

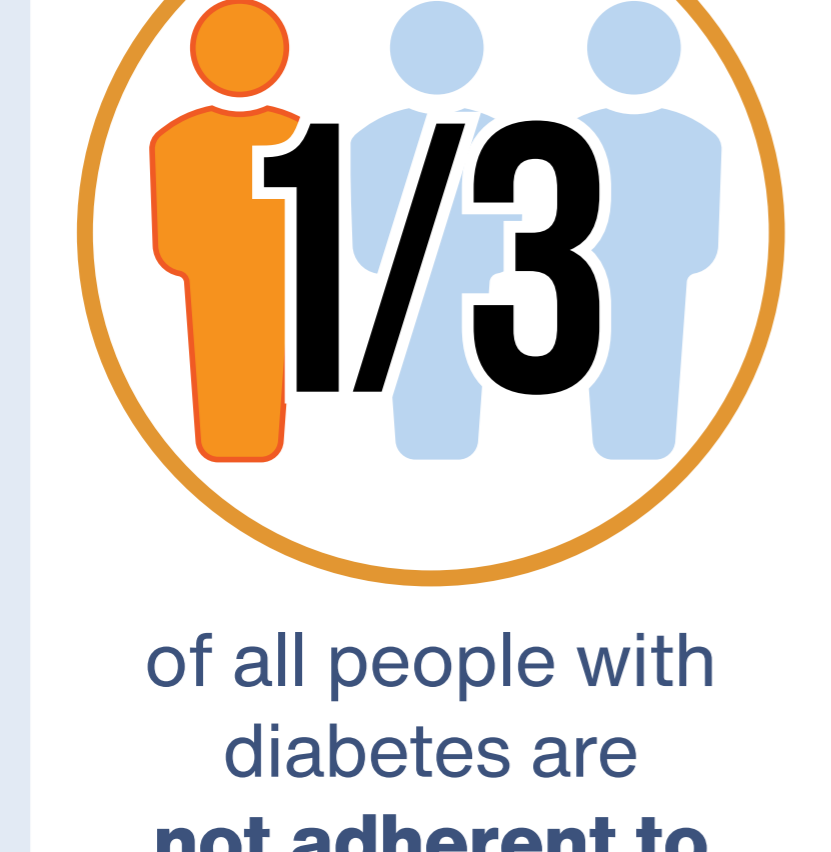
HOSPITALISTS' PERSPECTIVES ON

OPTIMIZING BASAL INSULIN IN TYPE 2 DIABETES:

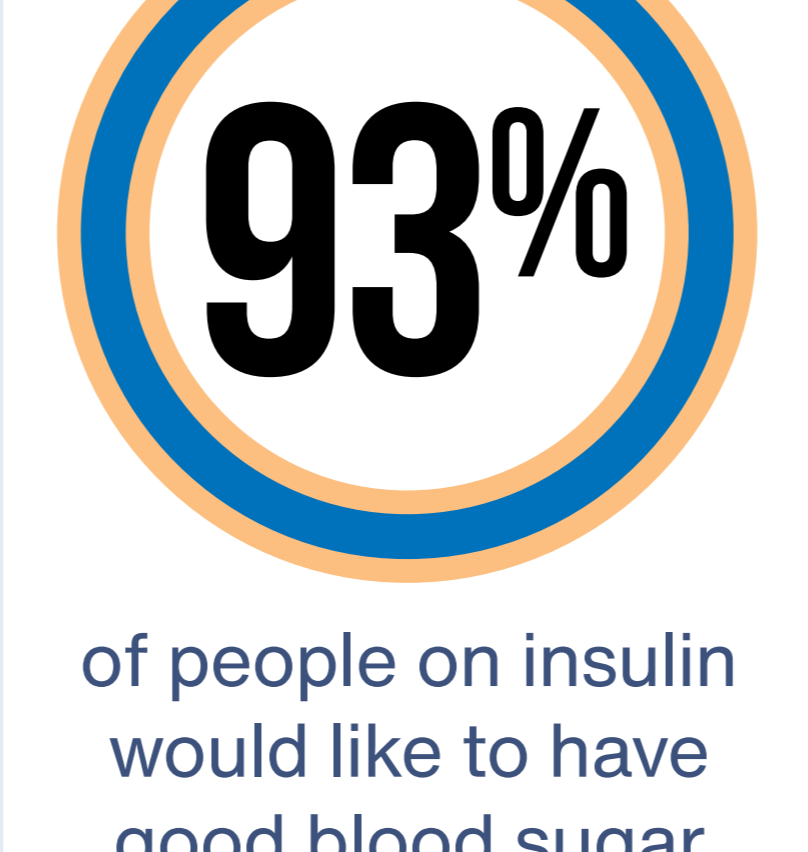
Evaluating Current and Emerging Therapies and Their Impact on Therapeutic Inertia and Transitions of Care



