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Review

Which Diabetes Patients Will Benefit the Most from Once-Weekly Basal Insulin Analogs? A Review with a Special Focus on Type 1 Diabetes Patients

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Abstract: Basal insulin analogs, typically administered once or twice daily, have been one of the two pillars of the multiple daily injection (MDI) insulin therapy of patients with type 1 diabetes (T1D) for the last twenty years. Recently, once-weekly basal insulin analogs have been developed and are in late-phase clinical trials. One of these analogs is insulin icodec (icodec), appropriately developed to bind reversibly to albumin and to be gradually released into the patient's circulation. Icodec has been tried mostly in clinical trials of adult patients with type 2 diabetes. A recent phase 3a clinical trial comprising adult patients with T1D was designed to evaluate icodec's efficacy and safety compared with a daily basal insulin analog (degludec) after a 26-week main phase plus a safety extension of another 26 weeks. Icodec showed non-inferiority to once-daily degludec in glycated hemoglobin (HbA1c) reduction at week 26, and no significant differences in time in range (TIR) (70–180 mg/dL) and in time above range (TAR) (>180 mg/dL). On the other hand, it was associated with increased rates of clinically significant hypoglycemia (blood glucose < 54 mg/dL) and severe hypoglycemia (external assistance need for recovery), remaining either below or close to the internationally recommended targets for hypoglycemia. Another once-weekly insulin analog, basal insulin Fc (BIF), has been investigated in a phase 2 clinical trial comprising adult patients with T1D, with equally promising results. These preliminary data suggest that once-weekly insulin analogs could be of use for some patients with T1D, for example, patients not taking insulin regularly or those who are on MDI and wish for fewer injections. In addition, due to its prolonged mode of action, it could decrease the risk of diabetic ketoacidosis and the need for hospitalization. Additionally, patients with T1D that struggle with wearing diabetes mellitus devices/closed-loop insulin pumps either due to the cost or due to skin issues may also benefit from long-acting insulin. There is increasing evidence of the benefits of adjunctive therapies to insulin in T1D patients, but these therapies are not FDA-approved due to a possible higher risk of diabetic ketoacidosis. These long-acting insulin analogues could be used with adjunctive therapies in selected patients. This review aims to present available data on the mode of action, clinical trial results, and possible benefits of once-weekly insulin analogs for patients with T1D. In addition, it intends to suggest a future research framework for important clinical questions, such as once-weekly insulin analog use and exercise, sick days, or surgery, that will enhance our knowledge regarding this indisputable innovation in insulin management.

Keywords: basal insulin; icodec; once-weekly analog; type 1 diabetes

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1. Introduction

Type 1 diabetes (T1D) is one of the most prevalent chronic diseases affecting children, adolescents, and adults globally, characterized by the destruction of insulin-producing pancreatic beta cells and subsequent insulin deficiency [1]. The incidence of childhood T1D varies considerably across different regions, with the United States recording an annual incidence of 22.3 per 100,000 in children and adolescents, demonstrating significant disparities among various ethnic groups [2,3]. Notably, countries like Finland or regions like Sardinia report the highest incidences of T1D, ranging from 45 to 65 cases per 100,000 children under the age of 15 [2,4].

Typically diagnosed during childhood, T1D follows a bimodal distribution, with peaks occurring around four to six years of age and during early puberty [5]. The cornerstone of T1D management is subcutaneous insulin administration, aiming to substitute the deficient hormone and achieve optimal blood glucose levels [6]. Various insulin formulations and delivery systems have been developed, including rapid-acting (e.g., lispro, aspart, glulisine), short-acting (e.g., regular insulin), intermediate-acting NPH insulin, and long-acting insulins (e.g., glargine, detemir, and degludec), with rapid-acting and long-acting variants being the most commonly utilized [6].

Basal insulin plays a pivotal role in T1D management. Available basal long-acting insulin analogs exhibit onset times ranging from 1 to 6 h and durations spanning from 20 to over 42 h [7]. First-generation long-acting basal insulin analogs, such as insulin glargine U100 and insulin detemir, have half-lives of approximately 12 h and 5–7 h, respectively, with durations of action up to 24 h. Degludec offers the longest duration, exceeding 42 h [8]. All basal insulin preparations, even degludec, are administered once or twice daily [8]. Two once-weekly basal insulins are currently under clinical development: insulin icodec and basal insulin Fc (BIF) (insulin efsitora alfa; LY3209590) [9]. A third once-weekly insulin analog, GZR4, is under investigation in a phase Ib clinical trial which will be completed by the end of 2024.

Research indicates a 22% probability of missing at least one basal insulin dose in a 14-day period, linked to poorer glycemic control [10] and increased rates of diabetic ketoacidosis [11]. Over the past two decades, extensive research has aimed to develop long-acting basal insulin analogs with more predictable, reliable, and stable pharmacokinetic and pharmacodynamic profiles, substantially reducing the risk of hypoglycemia compared to previous formulations [7].

