 2023;389:297-308. 2. Lingvay I et al. *JAMA.* 2023;330:228-237. 3. Bajaj HS et al. *Ann Intern Med.* 2023;176:1476-1485.

4. Rosenstock J et al. *N Engl J Med.* 2025;393:325-335. 8. Wysham C et al. *N Engl J Med.* 2024;391:2201-2211.

Patient Education Pointers for Preventing and Treating Hypoglycemia With Once-Weekly Insulins



Insulin Icodec¹

Insulin Efsitora²⁻⁴

Timing of Glucose-Lowering Effect

Maximal effect occurs during days 2-4 after each weekly injection

Effect is similar every date after each weekly injection

During Illness or Exercise

Both agents: do not change the dose

Adjust glucose intake or other glucose-lowering medications

Monitor glucose with hypoglycemia symptoms and treat per standard instructions

If Dose Is Forgotten

Both agents: administer ASAP if <4 days after the missed dose

Both agents: resume usual schedule if ≥ 4 days between doses

Continue QW dosing on the new day

Day of the week of administration can be changed, allowing ≥ 3 days between doses

1. <https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/awiqli-en-product-monograph-12-march-2024.pdf>.
2. Leohr J et al. ADA 2025. Poster 802-P. 3. Bergenstal RM et al. *Diabetes Obes Metab*. 2024;26:3020-3030.
4. https://cdn.clinicaltrials.gov/large-docs/32/NCT05662332/Prot_000.pdf.

Restrictions on the Use of Once-Weekly Insulins: Canadian and EU Prescribing Information^{1,2}

When Not to Use Once-Weekly Insulin

- Do not use in patients with a history of hypoglycemia unawareness
- Do not administer >1 dose/week
- Do not use to treat DKA
- Do not mix with other insulins
- Do not use in combination with other basal insulins
- SC administration only (not IM, IV, or CSII)



Open Questions in Once-Weekly Insulin



Pediatric use?



Use during pregnancy and lactation?



Use in individuals with hypoglycemia unawareness?



Use in patients with newly diagnosed T1DM?

1. <https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/awiqli-en-product-monograph-12-march-2024.pdf>.

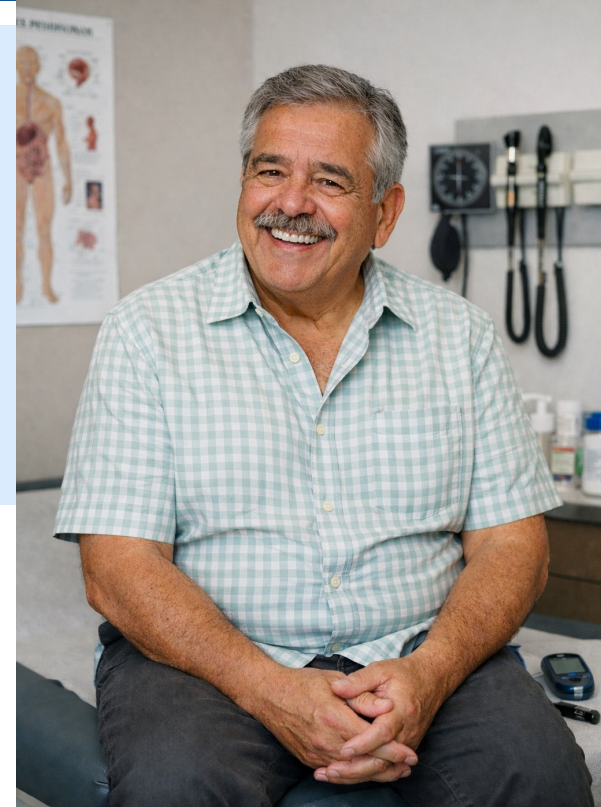
2. https://www.ema.europa.eu/en/documents/product-information/awiqli-epar-product-information_en.pdf.

Case Study Follow-Up at 3 Months: José, a Spanish Man Aged 66 Years

- **Medical history:** T2DM, 12 years
- **A1C:** ~~7.9%~~ (63 mmol/mol) → **7.2% (55 mmol/mol)**
- **Weight:** ~~90 kg~~ → **93 kg**
- **BMI:** ~~31 kg/m²~~ → **32 kg/m²**
- **eGFR:** 60 mL/min/1.73 m²;
UACR: 27 mg/g (3 mg/mmol)
- **Current medications**
 - **Icodec U-700 100 units once weekly**
 - Metformin 1,000 mg twice daily
 - Tirzepatide 10 mg once weekly
 - Empagliflozin 25 mg once daily

Patient Notes

- Retired, lives with wife
- ~~Worried that insulin will cause weight gain and hypoglycemia~~ → **reassured regarding minimal weight gain and one episode of level 1 hypoglycemia**
- ~~Would like to simplify treatment regimen~~ → **happy with glucose levels**



AI-generated patient image

The Insulin-Experienced Patient

Using Once-Weekly Insulin in Complex or Treatment-Resistant T2DM



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Scripps Whittier Diabetes Institute

San Diego, California

Director, Community Engagement Research

Scripps Research Translational Institute

La Jolla, California

Case Study:

Janine, a French Woman Aged 57 Years

- **Medical history:** T2DM, 8 years; TIA, 8 years ago
- **A1C:** 7.9% (63 mmol/mol)
- **Weight:** 80 kg
- **BMI:** 29 kg/m²
- **eGFR:** 46 mL/min/1.73 m²;
UACR: 102 mg/g (10 mg/mmol)
- **Current medications**
 - Dapagliflozin 10 mg once daily at bedtime
 - Glargine U-100 40 units once daily at bedtime

Patient Notes

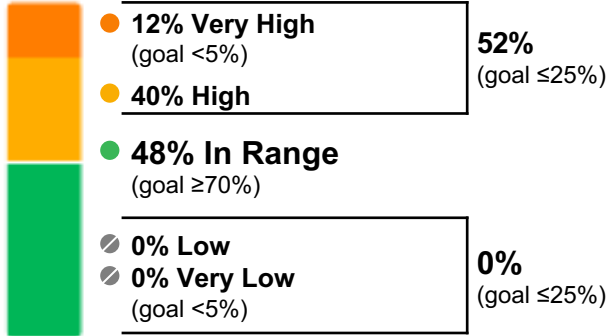
- Work requires frequent travel across time zones
- Missing ~2 injections/wk
- Had severe nausea and vomiting on two different GLP-1 RAs



AI-generated patient image

Ambulatory Glucose Profile: Janine, a French Woman Aged 57 Years

Time in Ranges



Glucose Metrics

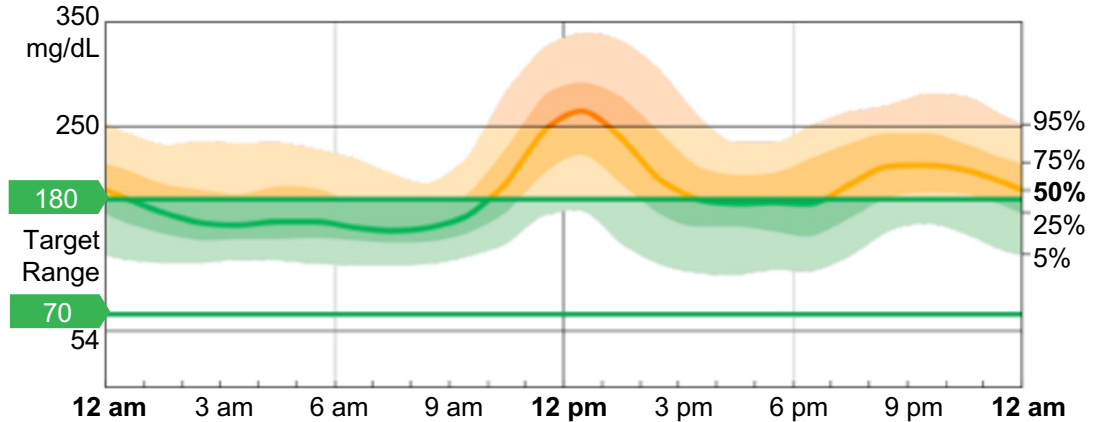
Average Glucose
(goal <154 mg/dL) **190 mg/dL**