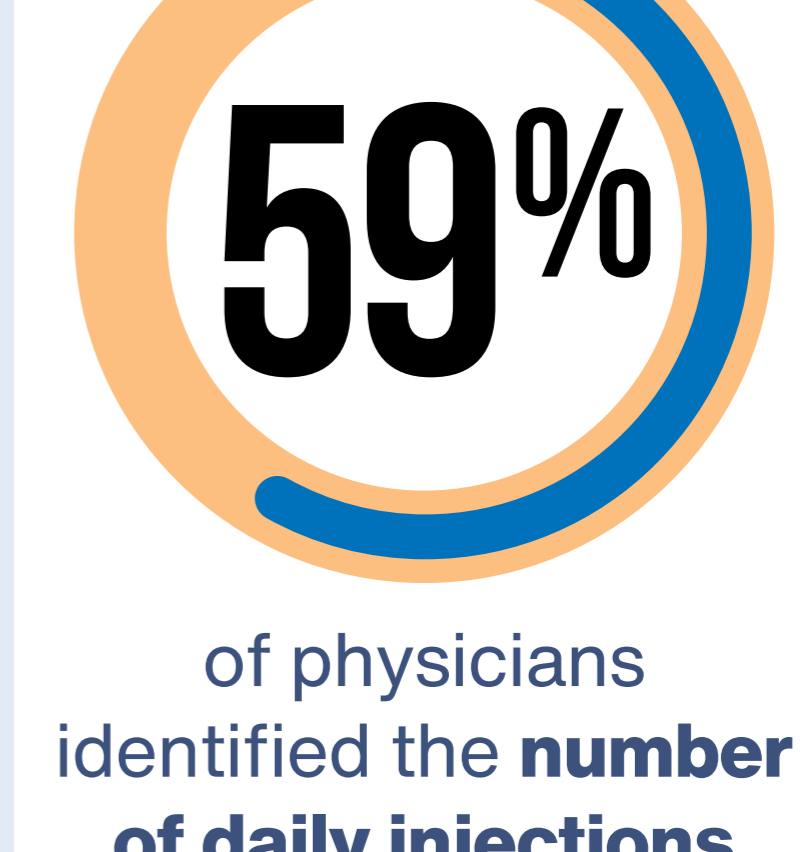
Injection Burden Is a Major Barrier to Insulin Adherence



of all people with diabetes are **not adherent to insulin therapy**



of people on insulin would like to have good blood sugar control **without daily injections**



of physicians identified the **number of daily injections** as a **difficulty for patients**

Patients struggle to maintain their daily insulin and other medication schedule.

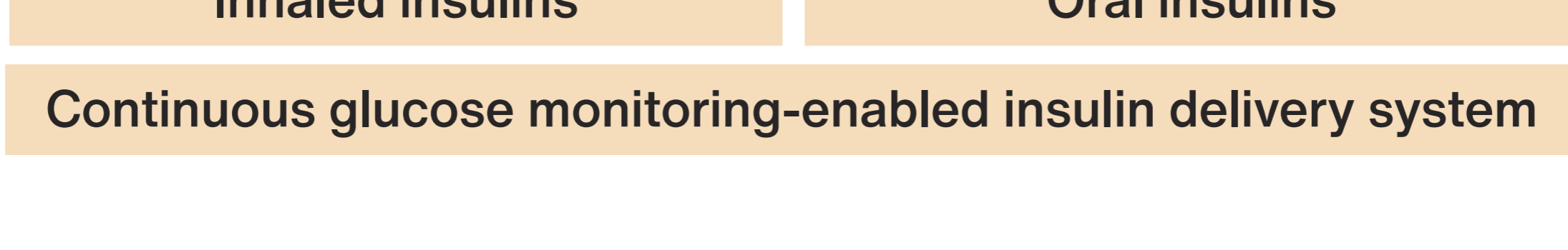
There are many reasons for this, including work schedules, travel, younger and older individuals, but regardless of reason, the burden is evident to physicians, caretakers, and patients.

