Less is More:
The Promise of Weekly Insulin in Type 2 Diabetes

Once-Weekly Insulin: Trials, Trends, and Tackling Inertia

This activity is jointly provided by

MLI

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This activity is supported by an educational grant from Lilly.

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Activity Overview

Target Audience

This activity is intended for PCPs and other members of the healthcare team in the U.S. who care for patients with T2D.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the place of novel insulin therapies, including once-weekly basal insulin, in treating type 2 diabetes

Agenda

- Introduction to Once-Weekly Insulin Formulations
- Clinical Trial Results
- Simplifying Data Interpretation

Accreditation Information

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute Inc, and ACOFP. Medical Learning Institute Inc is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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The American College of Osteopathic Family Physicians (ACOFP) is accredited by the American Osteopathic Association (AOA) to provide osteopathic continuing medical education for physicians.

ACOFP designates this enduring activity for a maximum of 0.25 AOA Category 1-A credits and will report continuing medical education (CME) credits commensurate with the physician's participation in this program.

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Participation information will be shared through the ACCME's Program and Activity Reporting System (PARS).

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The AAFP has reviewed Less is More: The Promise of Weekly Insulin in Type 2 Diabetes and deemed it acceptable for up to 0.25 Enduring Materials, Self-Study AAFP Prescribed credit(s). Term of Approval is from 02/18/2025 to 02/03/2026. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Eda Cengiz, MD, MHS, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Arecor, Eli Lilly, MannKind, Novo Nordisk, Portal Insulin, Tandem

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The following relationships have ended within the last 24 months:
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Research Support: AbbVie, Bayer, Eli Lilly, Novo Nordisk (all to institution)
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Method of Participation
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Intro to Once-Weekly Insulin Formulations

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Where Does Basal Insulin Fit?

ADA recommends starting basal insulin when:

- Individualized A1C targets are not achieved with non-insulin therapies (including either GLP-1 RA or SGLT2i)
- Individuals present with blood glucose ≥ 300 mg/dL or A1C > 10%
- Individuals have ongoing catabolism, and/or symptoms of glucotoxicity

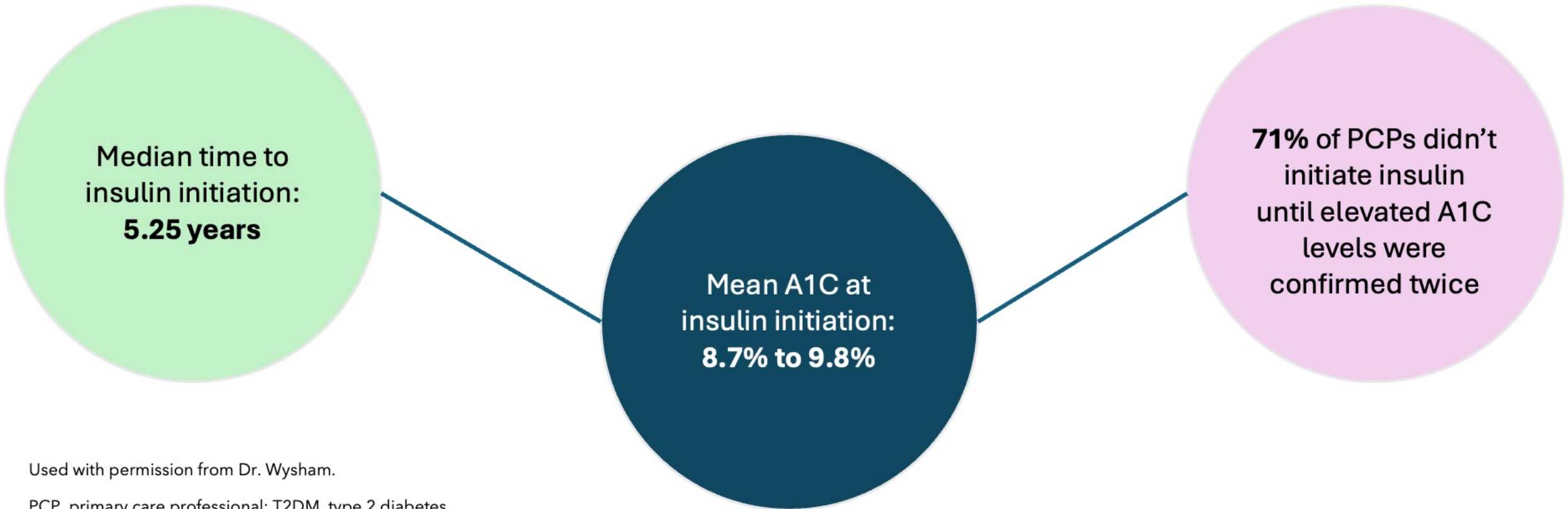
Used with permission from Dr. Wysham.

A1C, glycated hemoglobin; ADA, American Diabetes Association; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium/glucose co-transporter-2 inhibitor

ADA Professional Practice Committee. *Diabetes Care*. 2024;47(Suppl 1):S158-S178.

Is Basal Insulin Being Initiated Appropriately?

A review of 22 studies conducted over a 10-year period in people with T2D showed that initiation of basal insulin therapy is often delayed