This review aims to present current knowledge on once-weekly insulin analogs and their use in patients with T1D. It seeks to provide insights into its mechanism of action, clinical trial outcomes, and potential advantages. In addition, it intends to suggest a future research framework for important clinical questions, such as once-weekly insulin analog use and exercise, sick days, or surgery, that will enhance our knowledge regarding this indisputable innovation in insulin management.

2. Materials and Methods

PubMed and Google Scholar databases were searched for relevant studies on data regarding the novel basal insulin icodec. The following terms were used: basal insulin icodec, diabetes mellitus type 1, children, up to December 2024. We also reviewed the reference lists of the retrieved articles in search for other relevant articles that could have been missed in the initial search.

3. Main Characteristics of Icodec

3.1. Method of Administration, Pharmacokinetic and Pharmacodynamic Data

Insulin icodec (Novo Nordisk) is a basal insulin analog that works like any other insulin, namely by replacing insulin in individuals with diabetes who lack sufficient insulin production. It is administered subcutaneously [12], and it is the only insulin that has been tried in late-phase clinical trials that can be administered once weekly and thus can provide basal coverage over a full week following a single injection [12]. Pharmacokinetic data

showed a time to maximum plasma concentration of 16 h after subcutaneous administration and a mean half-life of 196 h, which means a half-life of more than a week [13,14].

Insulins designed for weekly administration should ideally maintain a consistent action profile throughout each day of the week, minimizing variations in insulin effects between daytime and nighttime hypoglycemia. However, they typically exhibit a peak-to-trough pattern over the span of a week, which mirrors the concept of administering higher insulin doses mid-week, potentially leading to tighter glucose control but an increased risk of hypoglycemia during those days [15]. Based on pharmacodynamic data, there appears to be a difference in the effect of the insulin dose administered early in the injection week compared to later in the week. Specifically, the difference in effect between day 3 and day 7 suggests that the insulin's potency could be approximately 1.36 times higher on day 3 compared to day 7 [12]. This implies that the impact of the insulin dose may decrease over the course of the week, with it being approximately one-third more potent earlier in the week than later.

Steady levels in the blood are reached after 3 to 4 once-weekly injections [16], so additional insulin may be needed in the transition period when switching from a daily basal insulin to insulin icodec. One unit of icodec provides the same glucose-lowering effect as one unit of comparable daily basal insulins, and an equivalent once-weekly dose is usually seven times that of daily basal insulin [12].

3.2. Production of Icodec

As already discussed, the development of insulin icodec involved meticulous molecular engineering, aiming to achieve a long half-life suitable for once-weekly insulin administration while ensuring an evenly distributed action throughout the week, without causing episodes of hypoglycemia.

Acylation has emerged as a viable technology in engineering insulin analogs, in order to create once-daily basal insulin analogs, like insulin detemir and insulin degludec, as well as longer-acting insulin analogs such as oral insulin 338 [17,18]. Icodec, as an insulin analogue, underwent a series of alterations to its amino acid structure. The addition of a 20-carbon-atom-long icosane fatty diacid (icosanedioic acid) at the C-terminal of the B-chain of the human insulin amino acid sequence enabled strong and reversible binding to albumin, an important factor in extending the duration of action [12]. Specifically, the affinity of icodec for albumin was approximately 9.5 times higher than that of insulin detemir.

Additionally, three amino acid substitutions (A14E, B16H, and B25H) contributed to enhancing molecular stability in insulin icodec. These substitutions resulted in a decrease in insulin receptor affinity, thereby slowing down its clearance from the body. Each substitution of amino acids resulted in a further reduction in insulin receptor affinity, consequently prolonging the half-life of icodec. After all these substitutions, the overall insulin receptor affinity of the molecule, without any chemical modification, is reduced to 5.5% relative to human insulin [12]. The high albumin binding affinity of the fatty diacid limits the number of insulin icodec molecules available to bind to the insulin receptor, further reducing the relative affinity from 5.5% to 0.03% in the presence of 1.5% human serum albumin. Moreover, the combination of A14E and B25H enhances solubility, enabling a formulation of 4.2 mM, which is seven times greater than that of a standard U100 insulin formulation. This explains why the dose volume can be low and similar to once-daily basal insulin dosing volumes [17]. In summary, the combination of alterations in icodec led to high affinity for albumin, improved stability, low insulin receptor binding affinity, and high solubility [12].

As a result, insulin icodec forms a circulating reservoir bound to albumin, initially inactive, but gradually and consistently activating insulin receptors, thereby sustaining its effect over an extended period suitable for weekly dosing [12]. This means that its prolonged action primarily results from reduced insulin receptor binding and a slower rate of insulin receptor-mediated clearance, rather than prolonged release from the injection site [13].

In vitro studies have shown that despite these modifications, icodec retains biological properties similar to native human insulin, with no increase in insulin-like growth factor-1 receptor binding or mitogenicity [12].

4. Basal Insulin-Fc (Insulin Efsitora Alfa, LY3209590)

Besides Icodec, BIF, known by its developmental designation LY3209590, is another innovative once-weekly basal insulin currently undergoing clinical evaluation by Eli Lilly. It is administered subcutaneously.