Peyrot M, et al. *Diabet Med.* 2012; Okemah J, et al. *Adv Ther.* 2018.

The Past, Present, and Future of Basal Insulin Innovation

The development of basal insulin therapy has evolved significantly, aiming to reduce injection frequency and improve patient adherence.

Some examples are once-weekly basal insulins:

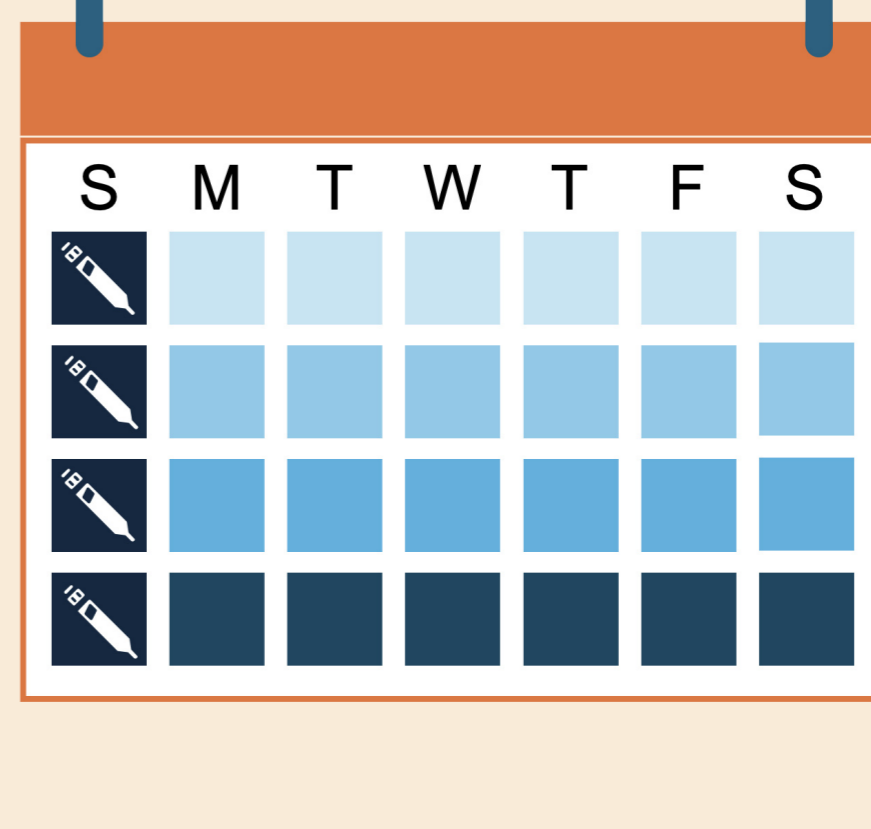


	Inhaled insulins	Oral insulins		
	Continuous glucose monitoring-enabled insulin delivery system			
	NPH insulin	1st-generation basal insulin analogues	Ultra long-acting basal insulin analogues	Once-weekly basal insulin analogues
Half-life	5-10 hours	~0.5 day	~1 day	~1 week to 17 days
Administration	Once daily/ twice daily	Once daily/ twice daily	Once daily	Once weekly

Images reproduced for educational purposes only from Protein Data Bank. 2007 (NPH); Whittingham, et al. *Biochemistry.* 1997 (determir); Drugbank Online. 2020 (glargine U100); Steensgaard DB, et al. *Biochemistry.* 2013 (degludec); Small Angle Scattering Biological Data Bank. 2019 (glargine U300).

Recognized Attributes of Once-Weekly Medications

- Greater convenience
- Better medication adherence
- Improved health-related quality of life
- Less overwhelming sense of treatment
- Easier for individuals in need of medical assistance



Polonsky WH, et al. *Diabetes Ther.* 2011; Polonsky WH, et al. *Diabetes Ther.* 2022.