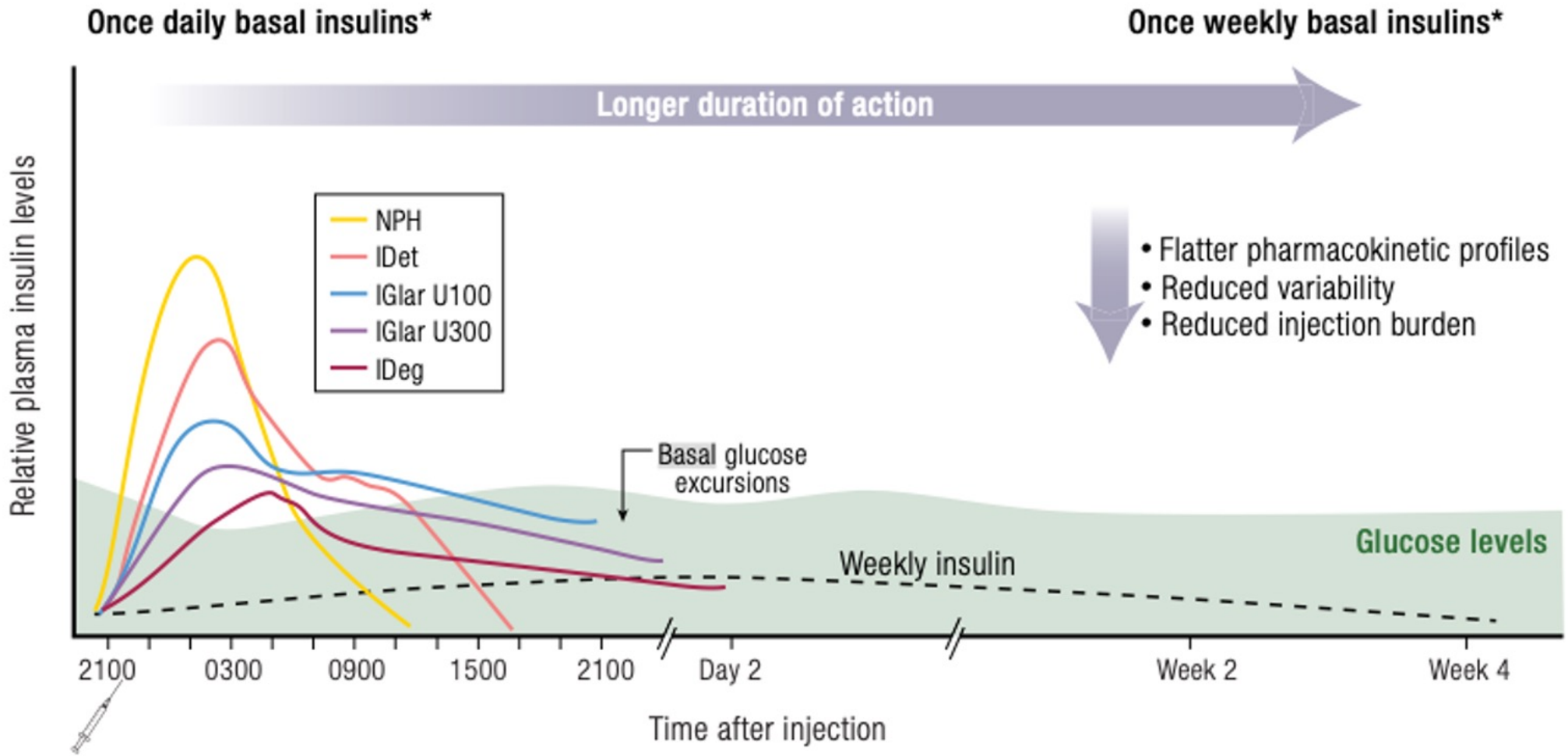


Used with permission from Dr. Wysham.

PCP, primary care professional; T2DM, type 2 diabetes.

Gavin JR, et al. *Diabetes Spectr*. 2023;36(4):379-384; Kostev K, et al. *J Diabetes Sci Technol*. 2019;13(6):1129-1134; Escalada J, et al. *Diabetes Res Clin Pract*. 2016;122:46-53.

Time Action Profiles of Current Insulins



Once-weekly basal insulin formulations are not currently approved by the FDA.

Rosenstock J, et al. *Endocrine Rev*. 2024;45(3):379-413.

Attributes of Once-Weekly Insulin Therapy

Clinical	Molecular
Improved or similar glycemic control with low hypoglycemia risk	Long half-life
Reduced treatment burden	More stable pharmacokinetics/ pharmacodynamics, with less inter-patient and intra-patient variability
Easier to overcome therapeutic inertia	Slower clearance

Better treatment acceptance and adherence

Once-weekly basal insulin formulations are not currently approved by the FDA.

Karakasis P, et al. *Diabetes Obes Metab*. 2023;25(12):3648-3661.

Clinical Trial Results

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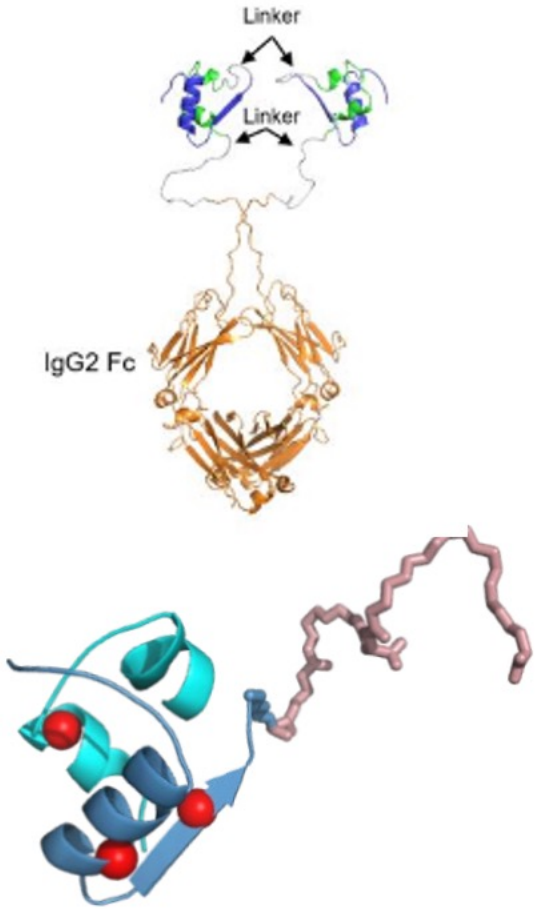
New Technologies to Increase Basal Insulin Half-Life



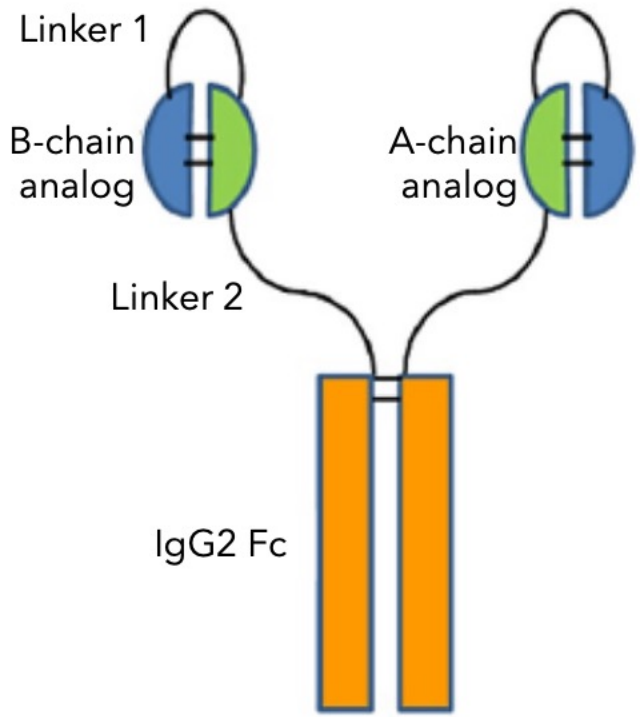
- **Insulin Efsitora alfa (Efsitora)**
  - Novel single-chain variant of insulin fused to human immunoglobulin G (IgG) Fc domain
  - Homo-dimer
  - Reduced insulin receptor potency with full agonism
  - Time-action profile (t½ = approx. 17 days) supports once-weekly dosing in humans
  - Currently in Phase III trials
- **Insulin Icodec (Icodec)**
  - Acylated insulin: 20-carbon fatty diacid sidechain
  - High albumin binding
  - Reduced enzymatic degradation
  - Reduced insulin receptor-mediated clearance
  - Time-action profile (t½ = approx. 8 days) supports once-weekly dosing in humans
  - Phase III complete

Once-weekly basal insulin formulations are not currently approved by the FDA.