This investigational insulin is constructed from a novel single-chain variant of insulin fused with a fragment crystallizable region derived from a human IgG2 antibody, interconnected by a peptide linker [9]. This intricate design is engineered to capitalize on the Fc fragment's intrinsic ability to prolong the insulin's half-life within the body, aiming for sustained therapeutic action over extended periods. It has a molecular weight of 64.1 kDa.

Functionally, BIF operates as a selective agonist for the insulin receptor, delivering comprehensive agonistic activity despite displaying a marginally decreased affinity for the receptor in comparison to native human insulin. While BIF achieves internalization by the insulin receptor to a degree analogous to that of human insulin, its efficacy is somewhat attenuated, notably presenting an approximately two-orders-of-magnitude lower potency relative to human insulin [9,19,20].

In clinical investigations, BIF has exhibited dose-proportional pharmacokinetics, alongside minimal variability observed between different days and among individual patients. Noteworthy findings from studies involving patients with type 2 diabetes (T2D) include the attainment of the maximum plasma concentration by approximately day 4 following a single subcutaneous dose. Additionally, BIF demonstrated an average half-life of around 17 days, indicative of its prolonged duration of action, with a sustained decrease in fasting glucose over the course of 1 week [21]. Because of the minimal fluctuations in insulin levels between the peak and trough concentrations, glucose levels are more consistent and stable, both on a day-to-day basis and within individual days.

5. Clinical Trials of Once-Weekly Analogs in Adult Patients with T2D

The once-weekly insulin analog, GZR4, is under investigation in a phase Ib clinical trial (ClinicalTrials.gov Identifier: NCT06202079) which will be completed by the end of 2024. In this trial, GZR4's efficacy, safety, and tolerability are being compared to once-daily insulin degludec administration in patients with T2D who had poor glycemic control either on oral medications or oral medications plus basal insulin.

During the last couple of years, clinical trials have been carried out to evaluate the efficacy and safety of once-weekly insulin icodec, mainly in adult patients with T2D. More specifically, the ONWARDS 1–5 program is a series of phase 3a clinical trials that examined once-weekly icodec efficacy and safety compared to available daily basal insulin analogues in adults with T2D in various therapeutic settings [22]. Published results showed that icodec is at least as effective as once-daily basal insulin at reducing glycated hemoglobin (HbA1c), without increasing hypoglycemic episodes, thus improving the overall glycemic control in these patients. Actually, HbA1c reduction was higher for the icodec group both in ONWARDS 1, 3, and 5 [23–25] trials that comprised insulin-naive patients and in ONWARDS 2 and 4 trials [26,27] that included patients already receiving daily basal insulin treatment. The findings of these clinical trials are shown in more detail in Table 1.

Table 1. Clinical trials assessing insulin icodec in adults.

	Diagnosis	Prior Insulin Treatment	Trial Design	Sample (*n*)	Intervention	HbA1c Reduction with Icodec Compared to the Comparator Group	Risk of Hypoglycemia
ONWARDS 1	T2D	No	Randomized open label	970	Icodec plus glucose-lowering agents vs. Glargine U100 plus glucose-lowering agents	Higher	Similar
ONWARDS 2	T2D	Yes	Randomized open label	520	Icodec +/− glucose-lowering agents vs. Degludec +/− glucose-lowering agents	Higher	Similar
ONWARDS 3	T2D	No	Randomized double-blind	580	Icodec plus glucose-lowering agents plus placebo vs. Degludec plus glucose-lowering agents plus placebo	Higher	Higher with Icodec
ONWARDS 4	T2D	Yes	Randomized open label	580	Icodec plus glucose-lowering agents plus aspart 2–4 times daily vs. Glargine U100 plus glucose-lowering agents plus aspart 2–4 times	Higher	Similar
ONWARDS 5	T2D	No	Randomized open label real-world elements	1096	Icodec +/− glucose-lowering agents vs. Once-daily basal analoques plus glucose-lowering agents	Higher	Similar
ONWARDS 6	T1D	Yes, multiple daily injections	Randomized open label	580	Icodec plus aspart $\geq$ 2 times daily vs. Degludec plus aspart $\geq$ 2 times daily	Non-inferior	Higher

Similar were the results of two phase 2 clinical trials investigating the safety and efficacy of once-weekly BIF. In these two trials, BIF was compared to insulin degludec in both insulin-naive adult patients with T2D [28] and in patients that were previously treated with basal insulin for T2D [29]. In the first study [28], 278 patients were randomly assigned to either BIF or degludec and were titrated to fasting glucose levels of 80–100 mg/dL. After a follow-up of 26 weeks, BIF demonstrated a non-inferior HbA1c change from baseline vs. degludec, with a treatment difference of 0.06% (90% CI −0.11, 0.24, $p = 0.56$). Level 2 hypoglycemia episodes were rare and not significantly different between the two groups. In the second study [29], 399 patients were enrolled and randomized to receive either BIF or degludec for 32 weeks. The results showed that BIF achieved a non-inferior HbA1c change from baseline of −0.7% vs. degludec. Importantly, hypoglycemia (defined as glucose levels $\leq$ 70 mg/dL [$\leq$3.9 mmol/L]) event rates in the BIF group were 25% lower than those in the degludec group. Authors of both studies suggest that BIF is a promising once-weekly insulin, and phase 3 clinical trials will follow.

