



Once-Weekly Basal Insulin: A Narrative Review of What Changes for Patients When Injections Fall from Daily to Weekly

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Abstract

Basal insulin given once a week rather than once a day reduces injections from 365 a year to 52, and two such insulins have completed phase 3 testing. In type 2 diabetes the results are favourable: across five trials, once-weekly icodec was superior or non-inferior to daily comparators for HbA1c reduction with similar rates of clinically significant or severe hypoglycaemia. In type 1 diabetes the picture differs. Both published phase 3 trials found non-inferior glycaemic control alongside significantly higher rates of combined level 2 or level 3 hypoglycaemia, and one reported a greater incidence of severe hypoglycaemia. Less widely noted, treatment satisfaction scores in the type 1 icodec trial favoured the daily regimen, with an estimated treatment difference of -1.09 (95% CI -1.85 to -0.34, $p = 0.0044$), so fewer injections did not translate into a more satisfied patient. This review sets out the trial evidence by diabetes type, the pharmacological reason the two differ, and what a half-life measured in weeks means when a dose is wrong.

Keywords: Once-weekly insulin; Insulin icodec; Insulin efsitora alfa; Hypoglycaemia; Treatment satisfaction

Introduction

Basal insulin analogues have been given daily since their introduction, and adherence to daily injection is imperfect for reasons that are unsurprising [1,2,31]. Barriers to starting and continuing insulin are well described [26,27], as is the flat profile achieved by earlier ultra-long analogues [21]. Reducing administration to once weekly has therefore been an obvious pharmacological target, and two candidates have now completed phase 3 programmes: insulin icodec and insulin efsitora alfa [3,4].

Both achieve weekly dosing through a very long half-life. Efsitora has a reported half-life of about 17 days with a peak-to-trough ratio of 1.14 across the week, producing an unusually flat profile (Figure 4) [4,5]. The molecular engineering behind weekly dosing has been described in detail [12,13], and earlier phase 2 work established the approach in type 2 and type

1 diabetes [22,23,24,25]. That flatness is the mechanism of benefit and, as this review argues, also the mechanism of the principal problem.

The evidence divides cleanly by diabetes type, and summarising the two together obscures the most important finding in the literature. This review therefore reports them separately.

Material and Methods

Search strategy: PubMed and the archives of the major diabetes, endocrinology and general medical journals were searched for trials of weekly basal insulin. Search terms combined once-weekly insulin, icodec and efsitora with type 1 diabetes, type 2 diabetes, hypoglycaemia, HbA1c and treatment satisfaction. Reference lists of the phase 3 reports [3,4] were screened by hand for related trials.

Eligibility: Studies were included if they compared a once-weekly basal insulin with a once-daily comparator in people with diabetes and reported glycaemic or hypoglycaemia outcomes. Phase 1 and phase 2 studies are cited where they establish pharmacokinetics and are identified as such.

Data extraction and handling: Design, population, comparator, primary endpoint and reported outcomes were extracted as published. Diabetes type is stated alongside every result, because the hypoglycaemia findings differ by type and pooling them would conceal the central signal. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

Type 2 diabetes: Across the ONWARDS programme, once-weekly icodec showed statistical superiority over the once-daily comparator in ONWARDS 1, 2, 3 and 5, and non-inferiority in ONWARDS 4, for reduction in HbA1c from baseline. Comparators were insulin degludec in ONWARDS 2 and 3 and insulin glargine U100 in ONWARDS 1 and 4. Rates of combined clinically significant or severe hypoglycaemia were similar to daily comparators across these trials (Figure 2) [3,6,7,8]. An earlier phase 2 trial had shown the same pattern in insulin-naïve type 2 diabetes [22].