GMI (goal <7%) **7.9%**

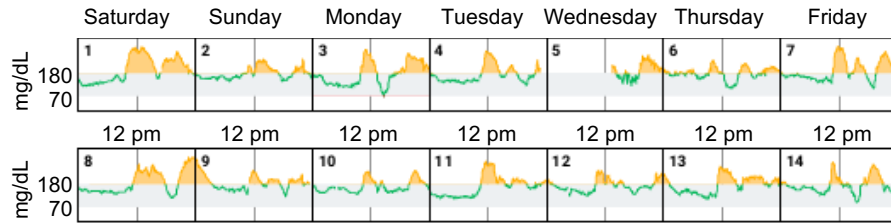
Coefficient of Variation
(goal <35%) **26.0%**

Time CGM Active **96.9%**

Ambulatory Glucose Profile



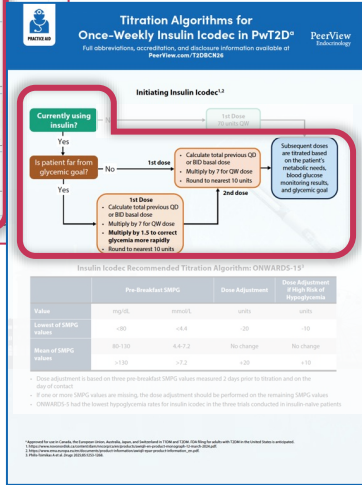
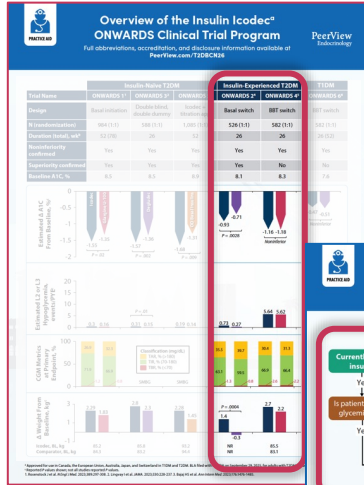
Daily Glucose Profile



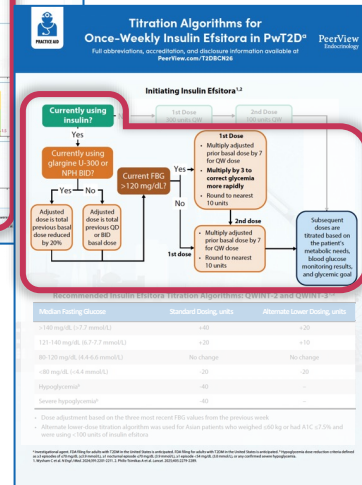
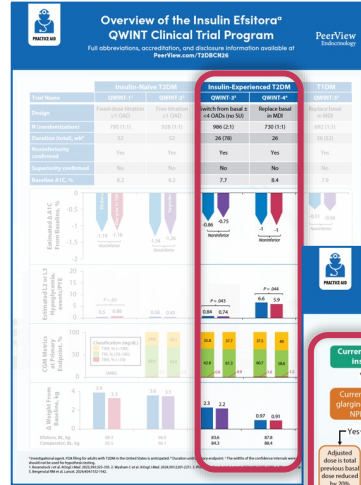
What are your recommendations for Janine?

Practice Aids Are Available to Assist in Your Practice

Insulin Icodec



Insulin Efsitora

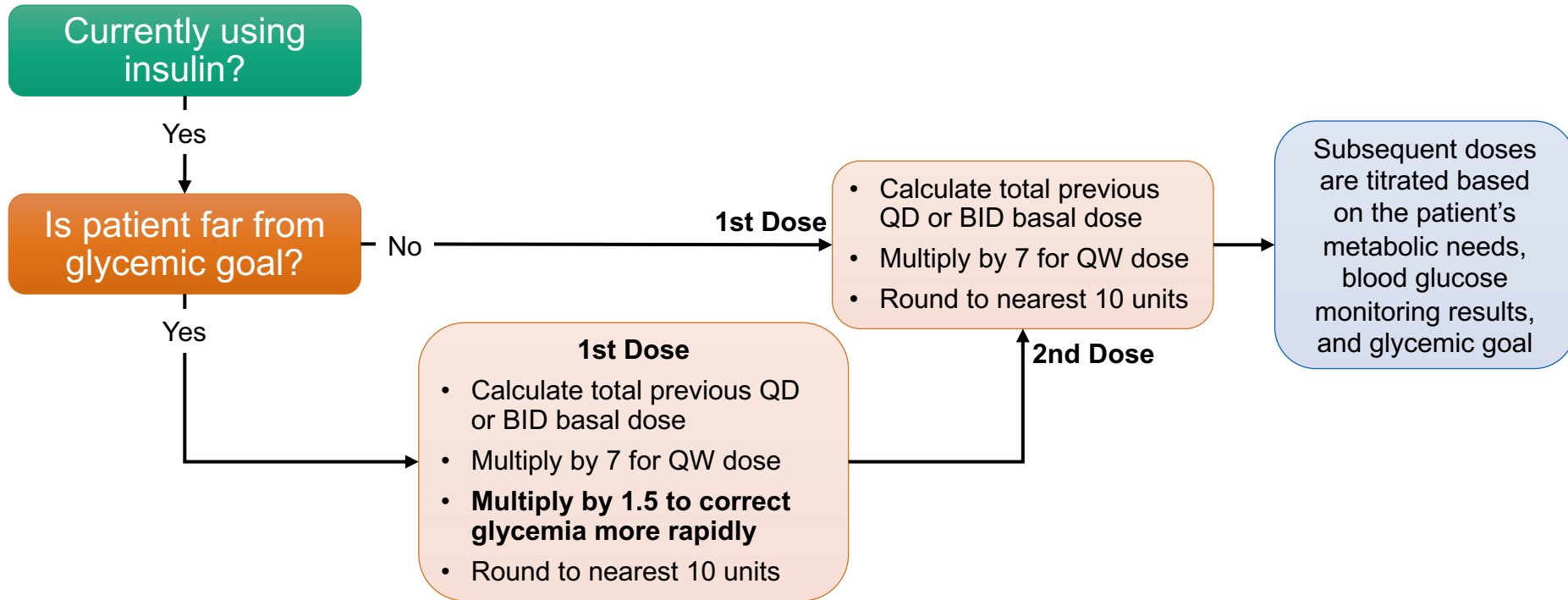


Scan to download!



Icodec Initiation and Titration Algorithm

From Canadian and EU Prescribing Information^{1,2}



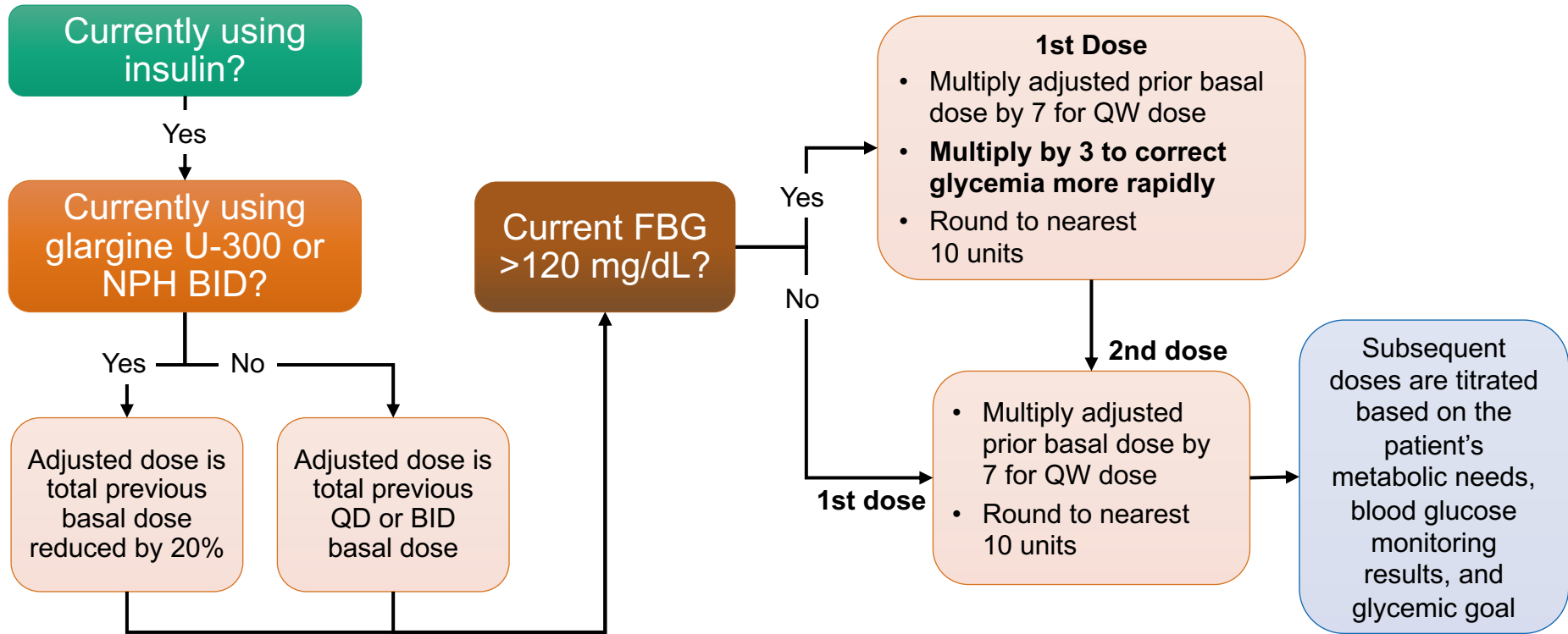
- In patients with a history of severe hypoglycemia on insulin therapy, a lower multiple may be appropriate

1. <https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/awiqli-en-product-monograph-12-march-2024.pdf>.