Moyers J, et al. *J Endocr Soc*. 2021;5 (suppl 1):A442; Heise T ,et al. *Diabetes Res Clin Pract*. 2021;175:108820.

Insulin Efsitora Alfa: An Insulin Analog Designed for Once-Weekly Administration

Insulin efsitora alfa is an insulin receptor agonist that combines a novel single-chain variant of insulin with a human IgG2 Fc domain. It is designed for once-weekly subcutaneous administration.



Adapted with permission from Dr. Wysham.

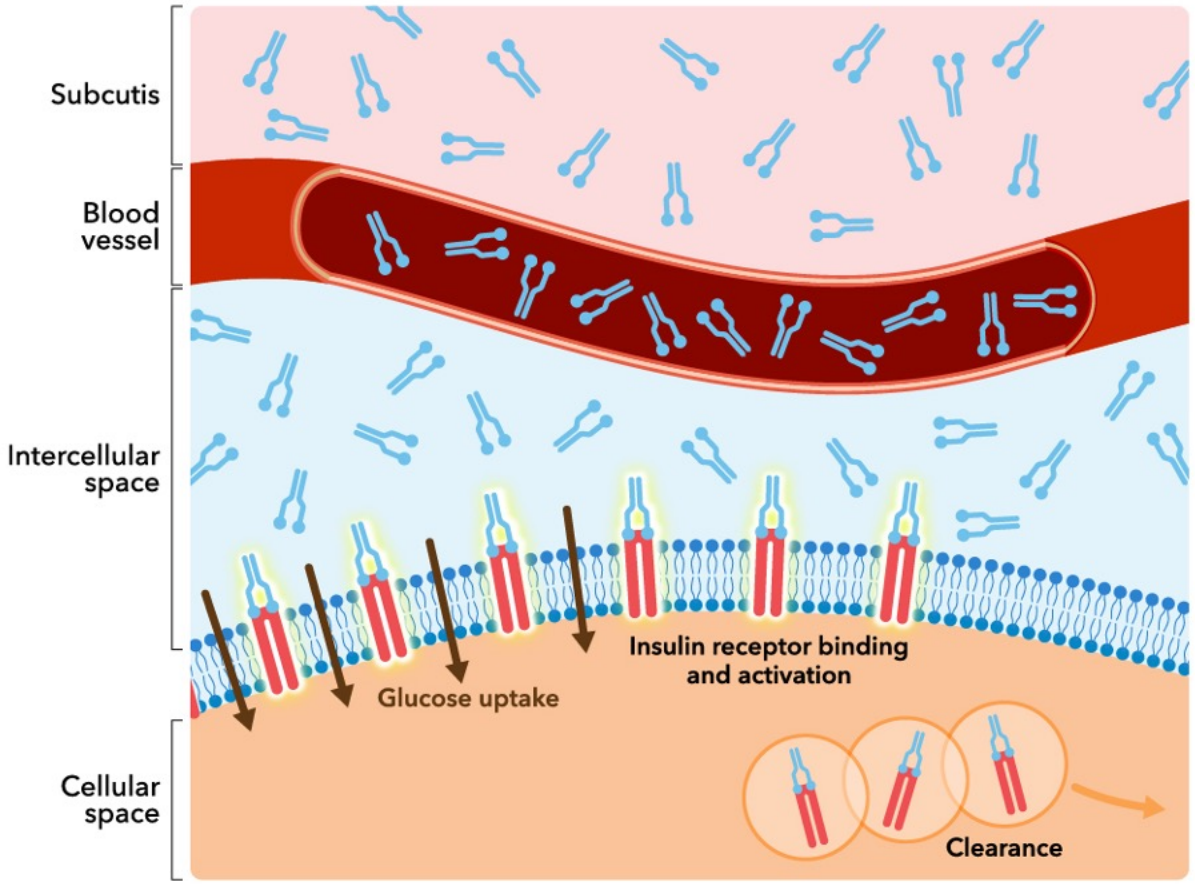
Efsitora alfa is not currently approved by the FDA.

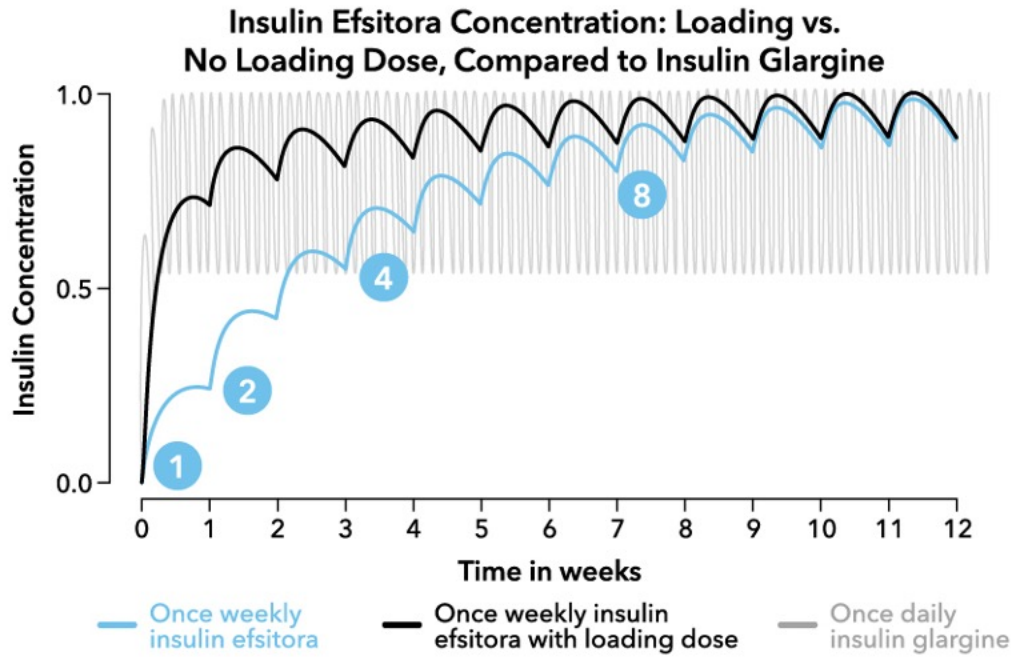
Fc-Rn, neonatal fragment crystallizable.

Figure reproduced from Moyers JS, et al., 2022, with permission as per Creative Commons license CC BY 4.0. https://creativecommons.org/licenses/by/4.0/.

Moyers JS, et al. *Pharmacol Exp Ther*. 2022;382(2):346-355.