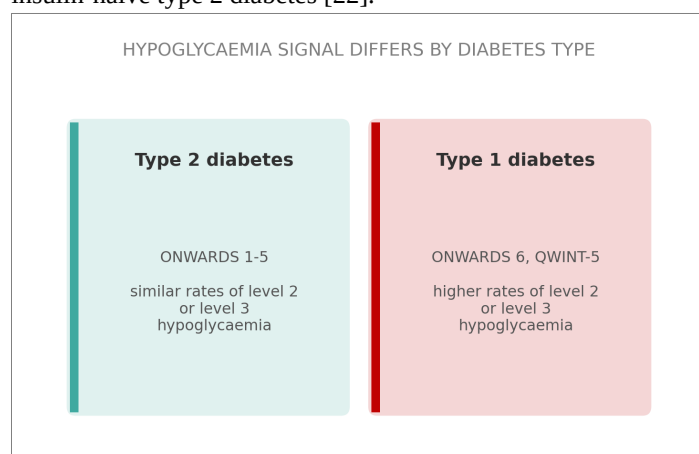


Figure 2: The hypoglycaemia signal separates by diabetes type [3,4,6,9]

Type 1 diabetes, icodec: ONWARDS 6 randomised adults with type 1 diabetes to once-weekly icodec or once-daily degludec within a basal-bolus regimen. Icodec was non-inferior to degludec for HbA1c reduction at week 26, but rates of combined clinically significant or severe hypoglycaemia were statistically significantly higher with icodec, a difference that persisted when evaluated over 57 weeks. Serious adverse events were reported in 24 participants (8 per cent) on icodec against 20 (7 per cent) on degludec. Time below 3.0 mmol/L sat at the threshold of the recommended target of less than 1 per cent during weeks 22 to 26 and below target during weeks 48 to 52 [3,9], against consensus targets for time in range and for reporting thresholds [16,17,18].

Type 1 diabetes, efsitora: QWINT-5 enrolled 893 adults with type 1 diabetes, randomised 692 to once-weekly efsitora or once-daily degludec, and 623 (90 per cent) completed (Figure 5). Mean HbA1c fell from 7.88 to 7.41 per cent with efsitora and from 7.94 to 7.36 per cent with degludec, a change of -0.51 against -0.56 percentage points, with an estimated treatment difference of 0.052 per cent (95% CI -0.077 to 0.181, $p = 0.43$), confirming non-inferiority (Figure 1). Rates of combined level 2 or level 3 hypoglycaemia were higher with efsitora over 52 weeks, as was the incidence of severe hypoglycaemia [4,10].

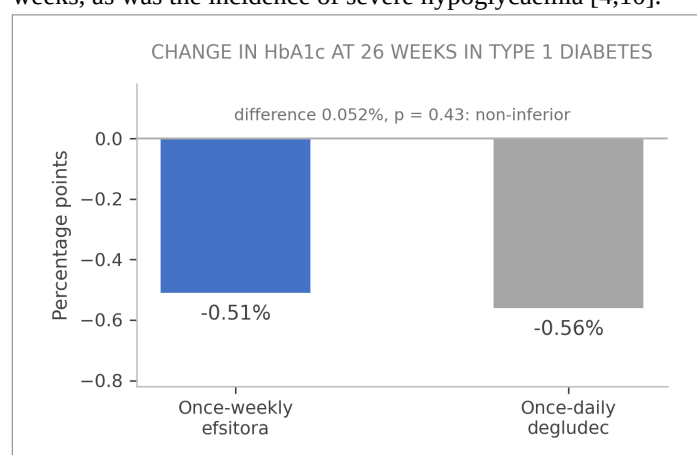


Figure 1: Change in HbA1c at 26 weeks in adults with type 1 diabetes [4,10]

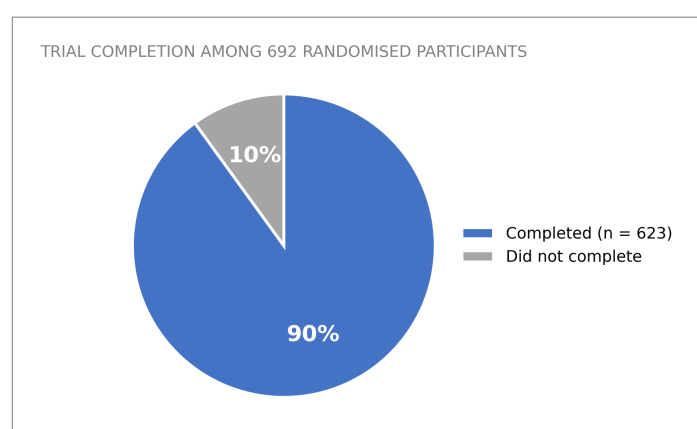


Figure 5: Completion among randomised participants in the type 1 efsitora trial [4]