2. https://www.ema.europa.eu/en/documents/product-information/awiqli-epar-product-information_en.pdf.

Efsitora Initiation and Titration Algorithm

From QWINT-2 and QWINT-4^{1,2,a}



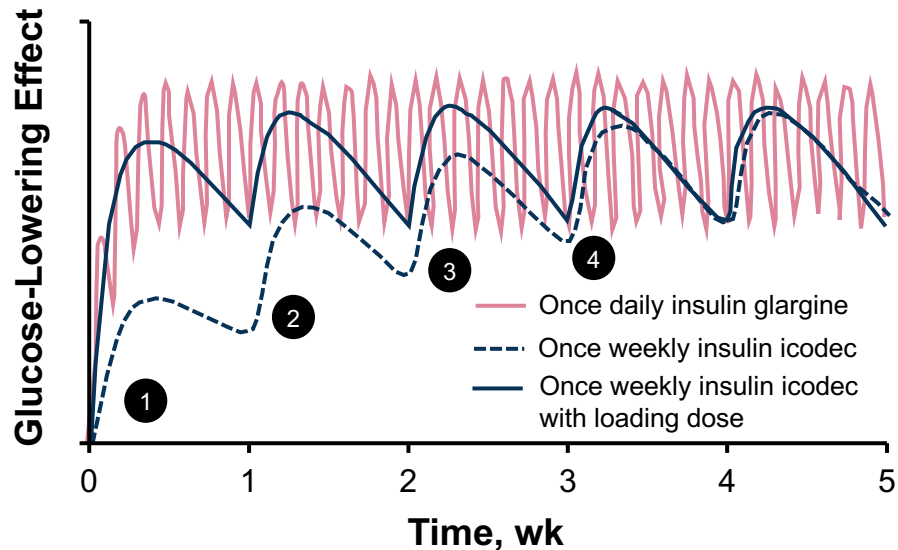
- In patients with a history of severe hypoglycemia on insulin therapy, a lower multiple may be appropriate

^a Investigational agent.

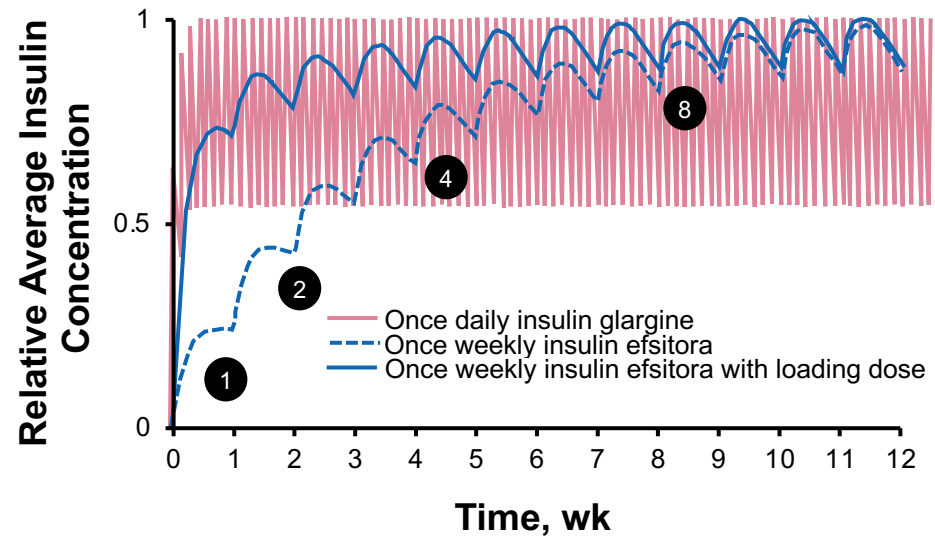
1. Wysham C et al. *N Engl J Med*. 2024;391:2201-2211. 2. Philis-Tsimikas A et al. *Lancet*. 2025;405:2279-2289.

Pharmacodynamics of Once-Weekly Insulins Illustrating the Effect of a One-Time Loading Dose¹

Icodec vs Glargine



Efsitora vs Glargine

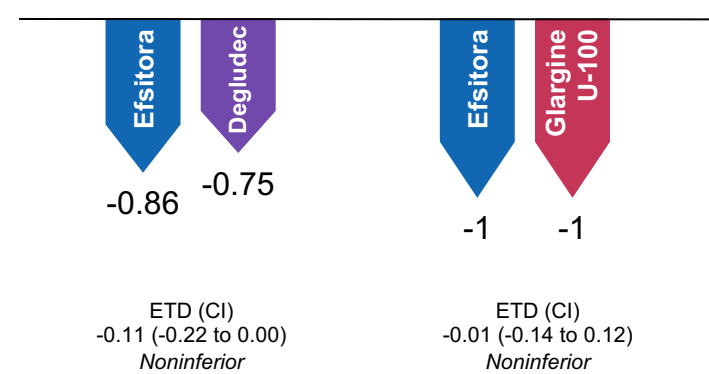
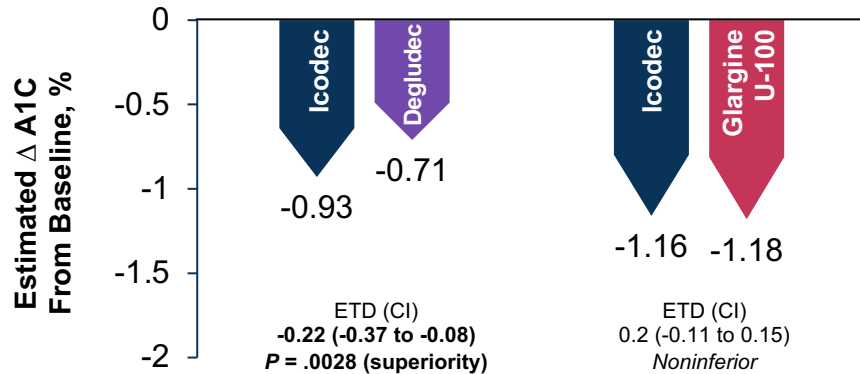


Numbers in black circles represent weekly injections.
1. Rosenstock J et al. *Endocr Rev.* 2024;45:379-413.