The main characteristics of novel long-acting basal insulins are found in Table 2.

Table 2. Main characteristics of novel long-acting basal insulins.

	Icodec	**BIF**	**GZR4**
Company	Novo Nordisk	Eli Lilly	Gan & Lee Pharmaceuticals
Administration	Subcutaneously Once weekly	Subcutaneously Once weekly	Subcutaneously Once weekly
Time to max plasma concentration	16 h	4th day	NA
Half-life	196 h	14–17 days	NA
Mechanism of prolongation of half-life	Addition of a C20-long icosane fatty diacid at the C-terminal of the B-chain of the human insulin. Three amino acid substitutions (A14E, B16H, and B25H).	Novel single-chain variant of insulin fused with a fragment crystallizable region derived from human IgG2 antibody.	Addition of a C22 fatty diacid-containing side chain at B29K.
Studies on adults with TID	Phase 3a [30]	Phase 2 [31]	None Phase 1b in T2D (ClinicalTrials.gov Identifier: NCT06202079)

6. Clinical Trials of Once-Weekly Insulins in Patients with T1D

In late 2023, the results of the ONWARDS 6 clinical trial were published by Russel-Jones et al. in The Lancet [30]. This is thus far the first and only large-scale phase 3a study comprising adult patients with T1D of various nationalities, carried out at 99 sites across 12 countries. More specifically, it was a randomized, open-label, treat-to-target trial that followed adult patients with T1D (HbA1c < 10.0% [<86 mmol/mol]) for 52 weeks, with a 26-week main phase and a 26-week safety extension. The trial population comprised 582 patients (337 men and 245 women), of whom 448 were Caucasian, 123 Asian, and 11 Black or African American. The patients had an average age of 44 years and an average diabetes duration of 20 years and were randomized either to receive once-weekly insulin icodec or daily basal insulin degludec, together with short-acting insulin aspart before meals (two or more daily injections) [30].

In both patient groups, basal insulin doses were adjusted according to a prespecified algorithm targeting a pre-breakfast self-monitored blood glucose level of 80–130 mg/dL (4.4–7.2 mmol/L). Regarding the primary endpoint of HbA1c reduction, icodec showed non-inferiority at week 26 compared to degludec, since, in the icodec group, HbA1c decreased by 0.47% compared to 0.51% in the degludec group, with an estimated treatment difference of 0.05% (95% CI: 0.13 to 0.23). At week 52, though, the estimated mean HbA1c reduction in the icodec group was statistically significantly inferior compared to the degludec group, namely −0.37% vs. −0.54%, with an estimated treatment difference of 0.17% (95% CI: 0.02 to 0.31), $p = 0.021$ [30].

Secondary supportive endpoints of the trial included CGM changes, changes in FPG, episodes of clinically significant or severe hypoglycemia, and weekly insulin dose. Regarding CGM measurements, the calculated time in range (70–180 mg/dL, TIR [3.9–10.0 mmol/L]) and time above range (>180 mg/dL, TAR [>10.0 mmol/L]) were both similar in the two groups in the middle and at the end of the study. More specifically, the calculated TIR was 14 h and 11 min per day for icodec vs. 14 h and 36 min per day for degludec at weeks 22–26, and 13 h and 45 min per day for icodec vs. 14 h and 18 min per day for degludec at weeks 48–52. The calculated TAR was 8 h and 53 min per day for patients in the icodec group vs. 8 h and 42 min per day for patients in the degludec group at weeks 22–26, and 9 h and

26 min per day vs. 8 h and 56 min per day, respectively, at weeks 48–52. What was different was the calculated time below range (<54 mg/dL TBR [(<3.0 mmol/L]), which was higher for the icodec group between weeks 22 and 26 (15 min/day for icodec vs. 10 min/day for degludec) but was the same between weeks 48 and 52 (12 min/day for both groups). The mean FPG levels decreased in both groups from baseline to both 26 and 52 weeks. For the icodec group, the mean FPG change was −15 mg/dL (−0.84 mmol/L) at the end of 26 weeks and −10 mg/dL (−0.58 mmol/L) at the end of 52 weeks. In the degludec group, a larger FPG reduction was observed, namely −34 mg/dL (−1.87 mmol/L) at both 24 and 52 weeks ($p = 0.0003$ and $p < 0.0001$, respectively) [30].

Hypoglycemia, defined as glucose levels < 54 mg/dL (<3.0 mmol/L) with continuous glucose monitoring (CGM), was statistically significantly higher in the icodec group compared to the control group. Similarly, episodes of severe hypoglycemia, meaning a hypoglycemic episode requiring another person's assistance for recovery, were also more frequent in the icodec group. More specifically, both simple and severe hypoglycemic events were 20 per patient-year of treatment in the icodec group compared to 10 events per patient-year of treatment for patients in the degludec group ($p < 0.0001$). Regarding serious adverse events, 39 were reported in 24 patients in the icodec group, with 25 events in 20 patients in the degludec group. Nevertheless, for the icodec group, time spent < 54 mg/dL (<3.0 mmol/L) and <70 mg/dL (<3.0 mmol/L) was either below or close to the internationally recommended targets, both at the end of the main phase and at the end of the safety extension period [30].