Insulin Efsitora: Dosing and Time to Steady State





Rosenstock J, et al. *Endocrine Rev*. 2024;45(3):379-413.

Insulin Efsitora: QWINT Phase III Trial Program

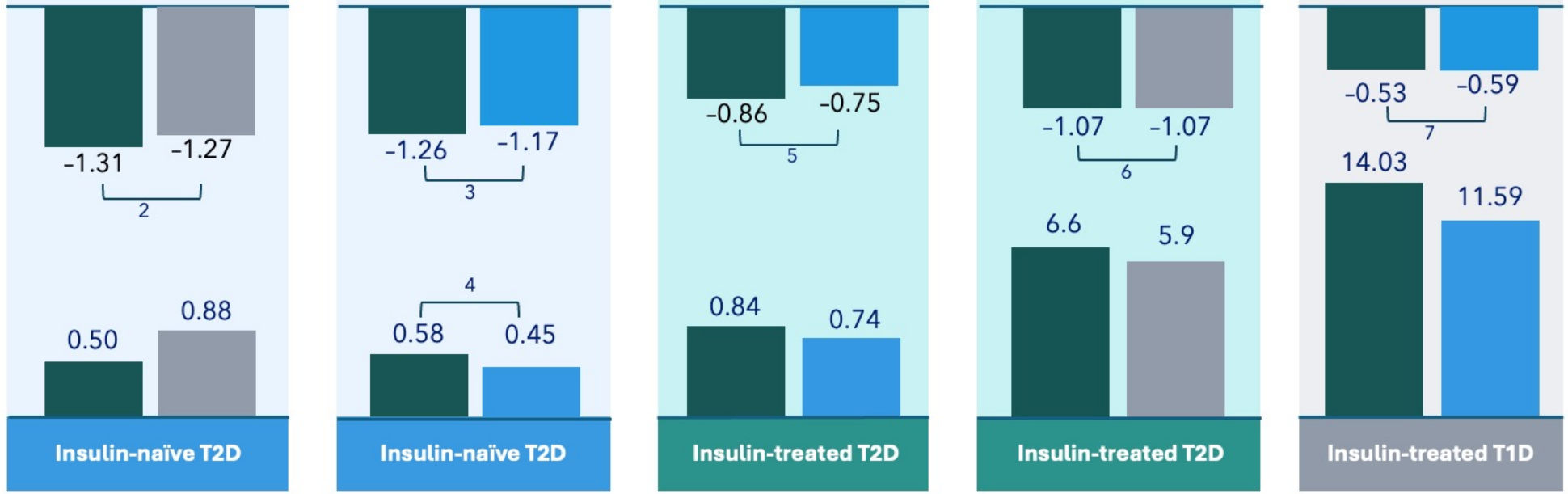
Phase III Trial Program	Duration (Weeks)	Patients Enrolled	Comparator: Weekly Insulin Icodec Versus Daily…	Study Population
QWINT-1 (NCT05662332)	52	670	Insulin glargine U100	Insulin-naïve patients
QWINT-2 (NCT05362058)	52	928	Insulin degludec	At least one glucose-lowering medication
QWINT-3 (NCT05275400)	78	986	Insulin degludec	Basal insulins ± up to three non-insulin drugs (except sulfonylureas)
QWINT-4 (NCT05462756)	26	730	Insulin glargine U100 (Both groups on bolus insulin lispro 2 to 4×/day)	Multiple daily insulin injections
	Total	***3 238***		
QWINT-5 (NCT05463744)	52	670	Insulin degludec	Patients with type 1 diabetes (T1D), previously treated with multiple daily insulin injections

QWINT 1: https://ClinicalTrials.gov/show/NCT05662332; QWINT 2: https://ClinicalTrials.gov/show/NCT05362058; QWINT 3: https://clinicaltrials.gov/study/NCT05275400; QWINT-4: https://ClinicalTrials.gov/show/NCT05462756; QWINT 5: https://clinicaltrials.gov/study/NCT05463744.

Insulin Efsitora: Efficacy and Safety of the Phase III QWINT Program

	QWINT 1	QWINT 2	QWINT 3	QWINT 4	QWINT 5
	BASAL INITIATION	BASAL INITIATION	BASAL SWITCH	BASAL SWITCH	BASAL/BOLUS SWITCH
Trial duration (weeks)	52	52	78	26	52
Baseline HbA_{1c} (%)		8.22%			
Non-inferiority confirmed	✓	✓	✓	✓	✓
Superiority confirmed		No			

Estimated change from baseline in HbA_{1c} (%)



Learning Point!

Hypoglycemia event rates[1]

Once-weekly insulin efsitora alfa | Once-daily insulin degludec | Once-daily insulin glargine

1. Events per participant-year of exposure; 2. 95% CI, -0.22 to 0.04; 3. 95% CI, 0.94 to 1.78; 4. 95% CI, -0.22 to 0.061; 5. 95% CI, -0.19 to 0.12; 6. 95% CI, -0.22 to 0; 7. 95% CI, -0.075% to 0.19%.

QWINT 1. https://www.clinicaltrials.gov/ct2/show/NCT05662332; QWINT 2. https://www.clinicaltrials.gov/ct2/show/NCT05362058; QWINT 3. https://www.clinicaltrials.gov/ct2/show/NCT05275400; QWINT 4. https://www.clinicaltrials.gov/ct2/show/NCT05462756; Eli Lilly and Company. With Once-a-Week Dosing, Insulin Efsitora Alfa Delivers A1C Reduction and Safety Profile Consistent with Daily Insulin. May 16, 2024; Eli Lilly and Company. In a first-of-its-kind fixed dose study, once weekly insulin efsitora alfa leads to A1C reduction similar to daily insulin. September 5, 2024; Bergenstal RM, et al. *Lancet.* 2024;404(10458):1132-1142; Wysham C, et al. *N Engl J Med.* 2024;391(23):2201-2211.