Once-Weekly and Once-Daily Basal Insulin Have Similar Efficacy in Insulin-Experienced PwT2DM

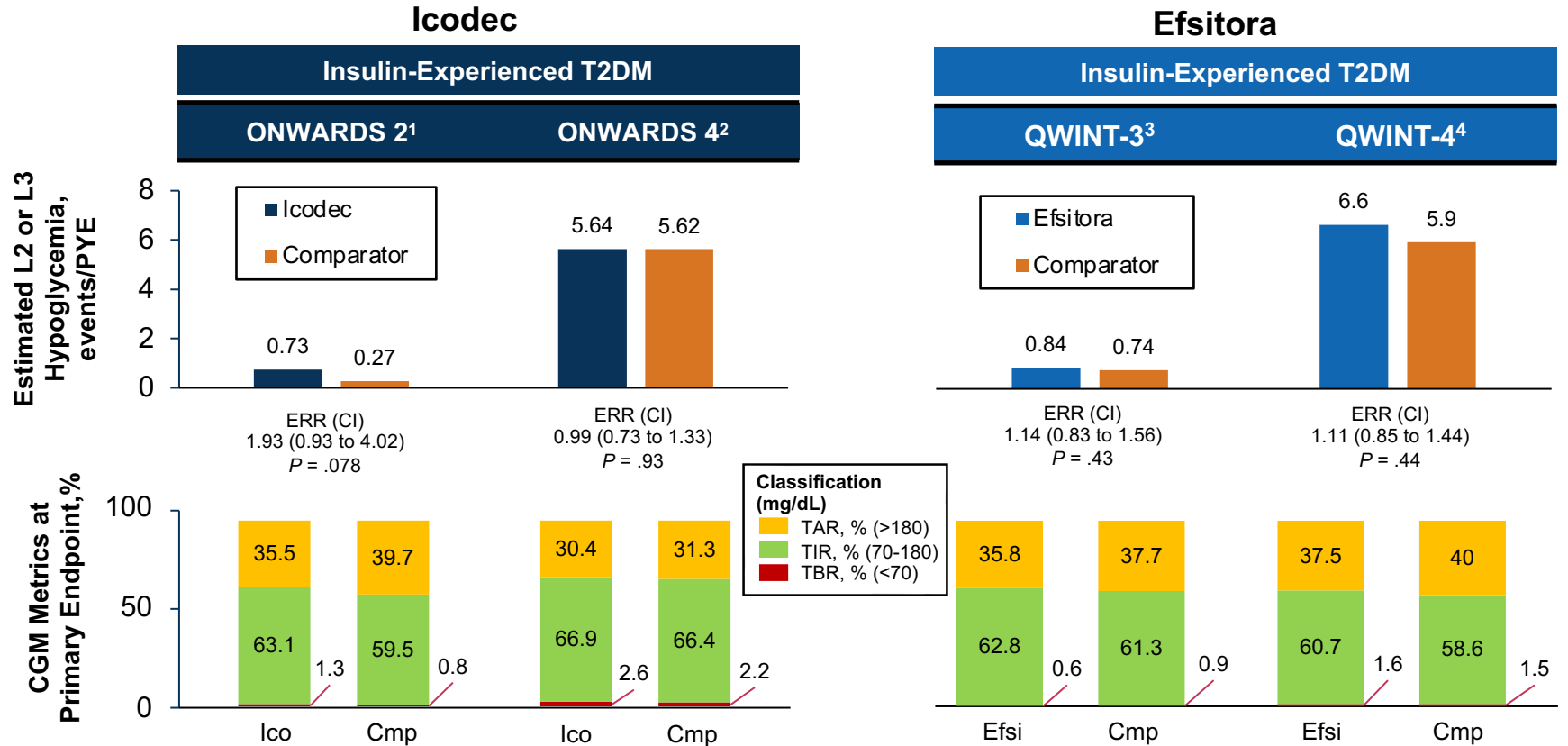
	Icodec	
	Insulin-Experienced T2DM	
Trial Name	ONWARDS 2 ¹	ONWARDS 4 ²
Design	Basal switch	BBT switch
Baseline A1C, %	8.1	8.3

	Efsitora	
	Insulin-Experienced T2DM	
Trial Name	QWINT-3 ³	QWINT-4 ⁴
Design	Switch from basal	Replace basal in MDI
Baseline A1C, %	7.7	8.4



1. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol.* 2023;11:414-425. 2. Mathieu C et al. *Lancet.* 2023;401:1929-1940.
 3. Philis-Tsimikas A et al. *Lancet.* 2025;405:2279-2289. 4. Blevins T et al. *Lancet.* 2025;405:2290-2301.

Hypoglycemia Incidence for Once-Weekly Insulins Is Generally Similar to Once-Daily Insulins



1. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol.* 2023;11:414-425. 2. Mathieu C et al. *Lancet.* 2023;401:1929-1940.
 3. Philis-Tsimikas A et al. *Lancet.* 2025;405:2279-2289. 4. Blevins T et al. *Lancet.* 2025;405:2290-2301.

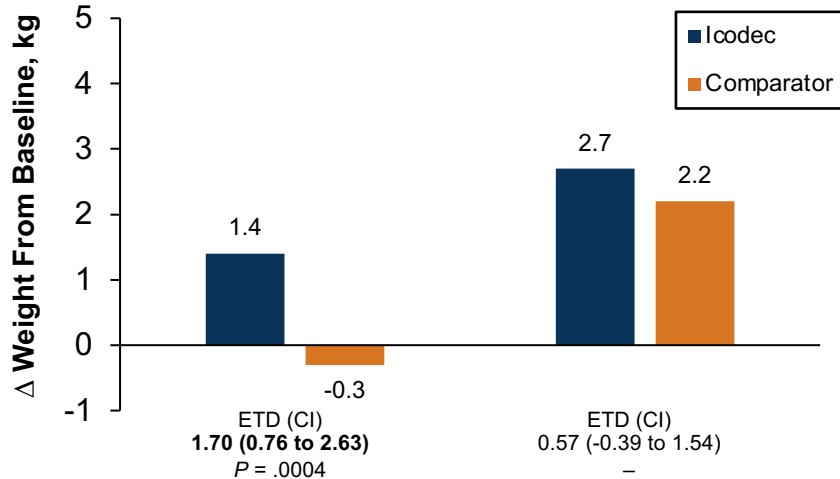
Comparable Weight Gain With Once-Weekly Insulins and Once-Daily Insulins in 3 of 4 Trials