Regarding total weekly insulin dose requirements, they were similar in both groups of patients, namely 311 units per week for icodec (~44 units/day) and 323 units per week for degludec (~46 units/day). What was different was the ratio of basal to bolus insulin. More specifically, in the icodec group, the average weekly basal dose was higher at 170 units per week (~24 units/day) vs. 151 units per week (~22 units/day) in the degludec group. On the contrary, the average weekly bolus dose in the icodec group was 132 units (~19 units/day) compared to the higher 161 units per week (~23 units/day) in the degludec group [30].

Regarding the other once-weekly insulin, BIF, the results of a phase 2 clinical trial that investigated its safety and efficacy in patients with T1D were recently published [31]. More specifically, 265 patients with T1D on a multiple daily injection regimen were randomly assigned to either once-weekly BIF or once-daily degludec over a 26-week treatment period. Both groups aimed for a fasting glucose of 80–100 mg/dL (4.4–5.6 mmol/L). At the end of the treatment period, patients in the BIF group had a non-inferior HbA1c decrease from baseline compared to those in the degludec group, with a statistically significant treatment difference of 0.17% (90% CI 0.01, 0.32; $p = 0.07$) in favor of degludec. The TIR percent showed no statistically significant difference between patients in the two groups (56.1% vs. 58.9%, respectively, $p = 0.112$), while the mean FPG levels were significantly higher in the BIF group (158.8 mg/dL) compared to the degludec group (143.2 mg/dL, $p = 0.003$). Regarding BIF's safety, hypoglycemia events identified by CGM showed no statistically significant difference between the two groups, either for level 1 ($p = 0.960$) or level 2 ($p = 0.517$) hypoglycemia, as well as for serious hypoglycemic events. Similarly to trials in patients with T2D, the authors of this trial concluded that once-weekly BIF is effective and safe for patients with T1D, and phase 3 trials will ensue. There are no studies assessing these long-acting insulins in children with T1D.

7. More Frequent Hypoglycemia Episodes with Once-Weekly Insulin Analogs: A Reason for Concern? Further Studies Are Needed

As mentioned, patients on icodec had a higher rate of hypoglycemia compared to those on degludec, but this observation, as it has been reported, should be evaluated in the light of the ONWARDS 6 clinical trial's specific characteristics [30]. Overall, episodes of severe hypoglycemia were low in both groups and actually lower than previously published treat-to-target studies investigating patients with T1D on degludec [32]. Hypoglycemia in patients on icodec could be related to the use of an intensive prespecified algorithm. In

addition, even if all participants used CGM throughout the study, pre-breakfast glucose measurements were used as the criterion for insulin titration, and, therefore, future studies or real-world data may show that insulin titration based on CGM data will lead to fewer hypoglycemic events. Another important observation was that during the second follow-up period, a slower weekly icodec titration reduced the risk of hypoglycemia while maintaining an acceptable glycemic control, thus raising the possibility of avoiding hypoglycemia with better icodec titration in the future. Certainly, various other aspects of once-weekly insulin analog administration, such as the specific time of injection, as well as other parameters such as the effects of exercise, must be further studied.

8. Who Could Benefit from Once-Weekly Insulin?

Once-weekly insulin is undoubtedly a substantial innovation in diabetes management. One of its obvious advantages is the much fewer injections needed, 52 instead of 365 per year, leading to a lower diabetes self-management burden, thus increasing the possibility of better compliance. This is certainly applicable to patients with T2D, where once-weekly insulin preparations can be combined with once-weekly GLP-1 analogs, leading to improved glycemic control, weight loss, and better cardiovascular health overall [33].

For patients with T1D, the apparent increased risk of hypoglycemia together with the limited once-weekly ability of basal insulin dose titration make icodec use a less attractive option. In particular, patients that use automated insulin delivery systems will probably achieve better glycemic control, decreased hypoglycemia risk, and larger freedom regarding food and exercise with the rapid advancement of the relevant technology and the possibility of fully closed-loop systems in the foreseeable future [34,35]. For these patients, once-weekly insulin analogs will be rather useless. Nevertheless, multiple daily injections (MDIs) remain the most frequently used diabetes treatment worldwide [36,37]. In such patients, a once-weekly basal insulin analog may help with improved adherence, thus leading to better glycemic control. In addition, the much fewer injections needed will definitely improve the quality of life of such patients. Finally, the relatively constant basal insulin throughout each week will probably reduce the risk of diabetic ketoacidosis, thus preventing related hospitalizations and morbidity.

