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REVIEW

Insulin Therapy for the Management of Diabetes Mellitus: A Narrative Review of Innovative Treatment Strategies

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ABSTRACT

The discovery of insulin was presented to the international medical community on May 3, 1922. Since then, insulin has become one of the most effective pharmacological agents used to treat type 1 and type 2 diabetes mellitus. However, the initiation and intensification of insulin therapy is often delayed in people living with type 2 diabetes due to numerous challenges associated with daily subcutaneous administration. Reducing the frequency of injections, using insulin pens instead of syringes and vials, simplifying treatment regimens, or administering insulin through alternative routes may help improve adherence to and persistence with insulin therapy among people living with diabetes. As the world commemorates the centennial of the commercialization of insulin, the aims of this article are to provide an overview of insulin therapy and to summarize clinically significant findings from phase 3 clinical trials evaluating less frequent dosing of insulin and the non-injectable administration of insulin.

Keywords: Adherence; Insulin; Persistence; Pharmacology; Treatment; Type 1 diabetes; Type 2 diabetes

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Key Summary Points
Globally, at least 200 million people living with diabetes require insulin therapy.
Initiation and intensification of insulin remains a major challenge for patients with type 2 diabetes.
Less frequent dosing of insulin and non-injectable administration of insulin may overcome this challenge, and several phase 3 clinical trials are evaluating these innovative treatment strategies.
Inhaled insulin is currently available for management of post-prandial hyperglycemia in people with type 1 or type 2 diabetes who prefer a non-injectable treatment option.
Once-weekly dosing of insulin has the potential to improve adherence to and persistence with insulin therapy among patients with diabetes.

INTRODUCTION

Between January and February 1922, insulin was successfully used to lower blood glucose levels and resolve glycosuria and ketonuria in a teenage boy living with diabetes mellitus (DM) [1, 2]. Groundbreaking research conducted at the University of Toronto during the period of insulin's discovery [3] were presented to an international audience for the first time at the Annual Meeting of the American Medical Association held on May 3, 1922 [4]. Thereafter, the physicochemical characterization of insulin [5–7] and the synthesis of highly pure preparations for treating DM [8, 9] enabled insulin to become the life-saving antidiabetic medication that it is today.

Globally, 150–200 million patients with DM require insulin therapy [10]. All patients with type 1 (T1DM) require lifelong insulin therapy, whereas 20–30% of patients with type 2 (T2DM) eventually require insulin as a result of progressive pancreatic β-cell dysfunction [10].

Insulin Structure–Function Relationship

Insulin, a peptide hormone that regulates carbohydrate metabolism in vertebrates, belongs to the $\alpha + \beta$ class of evolutionarily conserved globular proteins [11, 12]. It consists of 51 amino acids organized into two chains: the A chain (glycine^{A1}–asparagine^{A21}) and the B chain (phenylalanine^{B1}–threonine^{B30}). The amino acids that constitute the A and B chains influence the natural tendency of insulin to self-associate and bind the insulin receptor [13]. Modifying specific amino acids in the two chains alters molecular stability and the dynamics of hexamer-to-monomer dissociation without disrupting insulin's ability to lower blood glucose levels [1]. Consequently, most therapeutic insulins that are currently available have modified amino acids and different capacities for self-association compared to endogenous human insulin [14, 15].

The molecular pharmacology of various therapeutic insulins is summarized in Table 1.

Classifying Insulins

The earliest method for classifying therapeutic insulins was based on duration of action [16, 17]. More recently, therapeutic insulins—particularly those providing basal coverage—have been classified by generation [18, 19] in order to more effectively highlight the evolving therapeutic landscape. A generation-based approach to classification is useful because it allows clinically relevant characteristics of various insulin preparations to be emphasized, such as concentration, glycemic management, and approximate time–action profile.

First-generation insulins are prepared to the standardized concentration of 100 units/mL (U-100) [20, 21]. Second-generation insulins, in contrast, are prepared to a concentration of 200 units/mL (U-200), 300 units/mL (U-300), or 500 units/mL (U-500) [22]. Also included in the second generation are hepato-preferential insulins [23] as well as biosimilar and follow-on