Icodec

Insulin-Experienced T2DM

ONWARDS 2¹

ONWARDS 4²



Icodec, BL, kg

NR

85.5

Efsitora, BL, kg

83.6

87.8

Cmprtr, BL, kg

NR

83.1

Cmprtr, BL, kg

84.3

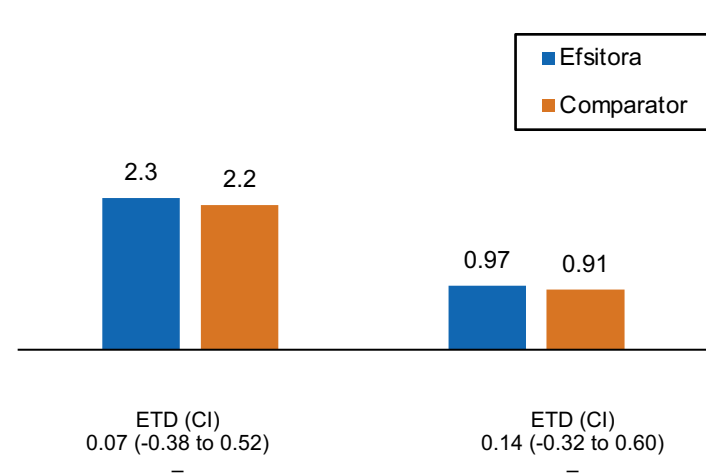
88.4

Efsitora

Insulin-Experienced T2DM

QWINT-3³

QWINT-4⁴



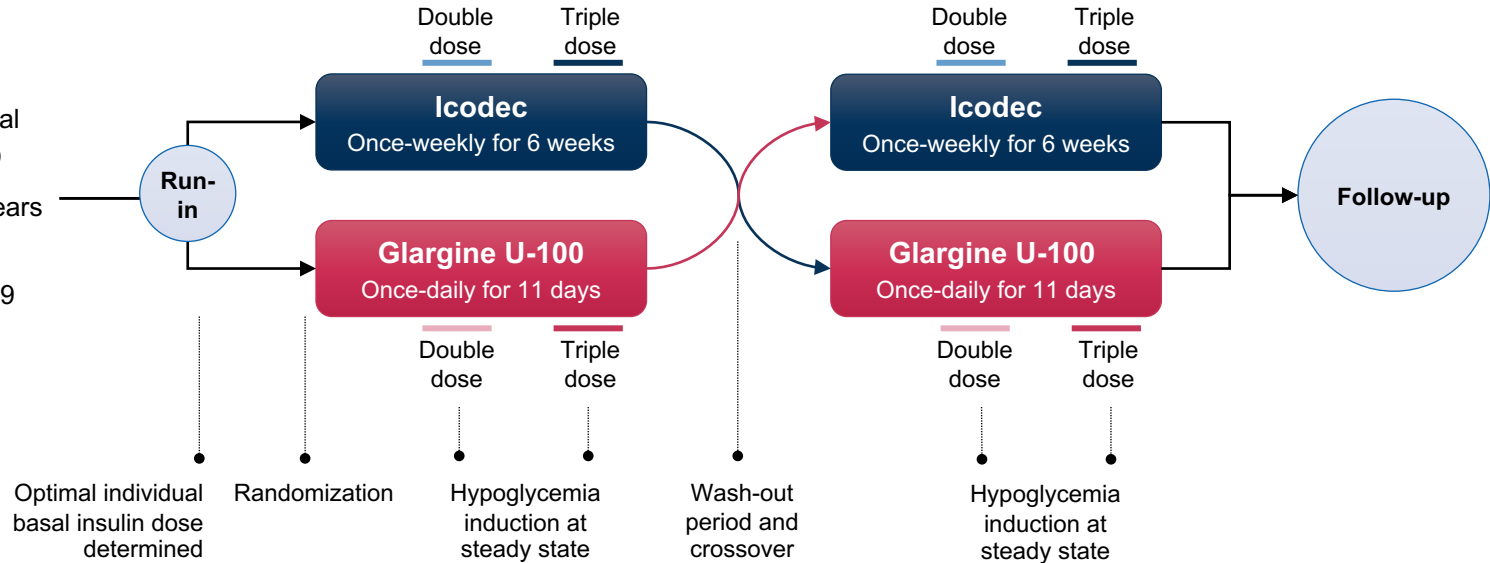
1. Philis-Tsimikas A et al. *Lancet Diabetes Endocrinol.* 2023;11:414-425. 2. Mathieu C et al. *Lancet.* 2023;401:1929-1940.

3. Philis-Tsimikas A et al. *Lancet.* 2025;405:2279-2289. 4. Blevins T et al. *Lancet.* 2025;405:2290-2301.

Hypoglycemia Frequency and Response After Double or Triple Doses of Icodec or Glargine: Crossover Study Design¹

N = 43

- T2DM on basal insulin ± OAD
- Age: 18-72 years
- A1C: ≤9.0%
- BMI: 18.5-37.9 kg/m²



Trial Information

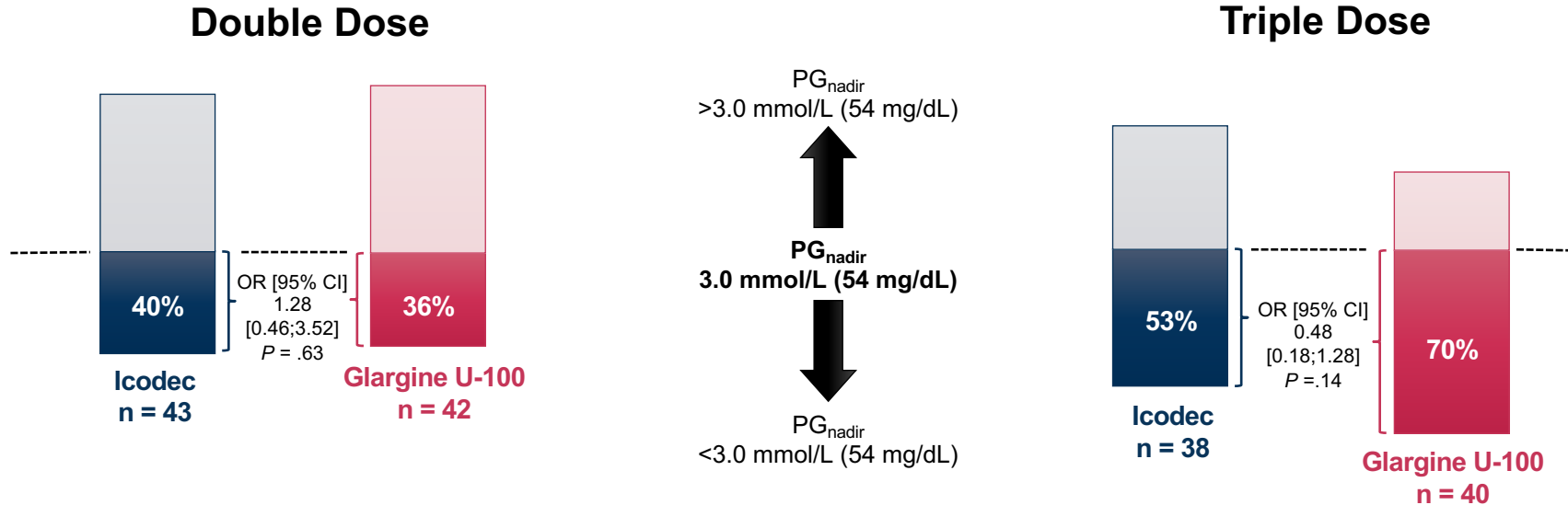
- Randomized
- Open label
- Two period crossover trial

Objectives

- Compare between once-weekly icodec and once-daily glargine U-100 in PwT2DM; specifically
 - Hypoglycemia frequency after double or triple doses
 - Physiological response to hypoglycemia after a triple dose in individuals with plasma glucose <3.0 mmol/L (54 mg/dL) and/or hypoglycemia symptoms

Clinically Significant Hypoglycemia With Icodec Double or Triple Dose Was Similar to Glargine¹

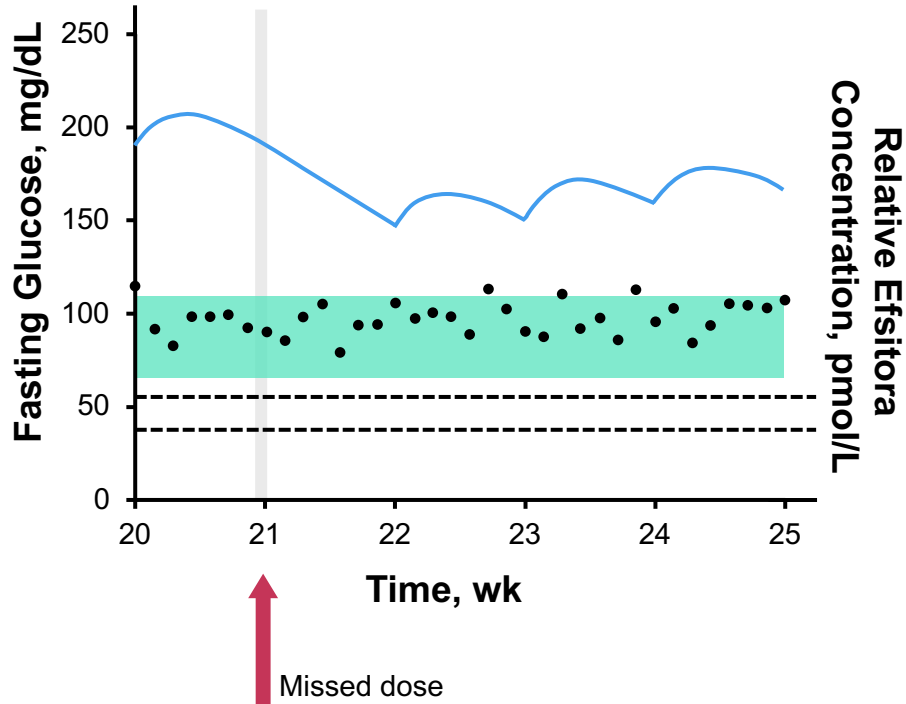
- All participants who completed the hypoglycemia clamp were included