Insulin Efsitora: Phase III – Safety Outcomes

QWINT-1, -2, and -3: Overall safety and tolerability profile of efsitora was similar to that of daily basal insulin therapies for the treatment of T2D

QWINT-2

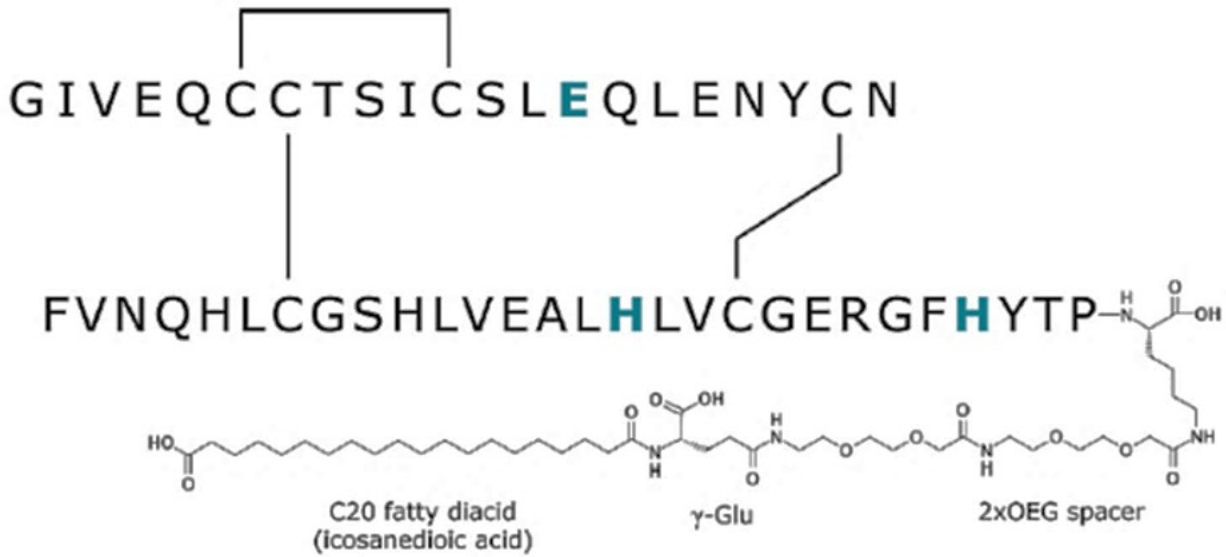
- Rates of serious adverse events (AEs): 8.8% with efsitora, 8.2% with degludec
- Rates of injection site reactions (all mild): 2.4% with efsitora, 1.7% with degludec
- Average change in bodyweight: +3.6 kg with efsitora, +3.5 kg with degludec

Eli Lilly and Company. With Once-a-Week Dosing, Insulin Efsitora Alfa Delivers A1C Reduction and Safety Profile Consistent with Daily Insulin. May 16, 2024. https://investor.lilly.com/news-releases/news-release-details/once-week-dosing-insulin-efsitora-alfa-delivers-a1c-reduction; Wysham C, et al. *N Engl J Med*. 2024;391(23):2201-2211; Eli Lilly and Company. In a first-of-its-kind fixed dose study, once weekly insulin efsitora alfa leads to A1C reduction similar to daily insulin. September 5, 2024. https://investor.lilly.com/news-releases/news-release-details/first-its-kind-fixed-dose-study-once-weekly-insulin-efsitora.

Insulin Icodec: An Insulin Analog Designed for Once-Weekly Administration

Insulin icodec is a novel ultralong-acting insulin analog with a C20 fatty diacid–containing side chain. It is designed for once-weekly subcutaneous administration

[CONSIDER SPEAKING TO THE WHY OF ONCE-WEEKLY BASAL INSULIN]



Adapted with permission from Dr. Wysham.

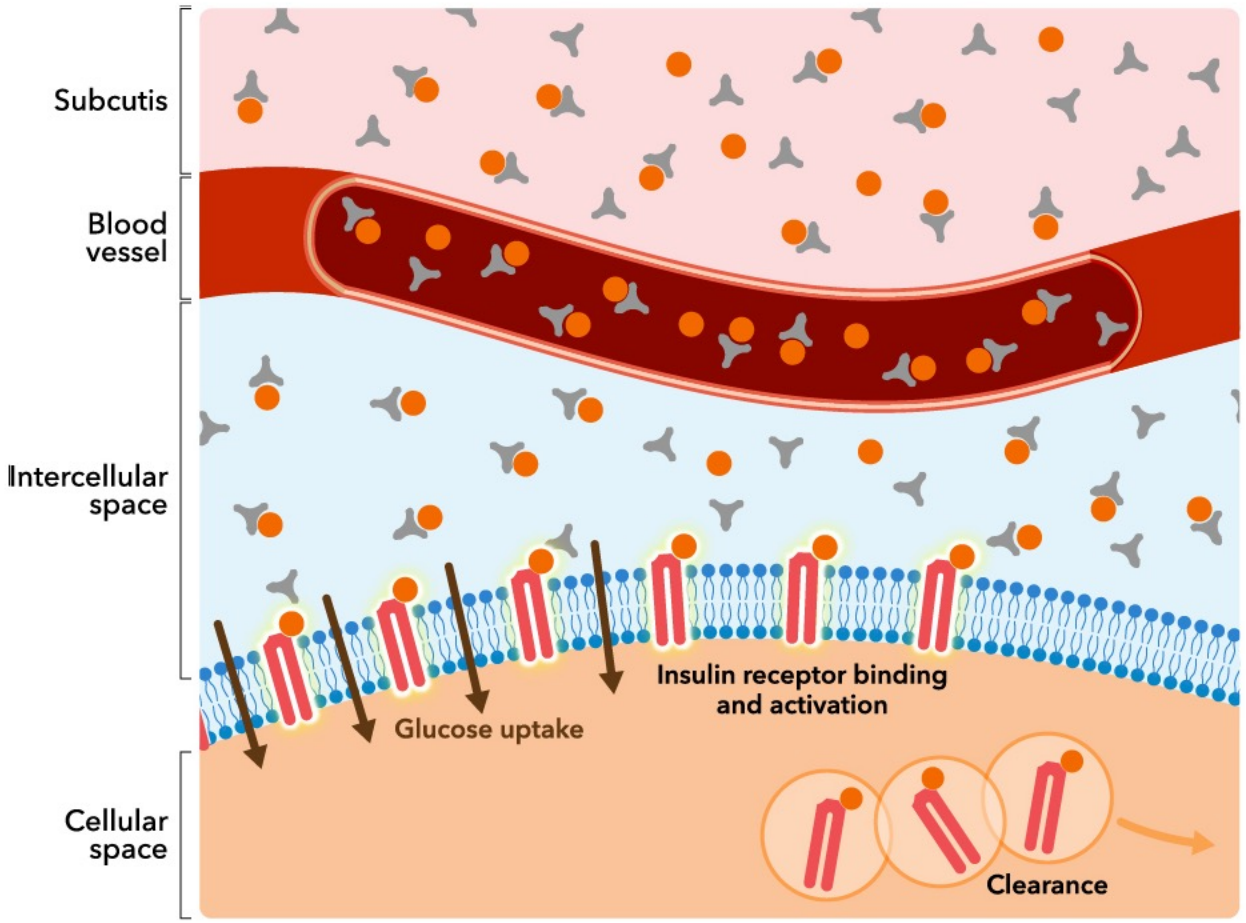
Icodec is not currently approved by the FDA.