Meta-analysis in type 1 diabetes: A systematic review and meta-analysis pooling five studies and 1,629 participants, 862 assigned to weekly and 851 to daily basal insulin, concluded that weekly icodec and efsitora provide HbA1c reduction similar to once-daily basal insulins in type 1 diabetes [11]. Risk of bias was judged low for two trials and of some concern for one.

Treatment satisfaction: This is the result least often quoted. In ONWARDS 6, change in Diabetes Treatment Satisfaction Questionnaire status scores was less favourable with icodec than with degludec, an estimated treatment difference of -1.09 (95% CI -1.85 to -0.34, $p = 0.0044$) (Figure 3) [9,11]. The satisfaction measures in the two type 1 trials used different versions of the instrument and could not be pooled [11].

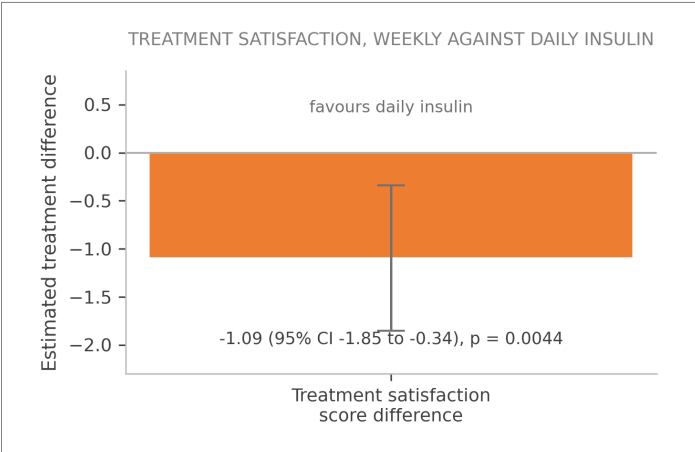


Figure 3: Treatment satisfaction with weekly against daily insulin in type 1 diabetes [9,11]

Trial	Population	HbA1c outcome	Hypoglycaemia
ONWARDS 1, 3, 5	Type 2, insulin-naïve	Superior	Similar to daily
ONWARDS 2	Type 2, switched	Superior	Similar to daily
ONWARDS 4	Type 2, basal-bolus	Non-inferior	Similar to daily
ONWARDS 6	Type 1, basal-bolus	Non-inferior	Significantly higher
QWINT-5	Type 1, basal-bolus	Non-inferior	Higher; more severe

Table 1: Phase 3 trials of once-weekly basal insulin by population, as reported by the original investigators [3,4,6,9,10]

The pharmacological reason: A half-life of about 17 days produces near-constant exposure, which suits a person whose basal requirement is stable and predictable (Figure 4) [5]. It suits far less well a person with no endogenous insulin whose basal requirement varies with activity, illness and menstrual cycle, and for whom the conventional response is to reduce the basal dose that evening. With a weekly insulin that option does not exist, and the dose given cannot be withdrawn (Figure 6) [4,9,12].

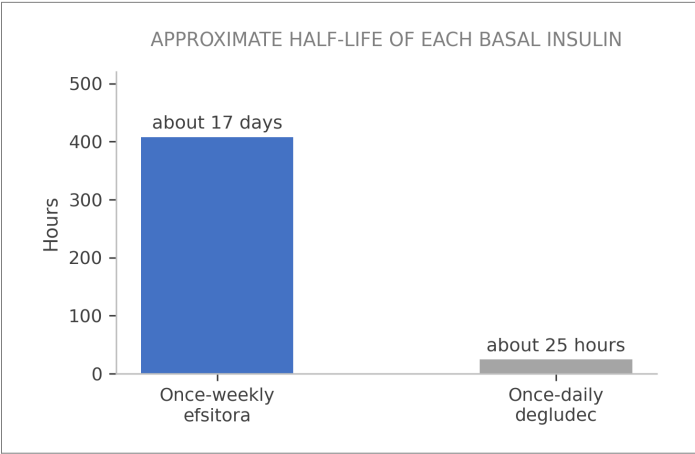


Figure 4: Approximate half-life of a weekly against a daily basal insulin [5]