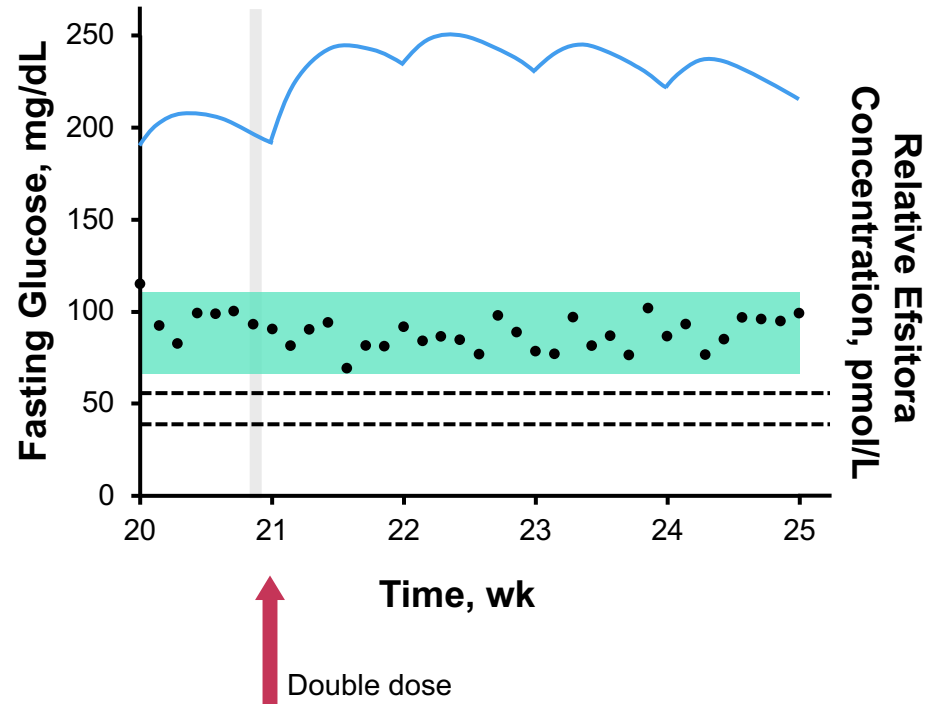
Comparable proportions of individuals experienced clinically significant hypoglycemia ($PG_{nadir} < 3.0$ mmol/L [54 mg/dL]) following both double and triple doses of icodec vs glargine U-100

Modeling Study: A Single Missed or Doubled Efsitora Dose Had Minimal Effects on TIR¹

Missed Dose

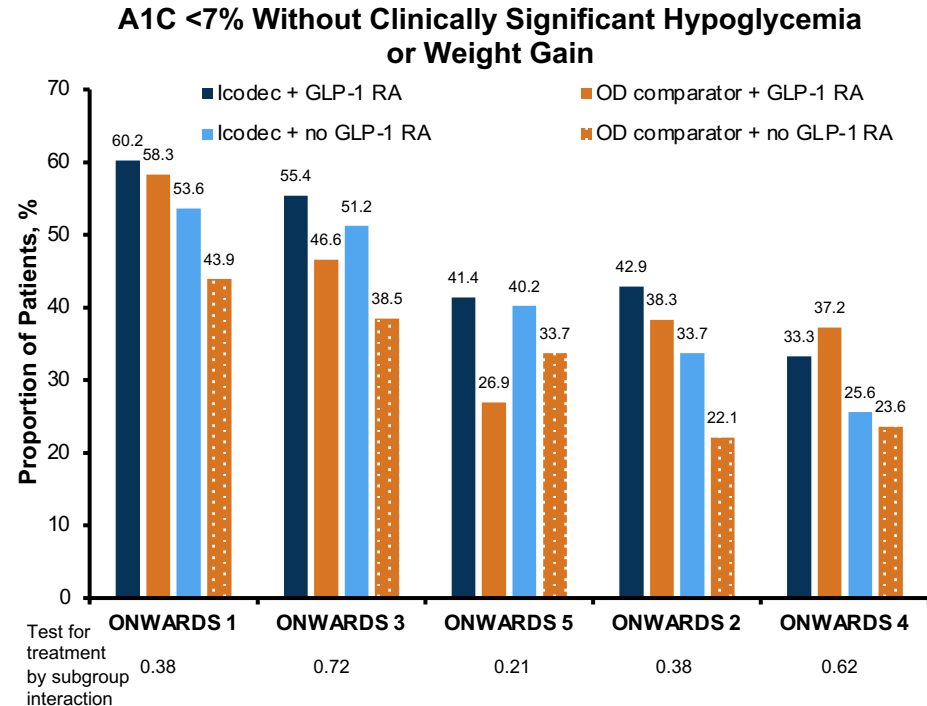
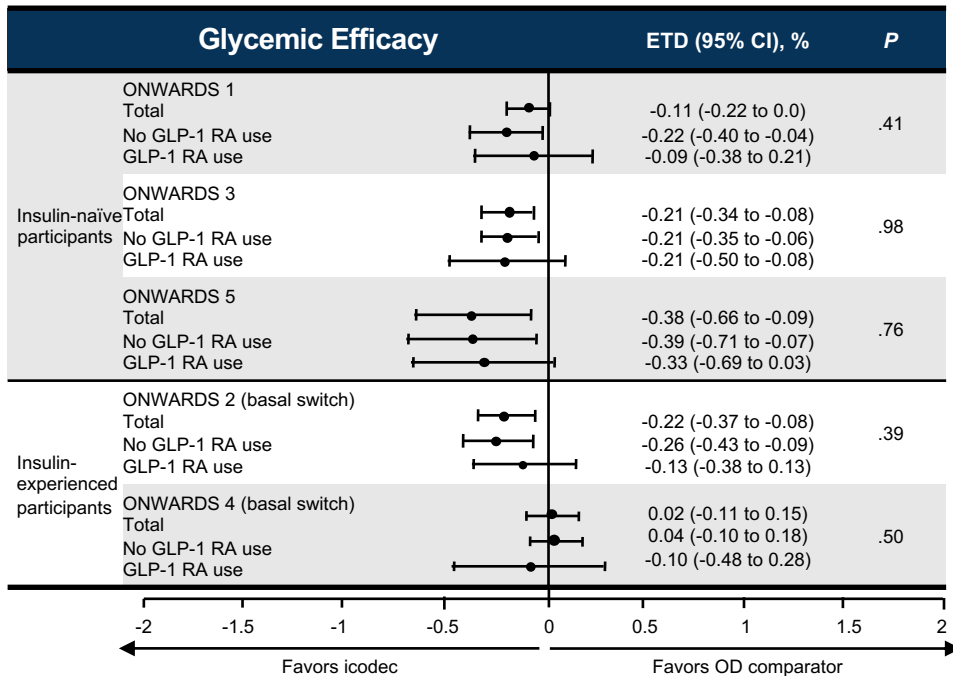


Doubled Dose



1. Pieber TR et al. *Endocr Pract.* 2024;30:863-869.

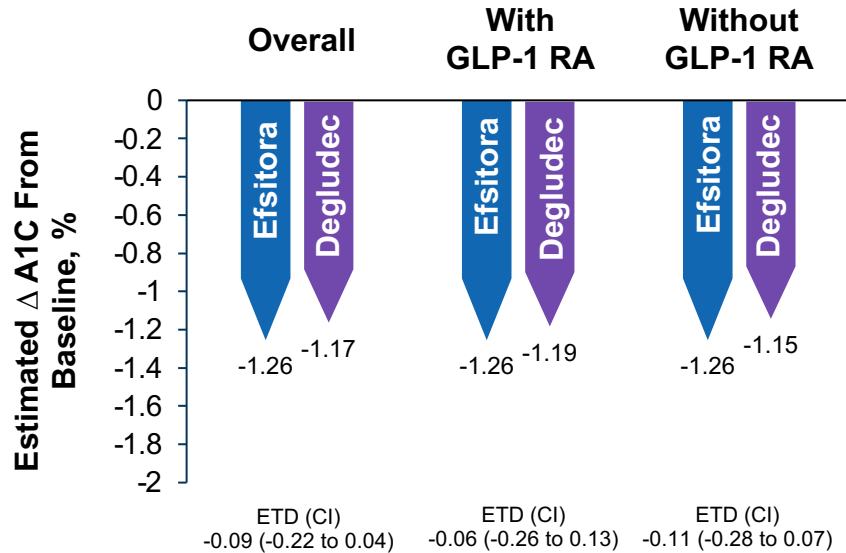
Icodec Efficacy Was Similar With or Without GLP-1 RAs: ONWARDS Program Subgroup Analysis¹