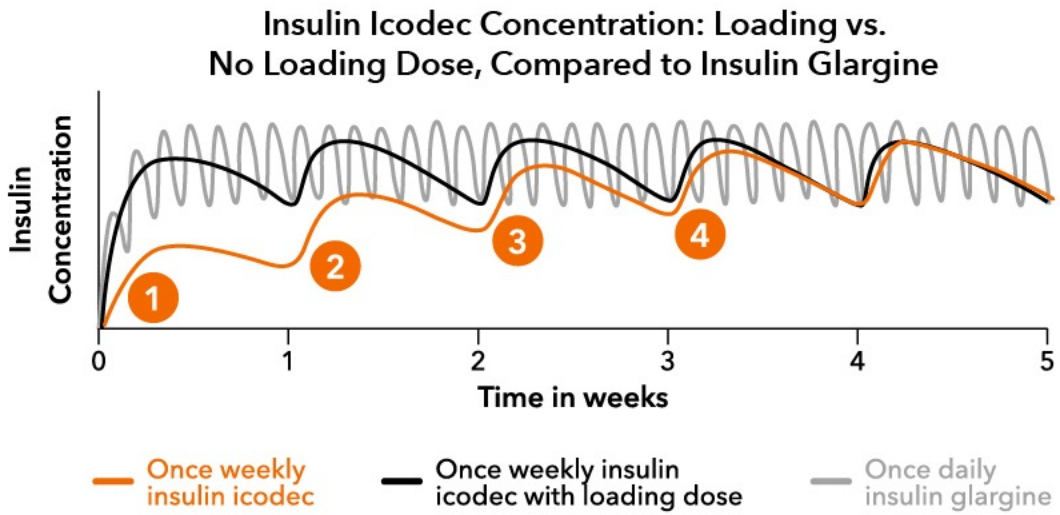
hIR, human insulin receptor; IGF-1R, insulin-like growth factor-1 receptor; IR, insulin receptor.

Figure reproduced from Nishimura E, et al., 2021, with permission as per Creative Commons license CC BY-NC-ND. https://creativecommons.org/licenses/by-nc-nd/4.0/.

Nishimura E, et al. *BMJ Open Diabetes Res Care*. 2021;9(1):e002301.

Insulin Icodec: Dosing and Time to Steady State (MOA)





MOA, mechanism of action.

Rosenstock J, et al. *Endocrine Rev*. 2024;45(3):379-413.

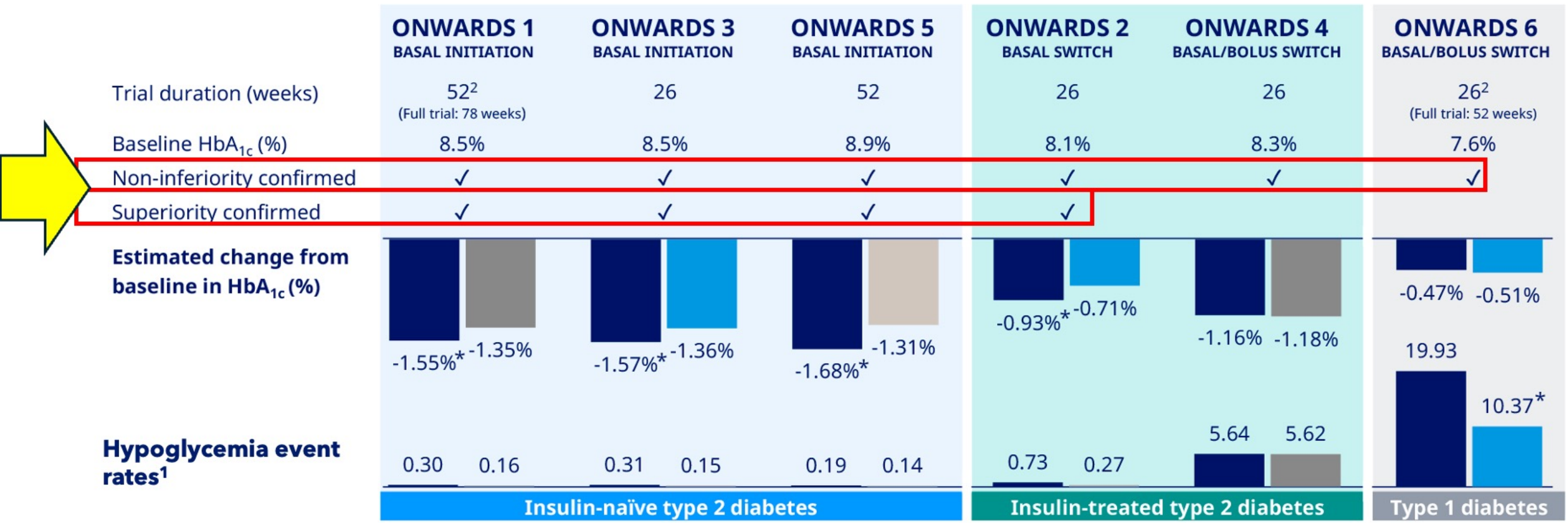
Insulin Icodec ONWARDS Phase III Trial Program

Phase III Trial Program	Duration (Weeks)	Patients Enrolled	Comparator: Weekly Insulin Icodec Versus Daily…	Study Population
ONWARDS 1 (NCT04460885)	78	984	Insulin glargine	Insulin-naïve
ONWARDS 2 (NCT04770532)	26	526	Insulin degludec	Previously treated w/ basal insulin
ONWARDS 3 (NCT04795531)	26	588	Insulin degludec	Insulin-naïve
ONWARDS 4 (NCT04880850)	26	582	Insulin glargine (Both groups on bolus insulin aspart 2 to 4×/day)	Previously treated w/ basal or bolus insulin
ONWARDS 5 (NCT04760626)	52	1085	Insulin glargine or insulin degludec (+mobile app)*	Insulin-naïve
	Total	***3 765***		
ONWARDS 6 (NCT04848480)	26	582	Insulin degludec (Both groups on bolus insulin aspart 2 to 4×/day)	T1D previously treated w/basal & bolus insulin

*Assessing insulin starts in a real-world setting using a dosing guide with minimal investigator intervention

Rosenstock J, et al. *N Engl J Med*. 2023;389(4):297-308; Philis-Tsimikas A, et al. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425; Lingvay I, et al. *JAMA*. 2023;330(3):228-237; Mathieu C, et al. *Lancet*. 2023;401(10392):1929-1940; Bajaj HS, et al. *Ann Intern Med*. 2023;176(11):1476-1485; Russell-Jones D, et al. *Lancet*. 2023 Nov 4;402(10413):1636-1647.