9. Future Research Framework

More research is obviously needed in various populations of patients with diabetes, in children and adolescents and in various clinical settings. Several technical details of once-weekly insulin administration must be clarified, including its optimal initiation and titration along with the prandial insulin titration in order to achieve the best glycemic control while avoiding hypoglycemia at the same time. Exercise intensity, frequency, and distribution throughout the week must be also studied, especially if pediatric populations are involved with their ever-changing physical activities. Sick day management and surgery preparation are two other special situations that need to be further studied.

10. Conclusions

Even if important clinical issues remain, once-weekly insulin analogs seem to represent an important breakthrough in diabetes management. In patients with T2D, several studies in phase 2 or 3a have shown the safety of the analogs, mostly with few episodes of hypoglycemia, as well as their efficacy, with a comparable and in some cases higher decrease in HbA1c, both in insulin-naive patients and in those that were previously receiving daily basal insulin. Data are still scarce regarding adult patients with T1D and are non-existent for pediatric and adolescent populations with T1D. Available data suggest that once-weekly insulin analogs are safe and effective in such patients and could be of use in, for example, patients not taking insulin regularly or those who are on MDIs and want fewer daily injections. In addition, due to their prolonged mode of action, these analogs could decrease the risk of diabetic ketoacidosis and the need for hospitalization. Additionally, patients with T1D that struggle with wearing diabetes mellitus devices/closed-loop insulin pumps

either due to the cost or due to skin issues may also benefit from long-acting insulins. There is increasing evidence of the benefits of adjunctive therapies to insulin in T1D patients, but these therapies are not FDA-approved due to a possible higher risk of diabetic ketoacidosis. These long-acting insulin analogues could be used with adjunctive therapies in selected patients. Further research is needed regarding important clinical questions, such as the optimal initiation and titration of once-weekly analogs, as well as exercise, sick days, or surgery management, that will enhance our knowledge regarding this indisputable innovation in diabetes management.

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References

1. Lawrence, J.M.; Divers, J.; Isom, S.; Saydah, S.; Imperatore, G.; Pihoker, C.; Marcovina, S.M.; Mayer-Davis, E.J.; Hamman, R.F.; Dolan, L.; et al. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001–2017. *JAMA* **2021**, *326*, 717–727. [CrossRef]
2. Libman, I.; Haynes, A.; Lyons, S.; Pradeep, P.; Rwagasor, E.; Tung, J.Y.; Jefferies, C.A.; Oram, R.A.; Dabelea, D.; Craig, M.E. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr. Diabetes* **2022**, *23*, 1160–1174. [CrossRef] [PubMed]
3. Divers, J.; Mayer-Davis, E.J.; Lawrence, J.M.; Isom, S.; Dabelea, D.; Dolan, L.; Imperatore, G.; Marcovina, S.; Pettitt, D.J.; Pihoker, C.; et al. Trends in Incidence of Type 1 and Type 2 Diabetes Among Youths-Selected Counties and Indian Reservations, United States, 2002–2015. *MMWR Morb. Mortal. Wkly. Rep.* **2020**, *69*, 161–165. [CrossRef]
4. Harjutsalo, V.; Sund, R.; Knip, M.; Groop, P.H. Incidence of type 1 diabetes in Finland. *JAMA* **2013**, *310*, 427–428. [CrossRef] [PubMed]
5. Felner, E.I.; Klitz, W.; Ham, M.; Lazaro, A.M.; Stastny, P.; Dupont, B.; White, P.C. Genetic interaction among three genomic regions creates distinct contributions to early- and late-onset type 1 diabetes mellitus. *Pediatr. Diabetes* **2005**, *6*, 213–220. [CrossRef]
6. Cengiz, E.; Danne, T.; Ahmad, T.; Ayyavoo, A.; Beran, D.; Ehtisham, S.; Fairchild, J.; Jarosz-Chobot, P.; Ng, S.M.; Paterson, M.; et al. ISPAD Clinical Practice Consensus Guidelines 2022: Insulin treatment in children and adolescents with diabetes. *Pediatr. Diabetes* **2022**, *23*, 1277–1296. [CrossRef] [PubMed]
7. Cheng, A.Y.Y.; Patel, D.K.; Reid, T.S.; Wyne, K. Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different. *Adv. Ther.* **2019**, *36*, 1018–1030. [CrossRef] [PubMed]
8. Biester, T.; Blaesig, S.; Remus, K.; Aschemeier, B.; Kordonouri, O.; Granhall, C.; Søndergaard, F.; Kristensen, N.R.; Haahr, H.; Danne, T. Insulin degludec's ultra-long pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes. *Pediatr. Diabetes* **2014**, *15*, 27–33. [CrossRef]
9. Moyers, J.S.; Hansen, R.J.; Day, J.W.; Dickinson, C.D.; Zhang, C.; Kahl, S.D.; Ruan, X.; Ding, L.; Brown, R.M.; Baker, H.E.; et al. Preclinical Characterization of Once Weekly Basal Insulin Fc (BIF). *J. Endocr. Soc.* **2021**, *5*, A442. [CrossRef]
10. Ekberg, N.R.; Hartvig, N.V.; Kaas, A.; Møller, J.B.; Adolfsson, P. Smart Pen Exposes Missed Basal Insulin Injections and Reveals the Impact on Glycemic Control in Adults With Type 1 Diabetes. *J. Diabetes Sci. Technol.* **2024**, *18*, 66–73. [CrossRef]
11. Flores, M.; Amir, M.; Ahmed, R.; Alashi, S.; Li, M.; Wang, X.; Lansang, M.C.; Al-Jaghbeer, M.J. Causes of diabetic ketoacidosis among adults with type 1 diabetes mellitus: Insulin pump users and non-users. *BMJ Open Diabetes Res. Care* **2020**, *8*, e001329. [CrossRef]
12. Nishimura, E.; Pridal, L.; Glendorf, T.; Hansen, B.F.; Hubálek, F.; Kjeldsen, T.; Kristensen, N.R.; Lützen, A.; Lyby, K.; Madsen, P.; et al. Molecular and pharmacological characterization of insulin icodec: A new basal insulin analog designed for once-weekly dosing. *BMJ Open Diabetes Res. Care* **2021**, *9*, e002301. [CrossRef]
13. Kjeldsen, T.B.; Hubálek, F.; Hjørringgaard, C.U.; Tagmose, T.M.; Nishimura, E.; Stidsen, C.E.; Porsgaard, T.; Fledelius, C.; Refsgaard, H.H.F.; Gram-Nielsen, S.; et al. Molecular Engineering of Insulin Icodec, the First Acylated Insulin Analog for Once-Weekly Administration in Humans. *J. Med. Chem.* **2021**, *64*, 8942–8950. [CrossRef]
14. Hövelmann, U.; Brøndsted, L.; Kristensen, N.R.; Ribel-Madsen, R.; Devries, J.H.; Heise, T.; Haahr, H. 237-OR: Insulin Icodec: An Insulin Analog Suited for Once-Weekly Dosing in Type 2 Diabetes. *Diabetes* **2020**, *69*. [CrossRef]