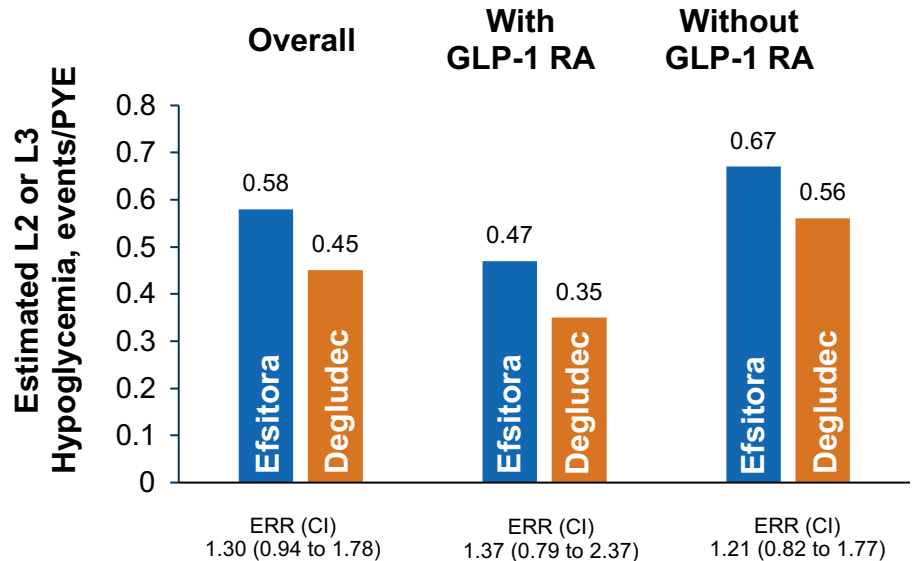
- GLP-1 RAs were used by 801 of 3,765 participants at baseline (21.3%)
- Icodec was similarly effective and safe with or without a GLP-1 RA included in the treatment regimen

Efsitora and Degludec Efficacy and Safety Were Similar With or Without GLP-1 RAs: QWINT-2 Subgroup Analysis^{1,a}

Glycemic Efficacy



Hypoglycemic Safety



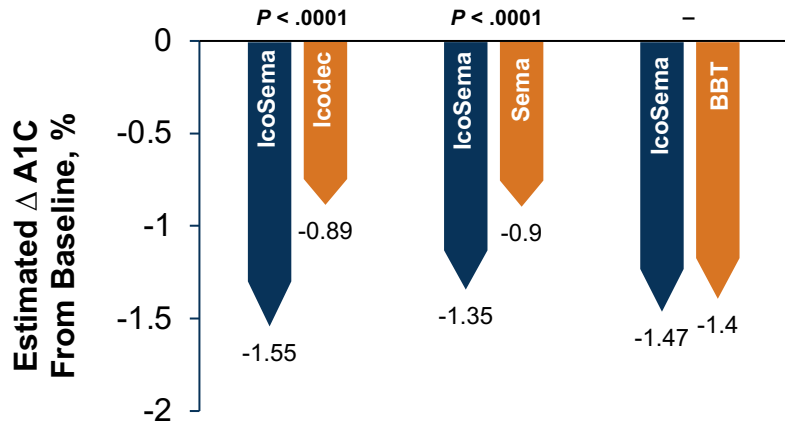
- GLP-1 RAs were used by 464 of 928 participants at baseline (50%)
- Efsitora was noninferior to degludec with or without a GLP-1 RA included in the treatment regimen

^a 95% CI not adjusted for multiplicity.

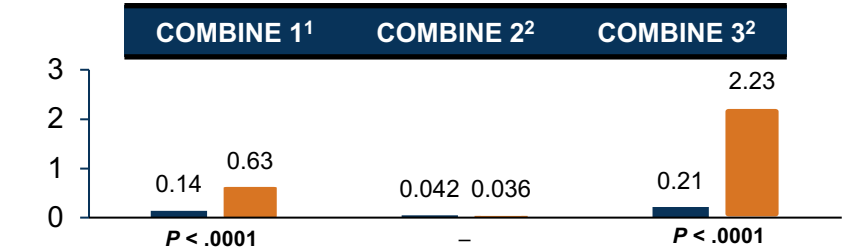
1. Wysham C et al. *N Engl J Med*. 2024;391:2201-2211.

Insulin Icodec Used in Combination With Semaglutide^a

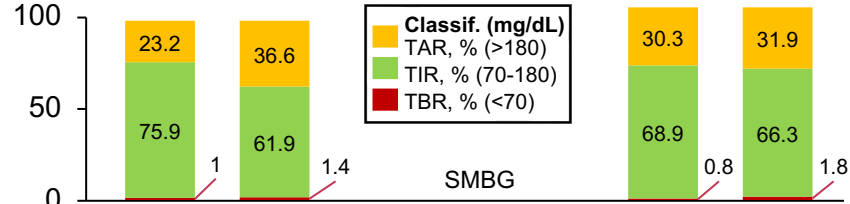
Trial Name	COMBINE 1 ¹	COMBINE 2 ²	COMBINE 3 ²
Design	IcoSema vs icodec	IcoSema vs semaglutide	IcoSema vs BBT ^b
N (randomization)	1,291 (1:1)	683 (1:1)	679 (1:1)
Duration, wk	52	52	52
Confirmed outcome	Superiority	Superiority	Noninferiority
Baseline A1C, %	8.2	8.0	8.3



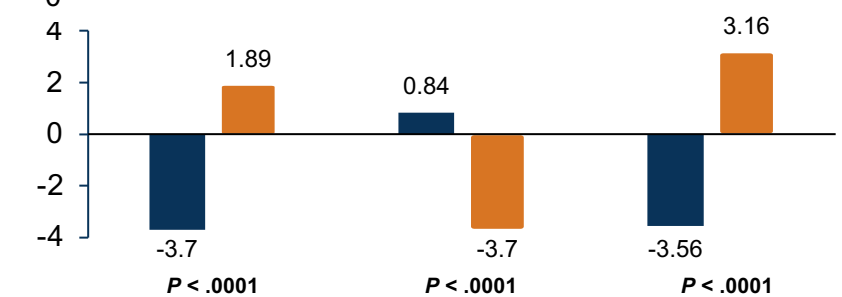
Est. L2 or L3 Hypoglycemia, events/PYE



CGM Metrics at Primary Endpoint, %



Δ Weight From Baseline, kg



IcoSema, BL, kg
Cmprtr, BL, kg

Trial	IcoSema, BL, kg	Comparator, BL, kg
COMBINE 1	83.7	85.3
COMBINE 2	87.6	90.8
COMBINE 3	85.3	86.2

^a IcoSema is an investigational agent. ^b MDI with glargine U-100 QD and aspart with meals 2-4 times daily.

1. Mathieu C et al. *Lancet Diabetes Endocrinol.* 2025;13:568-579. 2. Lingvay I et al. *Diabetologia.* 2025;68:739-751. 3. Billings LK et al. *Lancet Diabetes Endocrinol.* 2025;13:556-567.

Best Practices in the Use of Once-Weekly Insulins in the Perioperative Setting

Should once-weekly insulins be discontinued prior to elective procedures?¹

- ➔ **Yes**, if caloric intake will be reduced >24 h post-procedure or if ≥2 days preoperative liquid diet
- Discontinue **icodec** 4 weeks before, start once-daily basal insulin 2 weeks later (earlier if fasting hyperglycemia)
 - Discontinue **efsitora** 8 weeks before, start once-daily basal insulin 4 weeks later (earlier if fasting hyperglycemia)
 - Divide weekly basal dose by 7 to get daily basal dose
 - Reduce daily basal dose by 50% at the start of a liquid diet

What should we do in an emergency situation?¹

- No dose adjustment to the once-weekly insulin
- Manage hypoglycemia or hyperglycemia per usual protocols

What did we learn from clinical trials?²

- ONWARDS: similar numbers of hospitalizations for icodec and comparators
- Icodec continued during hospitalization in most patients
- Manage similarly to once-daily basal insulins

How do you transition from once-weekly insulin to once-daily insulin?³

Initiate daily basal insulin 2 weeks after the last icodec dose (or earlier if SMBG >10 mmol/L [>180 mg/dL])



Daily basal insulin dose is last icodec dose + 7



Monitor prebreakfast SMBG values daily



Titrate basal insulin once or twice weekly based on SMBG and the local label

PwT2DM Prefer Once-Weekly Insulin to Once-Daily Insulin: Summary of PROs From ONWARDS and QWINT^{1,2}

PRO Measure	Icodec: ONWARDS 1, 2, 5 ¹	Efsitora: QWINT 1-4 ²
DTSQs Treatment Satisfaction	Higher satisfaction due to convenience, willingness to continue, and recommend	Improved satisfaction, mainly due to reduced treatment burden and higher overall satisfaction
TRIM-D Compliance	Better compliance with app, fewer missed/delayed doses	Better compliance than glargine or degludec, indicating better adherence
TRIM-D Treatment Burden	Reduced treatment burden, especially convenience	Significant reduction in treatment burden compared with daily insulins
TRIM-D Diabetes Management	Improved management, especially treatment flexibility	Greater improvement, especially in managing daily activities
Quality of Life	High satisfaction with the insulin pen, easy to use	No significant differences between efsitora and daily insulins
Preference for Insulin	93.7% preferred icodec over previous daily insulin	Strong preference for efsitora, more likely to use