Table 1 Molecular pharmacology of therapeutic insulins

Insulin molecule	Modification	Molecular consequences	Pharmacological implications
Established			
Aspart	Pro^{B28} → Asp	Electrostatic repulsion: Asp^{B28} and Glu^{B21} Disruption of hydrophobic interactions in B-chain	Fast absorption and rapid duration of action due to unstable dimers
Faster aspart	Pro^{B28} → Asp Addition of niacinamide (vitamin B3) and arginine to pharmaceutical solution	Electrostatic repulsion: Asp^{B28} and Glu^{B21} Disruption of hydrophobic interactions in B chain	Fast absorption and ultra-rapid duration of action due to increased abundance of monomers as well as increased subcutaneous blood flow and local vasodilation
Degludec	Deletion of Thr^{B30}; acylation of hexadecanedioic acid to Lys^{B29} via γ-L-Glu spacer	Allosteric reorganization of hexamers: T_3R_3 → T_6 Self-association into linear multi-hexamer chains Reversible binding to human serum albumin (2.4-fold higher affinity than detemir)	Slow absorption and long duration of action due to formation of subcutaneous and circulating depots
Detemir	Deletion of Thr^{B30}; acylation of myristic acid to Lys^{B29}	Self-association into di-hexamers Reversible binding to human serum albumin	Slow absorption and long duration of action due to formation of subcutaneous and circulating depots
Glargine	Asn^{A21} → Gly; addition of di-arginine (Arg^{B31} and Arg^{B32}) after Thr^{B30}	Isoelectric precipitation Protection from deamidation at acidic pH	Slow absorption and long duration of action due to formation of loose or compact subcutaneous depot at physiological pH
Glulisine	Asn^{B3} → Lys; Lys^{B29} → Glu	Steric hindrance induced by Lys^{B3} Electrostatic repulsion: Glu^{B29} and Glu^{B21}; Lys^{B3} and Arg^{B22} Protection from deamidation at neutral pH	Fast absorption and rapid duration of action due to unstable dimers
Lispro	Pro^{B28} → Lys; Lys^{B29} → Pro	Steric hindrance: Lys^{B28} and Gly^{B20}–Gly^{B23} β-turn Disruption of hydrophobic interactions in B chain	Fast absorption and rapid duration of action due to unstable dimers
URLi	Pro^{B28} → Lys; Lys^{B29} → Pro Addition of treprostinil and citrate to pharmaceutical solution	Steric hindrance: Lys^{B28} and Gly^{B20}–Gly^{B23} β-turn Disruption of hydrophobic interactions in B chain	Fast absorption and ultra-rapid duration of action due to unstable dimers as well as increased local vascular permeability and vasodilation

Table 1 continued

Insulin molecule	Modification	Molecular consequences	Pharmacological implications
NPH	Crystalline suspension of zinc, phenols, and combination of insulin and protamine in 5:1 ratio	Formation of protamine-insulin conglomerate via electrostatic interactions	Slow absorption and intermediate duration of action due to formation of orthorhombic crystal heaps at injection site
RHI	Addition of zinc and *meta*-cresol to pharmaceutical solution	Allosteric reorganization: B1–B8 segment → α-helix	Slightly delayed absorption and short duration of action due to stable compact hexamers with slow rate of hexamer-to-monomer dissociation
Exubera	Dry powder mixture of recombinant human insulin, sodium citrate dihydrate, sodium hydroxide, mannitol, and glycine	Formation of stable microspheres (1.0–5.0 μm diameter) that contain vitrified insulin monomers	Fast absorption and rapid duration of action due to formation of microspheres that reach the alveoli and dissolve at physiological pH
Technosphere insulin	Dry powder mixture of recombinant human insulin, FDKP, and polysorbate 80	Self-assembly of stable microspheres (2.0–2.5 μm diameter) that adsorb insulin monomers	Fast absorption and ultra-rapid duration of action due to formation of microspheres that reach the alveoli and dissolve at physiological pH
Investigational			
BIL	Pro^{B28} → Lys; Lys^{B29} → Pro 20 kDa polyethylene glycol chain attached to Lys^{B28} via urethane bond	Large hydrodynamic size Limited passage through continuous vascular endothelium but ready passage through fenestrated hepatic sinusoidal endothelium Prolonged half-life and protection from enzymatic degradation due to PEGylation Reduced insulin receptor affinity and low receptor-mediated clearance Reduced renal clearance Minimal self-association	Slow absorption predominantly via lymphatic system and long duration of action due to formation of circulating depot Hepato-preferential insulin action due to reduced peripheral effects