15. Home, P. Making sense of weekly insulins. *Lancet Diabetes Endocrinol.* **2023**, *11*, 140–141. [CrossRef]
16. Bajaj, H.S.; Bergenstal, R.M.; Christoffersen, A.; Davies, M.J.; Gowda, A.; Isendahl, J.; Lingvay, I.; Senior, P.A.; Silver, R.J.; Trevisan, R.; et al. Switching to Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100 in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial. *Diabetes Care* **2021**, *44*, 1586–1594. [CrossRef]
17. Hubálek, F.; Refsgaard, H.H.F.; Gram-Nielsen, S.; Madsen, P.; Nishimura, E.; Münzel, M.; Brand, C.L.; Stidsen, C.E.; Claussen, C.H.; Wulff, E.M.; et al. Molecular engineering of safe and efficacious oral basal insulin. *Nat. Commun.* **2020**, *11*, 3746. [CrossRef]
18. Halberg, I.B.; Lyby, K.; Wassermann, K.; Heise, T.; Zijlstra, E.; Plum-Mörschel, L. Efficacy and safety of oral basal insulin versus subcutaneous insulin glargine in type 2 diabetes: A randomised, double-blind, phase 2 trial. *Lancet Diabetes Endocrinol.* **2019**, *7*, 179–188. [CrossRef]
19. Rosenstock, J.; Del Prato, S. Basal weekly insulins: The way of the future! *Metab.-Clin. Exp.* **2022**, *126*, 154924. [CrossRef]
20. Volk, C.; Zhang, C.; Moyers, J.S. 734-P: Cellular Internalization and Localization of Once-Weekly Basal Insulin Fc (BIF). *Diabetes* **2021**, *70*. [CrossRef]
21. Heise, T.; Chien, J.; Beals, J.; Benson, C.; Klein, O.; Moyers, J.S.; Haupt, A.; Pratt, E.J. Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus. *J. Endocr. Soc.* **2021**, *5*, A329. [CrossRef]
22. Philis-Tsimikas, A.; Bajaj, H.S.; Begtrup, K.; Cailleteau, R.; Gowda, A.; Lingvay, I.; Mathieu, C.; Russell-Jones, D.; Rosenstock, J. Rationale and design of the phase 3a development programme (ONWARDS 1-6 trials) investigating once-weekly insulin icodec in diabetes. *Diabetes Obes. Metab.* **2023**, *25*, 331–341. [CrossRef] [PubMed]
23. Rosenstock, J.; Bain, S.C.; Gowda, A.; Jódar, E.; Liang, B.; Lingvay, I.; Nishida, T.; Trevisan, R.; Mosenzon, O. Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin. *N. Engl. J. Med.* **2023**, *389*, 297–308. [CrossRef]
24. Lingvay, I.; Asong, M.; Desouza, C.; Gourdy, P.; Kar, S.; Vianna, A.; Vilsbøll, T.; Vinther, S.; Mu, Y. Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial. *JAMA* **2023**, *330*, 228–237. [CrossRef] [PubMed]
25. Bajaj, H.S.; Aberle, J.; Davies, M.; Donatsky, A.M.; Frederiksen, M.; Yavuz, D.G.; Gowda, A.; Lingvay, I.; Bode, B. Once-Weekly Insulin Icodec With Dosing Guide App Versus Once-Daily Basal Insulin Analogues in Insulin-Naive Type 2 Diabetes (ONWARDS 5): A Randomized Trial. *Ann. Intern. Med.* **2023**, *176*, 1476–1485. [CrossRef] [PubMed]
26. Philis-Tsimikas, A.; Asong, M.; Franek, E.; Jia, T.; Rosenstock, J.; Stachlewska, K.; Watada, H.; Kellerer, M. Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): A phase 3a, randomised, open label, multicentre, treat-to-target trial. *Lancet Diabetes Endocrinol.* **2023**, *11*, 414–425. [CrossRef] [PubMed]
27. Mathieu, C.; Ásbjörnsdóttir, B.; Bajaj, H.S.; Lane, W.; Matos, A.; Murthy, S.; Stachlewska, K.; Rosenstock, J. Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): A phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial. *Lancet* **2023**, *401*, 1929–1940. [CrossRef] [PubMed]