Case Study Follow-Up Visit at 6 Months: Janine, a French Woman Aged 57 Years

- **Medical history:** T2DM, 8 years; TIA, 8 years ago
- **A1C:** ~~7.9% (63 mmol/mol)~~ → **7.6% (60 mmol/mol)**
- **Weight:** ~~80 kg~~ → **82 kg**
- **BMI:** ~~29 kg/m²~~ → **29.3 kg/m²**
- **eGFR:** 46 mL/min/1.73 m²;
UACR: 102 mg/g (10 mg/mmol)
- **Current medications**
 - Dapagliflozin 10 mg once daily at bedtime
 - **Icodec U-700 227 units once weekly**
 - ~~Glargine U-100 40 units once daily at bedtime~~

Patient Notes

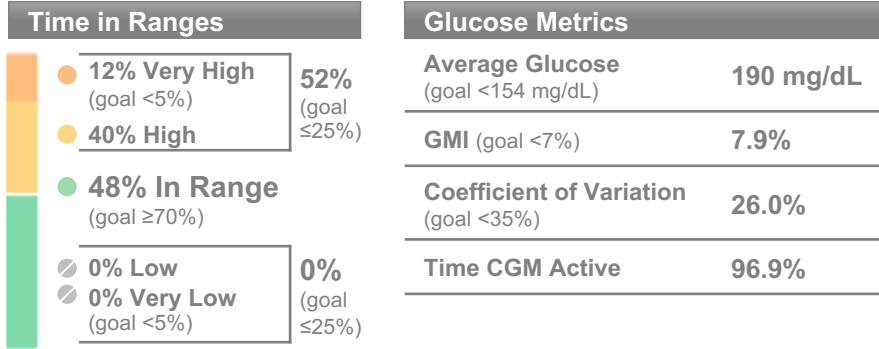
- Work requires frequent travel across time zones
- ~~Missing ~2 injections/wk~~ → **reports satisfaction with once-weekly basal insulin, and has missed only one dose since initiating 6 months ago**
- Had severe nausea and vomiting on two different GLP-1 RAs



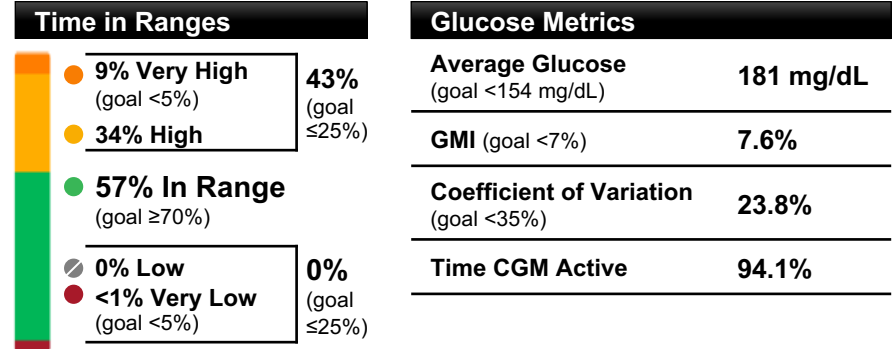
AI-generated patient image

Ambulatory Glucose Profile at 6-Month Follow-Up: Janine, a French Woman Aged 57 Years

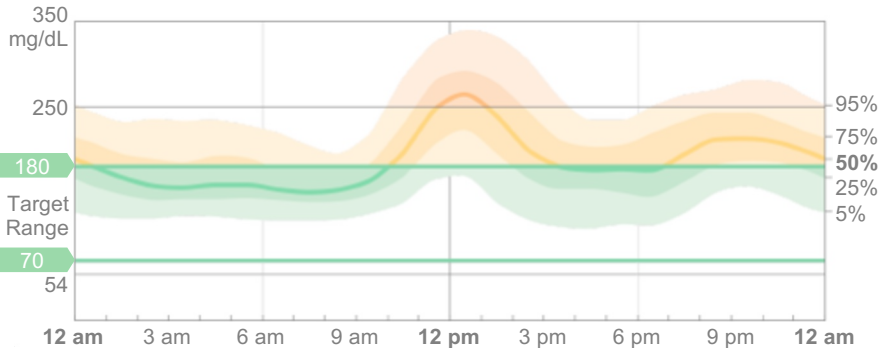
Prior to Once-Weekly Basal Insulin Initiation



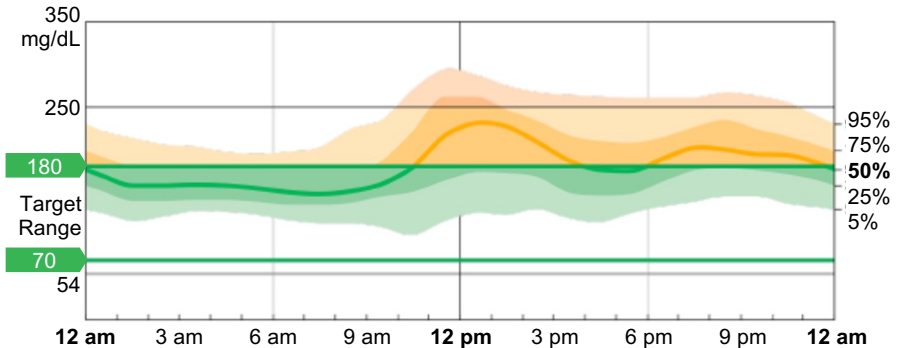
6 Mo After Once-Weekly Basal Insulin Initiation



Ambulatory Glucose Profile



Ambulatory Glucose Profile



What are your recommendations for Janine?

Closing and Key Takeaways



Prof. Chantal Mathieu, MD, PhD

Endocrinology
UZ Gasthuisberg
KULeuven
Leuven, Belgium

Recap of Key Clinical Decision Points



PwT2DM who can use once-daily basal insulin can use once-weekly basal insulin



Initial doses and titration steps for once-weekly insulin are usually 7 times as large as for once-daily insulin



Once-weekly insulins can be used with the same glucose-lowering medications as once-daily insulins

Thank You for Joining Us!

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on X @PeerView



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- Stay tuned for the online activity based on this event!

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Abbreviations

- A1C: glycated hemoglobin
- ADA: American Diabetes Association
- ATTD: Advanced Technologies & Treatments for Diabetes
- AUC: area under the curve
- BBT: basal-bolus therapy
- BID: twice daily
- CDS: Chinese Diabetes Society
- CGM: continuous glucose monitoring
- CPD: continuing professional development
- CSII: continuous subcutaneous insulin infusion
- DKA: diabetic ketoacidosis
- DPP-4: dipeptidyl peptidase-4
- DTSQs: Diabetes Treatment Satisfaction Questionnaire – status version
- EASD: European Association for the Study of Diabetes
- ECNU: Endocrine Certification in Neck Ultrasound
- ERR: event rate ratio
- ETD: estimated treatment difference
- FACE: Fellow of the American College of Endocrinology
- FBG: fasting blood glucose
- FG: fasting glucose
- GIP: glucose-dependent insulinotropic peptide
- GLP-1 RA: glucagon-like peptide-1 receptor agonist
- GLP-1: glucagon-like peptide-1
- GMI: glucose management indicator
- GUR: glucose utilization rate
- HCP: healthcare professional
- HHS: hyperglycemic hyperosmolar state
- IgG2: immunoglobulin G subclass 2
- JDS: Japan Diabetes Society
- MDI: multiple daily injections
- NPH: neutral protamine Hagedorn
- OAD: oral antidiabetic drug
- OR: overall response
- PDC: proportion of days covered
- PG: plasma glucose
- PRO: patient-reported outcome
- PwT2DM: person with type 2 diabetes mellitus
- PYE: patient-years of exposure
- QD: once daily
- QW: once weekly
- RHI: regular human insulin
- RPG: random plasma glucose
- SC: subcutaneous
- SGLT2: sodium-glucose cotransporter 2
- SGLT2i: sodium-glucose cotransporter 2 inhibitor
- SMBG: self-monitored of blood glucose
- SMPG: self-monitored plasma glucose
- T1DM: type 1 diabetes mellitus
- T2DM: type 2 diabetes mellitus
- TAR: time above range
- TBR: time below range
- TIR: time in range
- TRIM-D: Treatment-Related Impact Measure – Diabetes