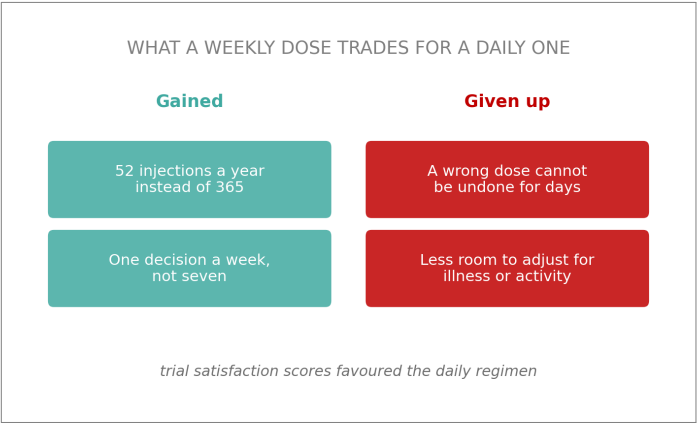


Figure 6: What a weekly dose trades against a daily one [4,9]

Consideration	Type 2 diabetes	Type 1 diabetes
Residual endogenous insulin	Usually present	Absent
Basal requirement	Relatively stable	Variable day to day
Trial hypoglycaemia signal	Similar to daily	Significantly higher
Ability to reduce a dose	Rarely needed acutely	Frequently needed
Overall trial conclusion	Favourable	Non-inferior, with a safety cost

Table 2: Why the same pharmacology behaves differently in the two conditions [3,4,9,10]

Reported outcome	Estimate	Interpretation
HbA1c difference, QWINT-5	0.052% (95% CI -0.077 to 0.181)	Non-inferior [4]
Treatment satisfaction, ONWARDS 6	-1.09 (95% CI -1.85 to -0.34)	Favours daily [9,11]
Efsitora half-life	About 17 days	Dose cannot be withdrawn [5]
Peak-to-trough ratio	1.14 across the week	Very flat profile [5]

Table 3: Key quantitative findings and what each supports

How the weekly agents were developed: Both molecules achieve weekly exposure by design rather than by formulation. Icodec was engineered with strong reversible albumin binding and reduced insulin receptor affinity to slow clearance, a strategy described in detail by its developers [12,13]. Phase 2 work in insulin-naïve type 2 diabetes and in patients switching from daily basal insulin established the dosing approach before the phase 3 programme [22,23], and parallel phase 2 studies evaluated the Fc-based agent in both type 2 and type 1 diabetes [24,25].

What the trials did not compare: No trial has set a weekly basal insulin against automated insulin delivery, which for many people with type 1 diabetes is the realistic alternative and which has randomised evidence of its own [14]. Nor has either weekly agent been compared with the other. Existing guidance for adult type 1 diabetes predates these trials and does not address weekly dosing [27], and consensus targets for time in range assume a regimen that can be adjusted day to day [16,17].

Discussion

The type 2 result is straightforward and good. Weekly icodec matched or beat daily comparators on HbA1c without a hypoglycaemia penalty across five trials, and for someone requiring basal insulin only, replacing 365 injections a year with 52 is a substantial simplification [3,6,7,8].

The type 1 result is not the same result, and the two should not be reported together as though weekly insulin had simply been shown to work. Both published phase 3 trials in type 1 diabetes found non-inferior HbA1c alongside significantly higher rates of clinically significant or severe hypoglycaemia, and QWINT-5 additionally reported a greater incidence of severe episodes [4,9,10]. Non-inferiority on the primary endpoint with a worse safety endpoint is not a neutral result.