Insulin Icodec: Efficacy and Safety of the Phase III ONWARDS Program



In people with type 2 diabetes: *No statistical difference in estimated hypoglycaemia events*

*P<0.001 (noninferiority);
P=0.02 (superiority)

Once-weekly insulin icodec | Once-daily insulin glargine U100 | Once-daily insulin degludec | Once-daily basal insulins

*Statistically significant. 1 Severe or clinically significant hypoglycaemia events (blood glucose <3 mmol/L) per patient year, included for end of trial/end main phase in-trial. 2 Duration refers to trial main phase.
ONWARDS 1: QW insulin icodec vs QD insulin glargine U100 both with non-insulin anti-diabetic treatment in insulin-naïve people with T2D; ONWARDS 2: QW insulin icodec vs QD insulin degludec in people with T2D switching from a QD insulin; ONWARDS 3: QW insulin icodec vs QD insulin degludec in insulin-naïve people with T2D; ONWARDS 4: QW insulin icodec vs QD insulin degludec both with mealtime insulin in people with T2D treated with basal and bolus insulin; ONWARDS 5: QW insulin icodec vs QD basal insulin with an app providing dosing recommendation in insulin-naïve people with T2D; ONWARDS 6: QW insulin icodec vs QD insulin degludec both with mealtime insulin in people with T1D
T1D: Type 1 diabetes; T2D: Type 2 diabetes. Note: Overview refer to primary end-points in main phases of trials

Bajaj HS, Goldenberg RM. *touchREV Endocrinol*. 2023;19(1):4-6.

Insulin Icodec: Phase IIIa Pooled Analysis – Safety Outcomes

Injection site reactions:

- **1.6%** of patients treated with icodec
- **2.3%** of icodec-treated patients with anti-insulin icodec antibodies
- **2.4%** of icodec-treated patients who did not develop anti-insulin icodec antibodies

Intra-patient variability:

- Randomized, open-label, crossover trial of 25 individuals with T2D
- **No clinically relevant difference** in exposure, and a similar glucose-lowering effect with subcutaneous administration in thigh, abdomen, upper arm

Awiqli® [product monograph]. Novo Nordisk Canada. 2024. https://www.novonordisk.ca/content/dam/nncorp/ca/en/products/awiqli-en-product-monograph-12-march-2024.pdf; Plum-Mörschel L, et al. *Clin Drug Investig*. 2023; 43(2):119–127.

Current Approval Status

Efsitora is under review

Icodec is approved under the brand name Awiqli® in the EU, Canada, Australia, Japan, and Switzerland for the treatment of both T1D and T2D and in China for the treatment of T2D

Efsitora and Icodec are not currently approved by the FDA.

Novo Nordisk. Novo Nordisk receives Complete Response Letter in the US for once-weekly basal insulin icodec. July 10, 2024. Accessed November 22, 2024. https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=168532.

Simplifying Data Interpretation

Background

CGM offers benefits over SMBG, and its utility for titrating novel insulin formulations is of great interest

In individuals with T2D, combining CGM-based titration with a once-weekly basal insulin could:

- Reduce the treatment burden by minimizing the number of required basal insulin injections
- Reduce the need for finger pricks for manual SMBG testing

FDA approved CGM over the counter (March 2024)

CGM, continuous glucose monitoring; SMBG, self-measured blood glucose.

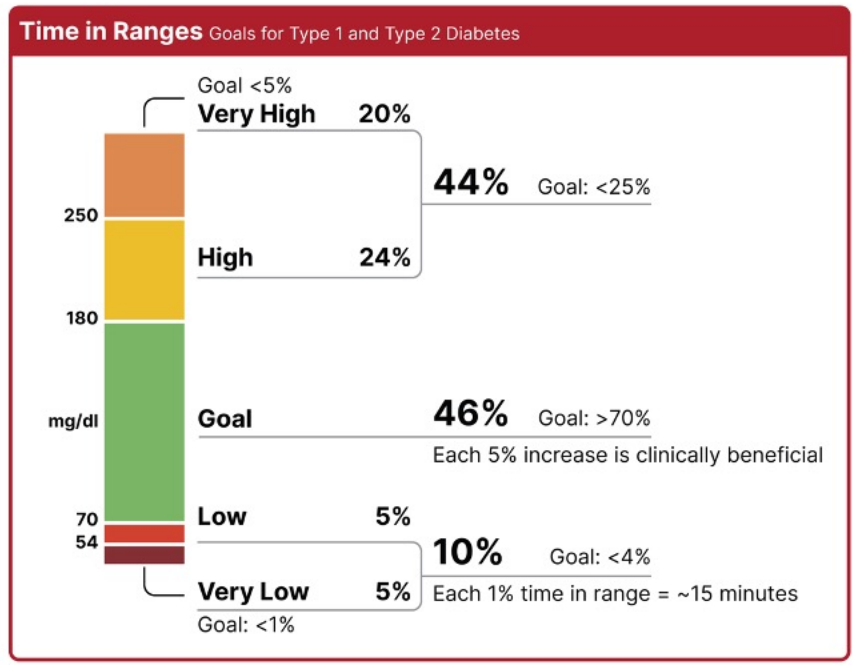
Mian Z, et al. *Am J Med Sci*. 2019;358(5):332–339; Edelman SV, et al. *Diabetes Care*. 2018;41(11):2265–2274; FDA Clears First Over-the-Counter Continuous Glucose Monitor. U.S. Food and Drug Administration. March 5, 2025. Accessed December 23, 2024. https://www.fda.gov/news-events/press-announcements/fda-clears-first-over-counter-continuous-glucose-monitor.

Key Metrics: The Ambulatory Glucose Profile (AGP) Report

KEY COMPONENTS:

1. Date range (14 days)
2. Percent time CGM is active (70%)
3. Average glucose
4. Glucose management indicator (GMI)
5. CV: Glucose variability (≤ 36%)
6. Time in range (> 70%)
7. AGP graph
8. Daily glucose patterns

AGP Report: Continuous Glucose Monitoring



Test Patient DOB: Jan 1, 1970

14 Days: August 8-August 21, 2021

Time CGM Active: 100%

Glucose Metrics

Average Glucose	**175 mg/dL**
Goal: <154 mg/dL	
Glucose Management Indicator (GMI)	**7.5%**
Goal: <7%	
Glucose Variability	**45.5%**
Defined as percent coefficient of variation Goal: <36%	

Learning Point!

How can time in range be increased?

Adapted with permission from Dr. Shubrook.

ADA Professional Practice Committee. *Diabetes Care*. 2024;47(Suppl 1):S158-S178.