Once-Weekly Basal Insulins Under Development

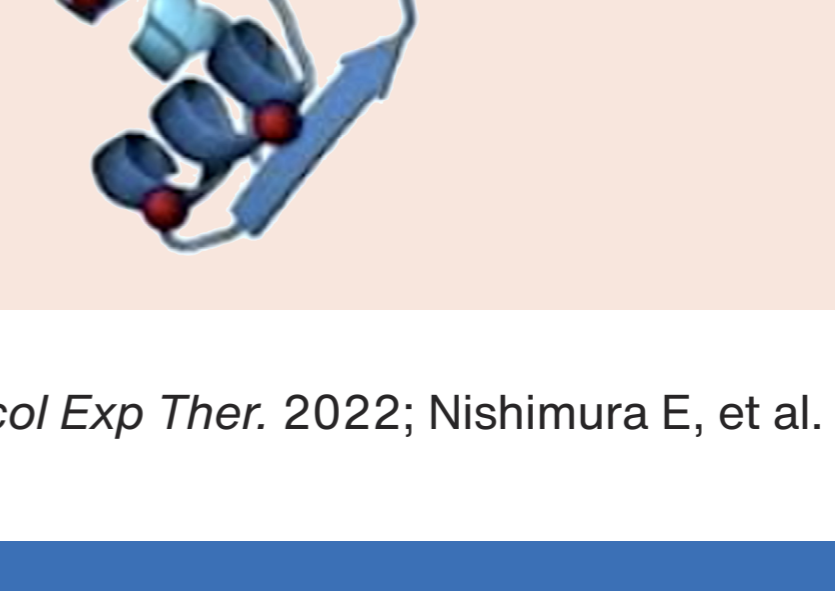
Efsitora alfa

- Fusion protein that combines a single-chain variant of insulin with a human IgG Fc domain
- In phase 3 of clinical development (QWINT Program)



Insulin icodec

- Novel basal insulin analogue that strongly, but reversibly, binds to albumin
- In phase 3 of clinical development (ONWARDS Program)



Images reproduced for educational purposes only from Moyers JS, et al. *Pharmacol Exp Ther.* 2022; Nishimura E, et al. *BMJ Open Diabetes Res Care.* 2021.

QWINT Program: Top-line Results in T2D

	QWINT-1 ¹ BASAL INITIATION		QWINT-2 ² BASAL INITIATION		QWINT-3 ¹ BASAL INITIATION		QWINT-4 ² BASAL INITIATION	
Trial duration	52 weeks		52 weeks		78 weeks		26 weeks	
Baseline HbA _{1c}	8.2%/8.3%		8.2%		7.8%		8.2%	
Non-inferiority confirmed	✓		✓		✓		✓	
Estimated change from baseline in HbA _{1c}	Efsitora alfa -1.31%	Glargine U100 -1.27%	Efsitora alfa -1.34%	Degludec U100 -1.26%	Efsitora alfa -0.86% at week 26	Glargine U100 -0.75% at week 26	Efsitora alfa -1.07%	Degludec U100 -1.07%
Estimated rate of severe or clinically significant hypoglycemia	0.50 events/PYE	0.88 events/PYE	0.58 events/PYE	0.45 events/PYE	0.84 events/PYE	0.74 events/PYE	6.6 events/PYE	5.9 events/PYE
	Insulin-naïve T2D				Insulin-experienced T2D			

*Blood glucose <54 mg/dL (<3.0 mmol/L).

1. Lilly. QWINT-1/-3 news release. 2024; 2. Lilly. QWINT-2/-4 news release. 2024.

ONWARDS Program in T2D: Topline Results

	ONWARDS 1 BASAL INITIATION		ONWARDS 3 BASAL INITIATION		ONWARDS 5 BASAL INITIATION		ONWARDS 2 BASAL SWITCH		ONWARDS 4 BASAL/BOLUS SWITCH	
Trial duration (weeks)	52		26		52		26		26	
Baseline HbA _{1c}	8.5		8.5		8.9		8.13		8.3	
Non-inferiority confirmed	✓		✓		✓		✓		✓	
Superiority confirmed	✓		✓		✓		✓		✓	
Endpoint assessed (week)	52		26		52		26		26	
Estimated change from baseline in HbA _{1c} (%)	Icodec -1.55	Glargine U100 -1.35	Icodec -1.57	Degludec -1.36	Icodec with dosing guide app -1.68	Once-daily basal insulin* -1.31	Icodec -0.93	Degludec -0.71	Icodec -1.16	Glargine U100 -1.18
Estimated rate of clinically significant hypoglycemia (event per PYE)	0.3	0.16	0.31	0.15	0.19	0.14	0.73	0.27	5.64	5.62
	Insulin-naïve T2D						Insulin-experienced T2D			