The explanation is pharmacological rather than incidental. A very flat profile with a 17-day half-life is an advantage where basal requirement is stable, which is typical in type 2 diabetes with residual endogenous secretion. In type 1 diabetes basal requirement moves with activity, intercurrent illness and other factors, and the standard response is to reduce the basal dose for that day. A weekly insulin removes that lever entirely: the dose is already in the subcutaneous tissue and will remain active for days [5,12]. Investigators have suggested that dose initiation and titration algorithms need further evaluation in type 1 diabetes, which is a reasonable reading [4,13]. Comparisons between daily analogues have previously turned on exactly this kind of hypoglycaemia endpoint [32,33].

The satisfaction finding deserves more attention than it has received. The entire rationale for weekly dosing is that patients would prefer it, and in the one type 1 trial reporting a status-version satisfaction score, patients on the weekly insulin were less satisfied than those on daily, at $p = 0.0044$ [9,11]. That is an unusual result to find at the heart of a convenience argument. It is compatible with the hypoglycaemia data, since being unable to correct a dose is unpleasant independently of the eventual HbA1c, and it suggests that convenience assumed by prescribers is not the same as convenience experienced by patients [15,30]. Severe hypoglycaemia and impaired awareness persist in type 1 diabetes even with modern technology [19,20], and hypoglycaemia is not confined to type 1 [28,29].

None of this argues that weekly insulin has no role in type 1 diabetes. It argues that the population in which the benefit is clearest is type 2 diabetes on basal therapy, and that offering it in type 1 diabetes should involve saying plainly that the trials found more hypoglycaemia and lower satisfaction, rather than presenting it as fewer injections for the same result.

The satisfaction result also complicates the health economic argument. Weekly dosing is frequently justified on adherence grounds, on the reasoning that a person asked to inject once a week will do so more reliably than one asked to inject daily [1,31]. That reasoning is plausible and untested in these trials, which measured administration under study conditions rather

than adherence over years. If the adherence benefit is the principal justification, it has not yet been demonstrated, and the satisfaction data give some reason to doubt that patients experience the regimen as simpler [9,11,15].

Where the weekly agents look most useful is therefore the population in which they were most convincingly tested: type 2 diabetes requiring basal insulin, particularly where administration depends on another person, as in residential care or where a district nurse attends. In that setting replacing seven visits with one is a substantial operational gain and the hypoglycaemia data raise no comparable concern [6,7,8,22]. Extending the same reasoning to type 1 diabetes is where the evidence stops supporting the intuition [3,4,9,10].

Study limitations

The limitations belong to the underlying literature. All phase 3 trials in this field are manufacturer-sponsored, and the two agents have been tested by their respective sponsors rather than against each other [3,4]. The type 1 trials are open-label, which matters particularly for a self-reported satisfaction endpoint [9,10]. Follow-up is 26 to 57 weeks against a therapy intended for decades, so the durability of the hypoglycaemia signal is unknown [9]. The meta-analysis in type 1 diabetes pools only five studies including phase 1 and phase 2 trials, and judged one trial to be of some concern for bias [11]. Satisfaction was measured with different versions of the instrument in the two type 1 trials and could not be pooled [11]. Trial populations are not representative of people with the most unstable glycaemia, who are typically excluded. Titration algorithms were trial-specific and may not reflect how the drugs would be used in practice [4,13]. And no trial has compared a weekly basal insulin against automated insulin delivery, which is the relevant comparator for many people with type 1 diabetes [14]. Consensus guidance for adult type 1 diabetes does not yet address weekly basal insulin [27], and the pharmacology of prandial cover is unchanged by it [34].

Conclusion

Once-weekly basal insulin does what it was designed to do in type 2 diabetes: equal or better glycaemic control with no hypoglycaemia penalty and one injection a week instead of seven. In type 1 diabetes the same pharmacology produces non-inferior HbA1c together with significantly more clinically significant or severe hypoglycaemia in both published phase 3 trials, and in the trial that measured it, lower treatment satisfaction than the daily comparator. The reason is that a 17-day half-life removes the ability to reduce today's basal dose, which is a routine manoeuvre for someone with no endogenous insulin. Fewer injections is a real benefit and it is not free, and the trial evidence is clear about who pays for it.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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