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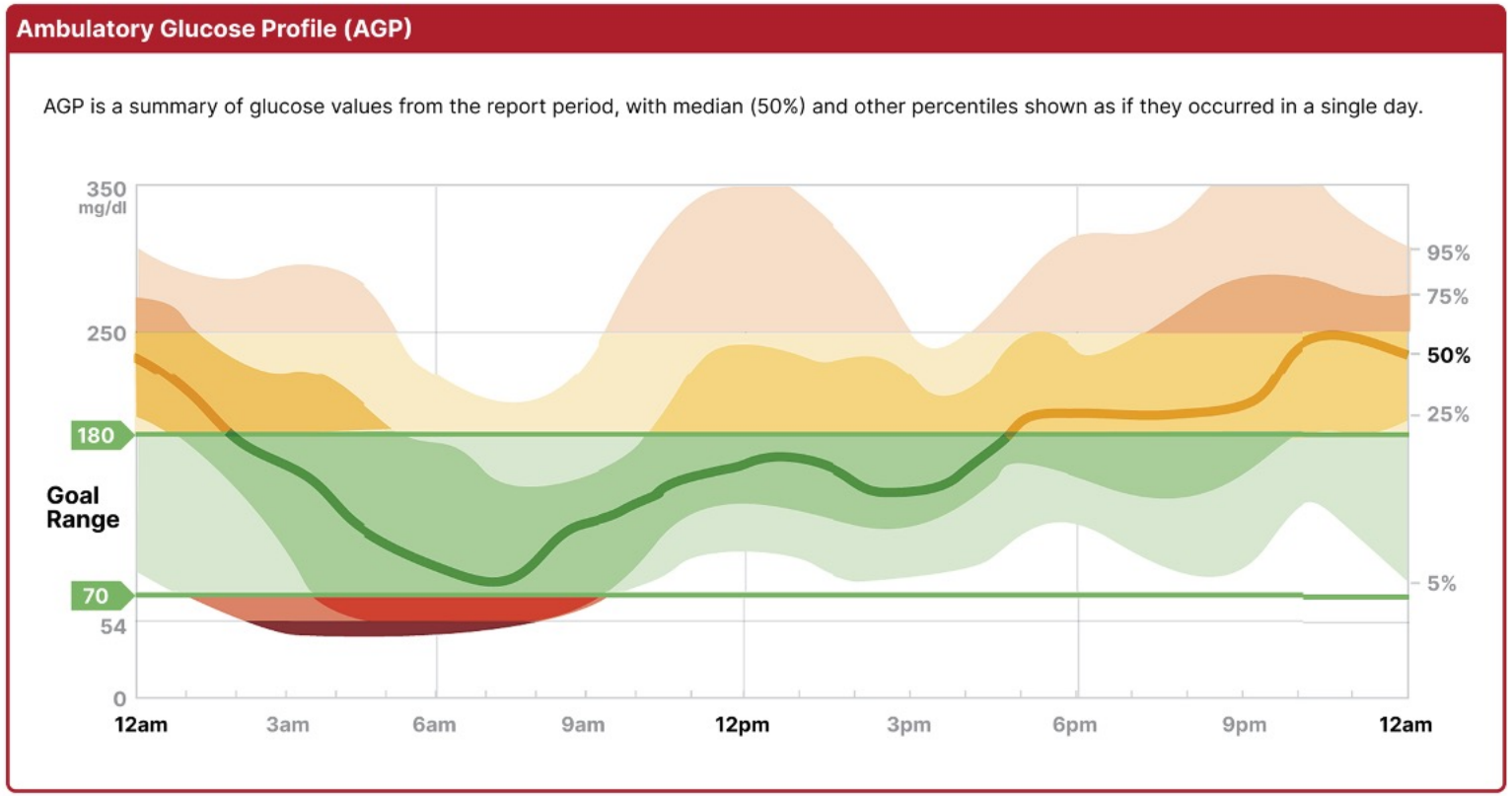
7. AGP graph
8. Daily glucose patterns



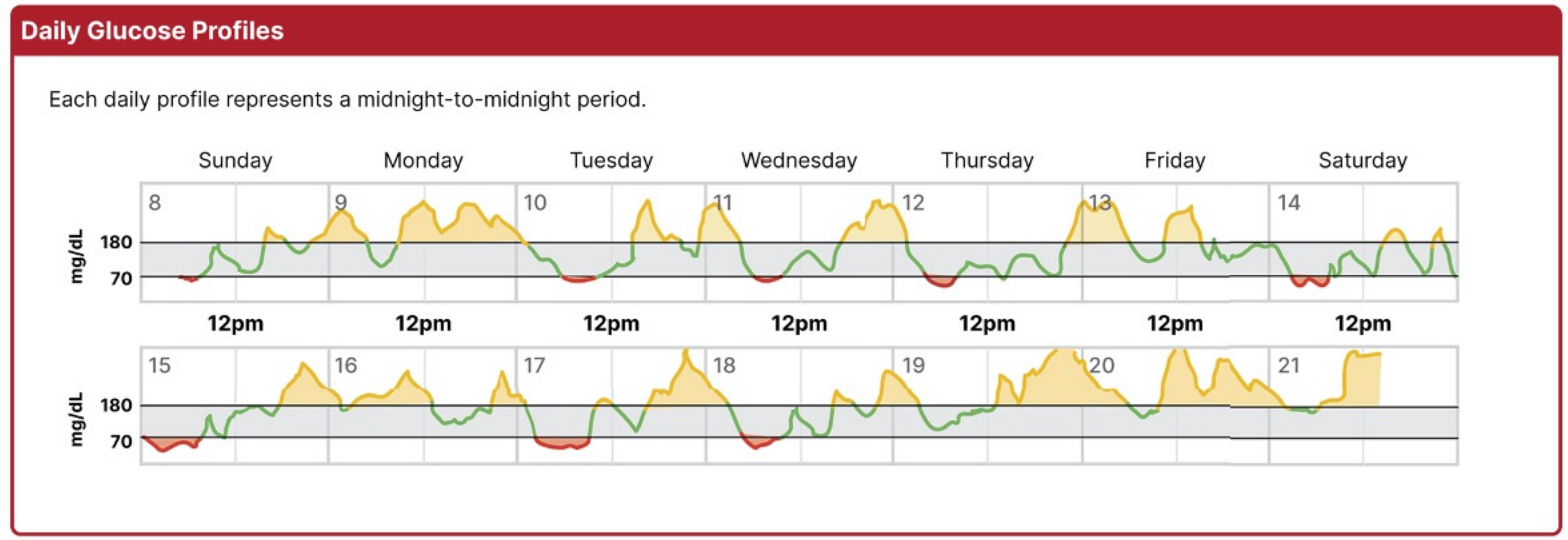
Adapted with permission from Dr. Shubrook.

ADA Professional Practice Committee. *Diabetes Care*. 2024;47(Suppl 1):S158-S178.

Key Metrics: The Ambulatory Glucose Profile (AGP) Report

KEY COMPONENTS:

1. Date range (14 days)
2. Percent time CGM is active (70%)
3. Average glucose
4. Glucose management indicator (GMI)
5. CV: Glucose variability (≤36%)
6. Time in range (>70%)
7. AGP graph
8. Daily glucose patterns



Adapted with permission from Dr. Shubrook.

ADA Professional Practice Committee. *Diabetes Care*. 2024;47(Suppl 1):S128-S145.

In Brief...

- *Combining CGM-based titration with a once-weekly basal insulin may reduce the treatment burden for patients with T2D*
- *Evidence supports the impact of data utilization in improved patient outcomes*