Reproduced for educational purposes only from Bajaj HS, Goldenberg RM. *touchREV Endocrinol.* 2023;19:4-6.

ONWARDS Trials: Results

Among participants receiving icodec who were hospitalized during the ONWARDS trials:

- ✓ Most participants continued once-weekly icodec treatment to trial completion despite hospitalization
- ✓ Overall, the icodec dose remained fairly stable and uninterrupted during hospitalization
- ✓ No substantial changes in glycemic control were observed before, during, or after hospitalization
- ✓ Reported hypoglycemia rates were low, with no evidence to suggest differences before, during, or after hospitalization

Phillis-Tsimikas A, et al. *EASD* 2023. Abstract 781.

Once-Weekly Insulin May Redefine Diabetes Management



Reduction in basal insulin injections from **at least 365 per year to just 52**



Once-weekly insulin has the potential to **facilitate insulin initiation and improve treatment adherence and persistence** in diabetes



Research to date has demonstrated once-weekly insulins have **comparable glucose-lowering efficacy and safety** vs daily basal insulins

Key Take-Aways Once-Weekly Insulins From the Early Evidence

Efsitora and Icodec:

Sufficiently long durations, flat PD profiles, and low PD variability support once-weekly dosing, with important considerations

- Steady state is likely to take approximately 3-4 weeks of dosing
- Patients switching from a once-daily to once-weekly insulin may require an initial loading dose
- Research to date has demonstrated once-weekly insulins have comparable glucose-lowering efficacy and safety vs daily basal insulins in type 2 diabetes
- Clinicians and patients will need to learn how to initiate and titrate once-weekly insulin
- Need to address management questions related to exercise, sick days, and hospitalizations and procedures

Abbreviations

HbA_{1c}: glycosylated hemoglobin
Ig: immunoglobulin
NPH: neutral protamine Hagedorn

PD: pharmacodynamic
PYE: patient-year of exposure
T2D: type 2 diabetes

References

Bajaj HS, Goldenberg RM. *touchREV Endocrinol.* 2023;19:4-6.
Heise T, et al. *J Endocr Soc.* 2021;5(suppl 1):A329.
Insulin glargine. Drugbank Online. 2020. <https://go.drugbank.com/drugs/DB00047>.
Insulin glargine (Toujeo®), oligomeric composition Small Angle Scattering Biological Data Bank. 2019.
Lilly. QWINT-1/-3 news release. 2024. <https://investor.lilly.com/news-releases/news-release-details/first-its-kind-fixed-dose-study-once-weekly-insulin-efsitora>
Lilly. QWINT-2/4 news release. 2024. <https://investor.lilly.com/news-releases/news-release-details/once-week-dosing-insulin-efsitora-alfa-delivers-a1c-reduction>
Moyers JS, et al. *Pharmacol Exp Ther.* 2022;382:346-355.
Nishimura E, et al. *BMJ Open Diabetes Res Care.* 2021;9:e002301.
Okemah J, et al. *Adv Ther.* 2018;35:1735-1745.
Peyrot M, et al. *Diabet Med.* 2012;29:682-689.
Phillis-Tsimikas A, et al. *EASD* 2023. Abstract 781.
Polonsky WH, et al. *Diabetes Obes Metab.* 2011;13:144-149.
Polonsky WH, et al. *Diabetes Ther.* 2022;13:175-187.
Steensgaard DB, et al. *Biochemistry.* 2013;52:295-309.
Structure of human insulin cocrystallized with protamine. Protein Data Bank. 2007. <https://www.rcsb.org/structure/2omi>
Whittingham JL, et al. *Biochemistry.* 1997;36:2826-2831.