28. Bue-Valleskey, J.M.; Kazda, C.M.; Ma, C.; Chien, J.; Zhang, Q.; Chigutsa, E.; Landschulz, W.; Haupt, A.; Frias, J.P. Once-Weekly Basal Insulin Fc Demonstrated Similar Glycemic Control to Once-Daily Insulin Degludec in Insulin-Naive Patients With Type 2 Diabetes: A Phase 2 Randomized Control Trial. *Diabetes Care* **2023**, *46*, 1060–1067. [CrossRef]
29. Frias, J.; Chien, J.; Zhang, Q.; Chigutsa, E.; Landschulz, W.; Syring, K.; Wullenweber, P.; Haupt, A.; Kazda, C. Safety and efficacy of once-weekly basal insulin Fc in people with type 2 diabetes previously treated with basal insulin: A multicentre, open-label, randomised, phase 2 study. *Lancet Diabetes Endocrinol.* **2023**, *11*, 158–168. [CrossRef]
30. Russell-Jones, D.; Babazono, T.; Cailleteau, R.; Engberg, S.; Irace, C.; Kjaersgaard, M.I.S.; Mathieu, C.; Rosenstock, J.; Woo, V.; Klonoff, D.C. Once-weekly insulin icodec versus once-daily insulin degludec as part of a basal-bolus regimen in individuals with type 1 diabetes (ONWARDS 6): A phase 3a, randomised, open-label, treat-to-target trial. *Lancet* **2023**, *402*, 1636–1647. [CrossRef]
31. Kazda, C.M.; Bue-Valleskey, J.M.; Chien, J.; Zhang, Q.; Chigutsa, E.; Landschulz, W.; Wullenweber, P.; Haupt, A.; Dahl, D. Novel Once-Weekly Basal Insulin Fc Achieved Similar Glycemic Control With a Safety Profile Comparable to Insulin Degludec in Patients With Type 1 Diabetes. *Diabetes Care* **2023**, *46*, 1052–1059. [CrossRef] [PubMed]
32. Davies, M.J.; Gross, J.L.; Ono, Y.; Sasaki, T.; Bantwal, G.; Gall, M.A.; Niemeyer, M.; Seino, H. Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: A 26-week randomized, open-label, treat-to-target non-inferiority trial. *Diabetes Obes. Metab.* **2014**, *16*, 922–930. [CrossRef] [PubMed]
33. Polonsky, W.H.; Fisher, L.; Hessler, D.; Bruhn, D.; Best, J.H. Patient perspectives on once-weekly medications for diabetes. *Diabetes Obes. Metab.* **2011**, *13*, 144–149. [CrossRef]
34. Tauschmann, M.; Thabit, H.; Bally, L.; Allen, J.M.; Hartnell, S.; Wilinska, M.E.; Ruan, Y.; Sibayan, J.; Kollman, C.; Cheng, P.; et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: A multicentre, 12-week randomised trial. *Lancet* **2018**, *392*, 1321–1329. [CrossRef]
35. Breton, M.D.; Kanapka, L.G.; Beck, R.W.; Ekhlaspour, L.; Forlenza, G.P.; Cengiz, E.; Schoelwer, M.; Ruedy, K.J.; Jost, E.; Carria, L.; et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. *N. Engl. J. Med.* **2020**, *383*, 836–845. [CrossRef]

36. Foster, N.C.; Beck, R.W.; Miller, K.M.; Clements, M.A.; Rickels, M.R.; DiMeglio, L.A.; Maahs, D.M.; Tamborlane, W.V.; Bergenstal, R.; Smith, E.; et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016–2018. *Diabetes Technol. Ther.* **2019**, *21*, 66–72. [CrossRef]
37. Renard, E.; Ikegami, H.; Daher Vianna, A.G.; Pozzilli, P.; Brette, S.; Bosnyak, Z.; Lauand, F.; Peters, A.; Pilorget, V.; Jurišić-Eržen, D.; et al. The SAGE study: Global observational analysis of glycaemic control, hypoglycaemia and diabetes management in T1DM. *Diabetes Metab. Res. Rev.* **2021**, *37*, e3430. [CrossRef]