Table 1 continued

Insulin molecule	Modification	Molecular consequences	Pharmacological implications
Icodec	Tyr^{A14} → Glu; Tyr^{B16} → His Phe^{B25} → His; deletion of Thr^{B30} Acylation of icosanedioic acid to Lys^{B29} via 2xOEG-γ-L-Glu spacer	Prolonged half-life due to increased stability and protection from enzymatic degradation Reduced insulin receptor affinity and low receptor-mediated clearance Reversible binding to human serum albumin (tenfold higher affinity than detemir) Minimal self-association	Slow absorption and ultra-long duration of action due to formation of circulating depot
Insulin efsitora alfa	Ile^{A10} → Thr;Tyr^{A14} → Asp; Asn^{A21} → Gly Tyr^{B16} → Glu; Phe^{B25} → His; Thr^{B27} → Gly; Pro^{B28} → Gly; Lys^{B29} → Gly; Thr^{B30} → Gly Single-chain insulin variant fused to human IgG2 Fc domain via peptide linker	Prolonged half-life and protection from degradation due to increased stability and binding to FcRn Reduced insulin receptor affinity and low receptor-mediated clearance Reduced renal clearance Minimal self-association	Slow absorption and ultra-long duration of action due to formation of circulating depot
ORMD-0801	RHI formulated with proprietary POD technology	Protection from enzymatic degradation due to presence of soybean trypsin inhibitor, aprotinin, and a chelating agent Paracellular transport of insulin through intestinal epithelium due to presence of polysorbate 80, disodium ethylenediaminetetraacetic acid, chelating agent, and bile salts	Absorption in small intestine and entry into hepatic portal system due to pH-sensitive enteric coating and absorption enhancers Prolonged action due to secondary hepatic effect (suppression of gluconeogenesis and glycogenolysis)

BIL basal insulin peglispro, *Fc* fragment crystallizable, *FcRn* neonatal Fc receptor, *FDKP* fumaryl diketopiperazine, *IgG2* immunoglobulin G2, *NPH* neutral protamine Hagedorn, *OEG* oligoethylene glycol, *POD* protein oral delivery, *RHI* regular human insulin, *URLi* ultrarapid lispro

insulins, which have comparable physicochemical properties to the U-100 insulin preparations that are no longer under patent protection [24]. Finally, third-generation insulins comprise inhaled insulin preparations [25], oral insulin preparations [26], ultra-rapid-acting insulin preparations [27], ultra-long-acting insulin preparations [28], fixed-ratio co-formulations of basal and prandial insulin [29], and fixed-ratio combinations of basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) [30].

Table 2 summarizes the classification of therapeutic insulins according to generation.

Aims

Initiation and intensification of insulin in patients with T2DM is often delayed due to limited acceptance of, adherence to, or

Table 2 Classification of therapeutic insulins according to generation

Insulin preparation	Concentration	Glycemic management	Time of onset	Time to peak action	Duration of action
1st generation: standardized insulins					
Aspart	U-100	Prandial	9–21 min	1–3 h	3–5 h
Detemir	U-100	Basal	1–2 h	4–7 h Modest peak	5.7–23.2 h
Glargine	U-100	Basal	2–4 h	8–12 h Modest peak	10.8–24 h
Glulisine	U-100	Prandial	9–21 min	1–3 h	3–5 h
Lispro	U-100	Prandial	9–21 min	1–3 h	3–5 h
NPH	U-100	Basal	2–4 h	4–12 h	12–24 h
NPH + RHI	U-100	Basal + prandial	30 min–1 h	2–5 h	10–16 h
Protaminated aspart + aspart	U-100	Basal + prandial	5–30 min	1–12 h	15–18 h
Protaminated lispro + lispro	U-100	Basal + prandial	10–15 min	1–12 h	10–16 h
RHI	U-100	Prandial	30 min–1 h	2–4 h	5–8 h
2nd generation: concentrated, hepato-preferential, biosimilar, and follow-on insulins					
Degludec	U-100 U-200	Basal	30 min–1.5 h	No peak	> 42 h
Glargine	U-300	Basal	2–6 h	No peak	30–36 h
Lispro	U-200	Prandial	9–21 min	1–3 h	3–5 h
RHI	U-500	Basal + prandial	< 15 min	4–8 h	13–24 h
BIL	900 nmol/mL	Basal	N/A	No peak	> 36 h
Biosimilar aspart	U-100	Prandial	9–21 min	1–3 h	3–5 h
Biosimilar glargine	U-100	Basal	2–4 h	8–12 h Modest peak	10.8–24 h
Follow-on lispro	U-100	Prandial	9–21 min	1–3 h	3–5 h
3rd generation: fixed-ratio co-formulation/combination, oral, inhaled, and ultra-insulins					
Delgludec + aspart	U-100	Basal + prandial	10–20 min	30 min–1.5 h	> 24 h
Degludec + liraglutide	Degludec U-100 3.6 mg/mL liraglutide	Basal + prandial	30 min–1.5 h	No peak	24 h
Glargine + lixisenatide	Glargine U-100 33 or 50 μg/mL lixisenatide	Basal + prandial	2–4 h	No peak	20–24 h

Table 2 continued

Insulin preparation	Concentration	Glycemic management	Time of onset	Time to peak action	Duration of action
Faster aspart	U-100	Prandial	6–12 min	1–3 h	3–5 h
Icodec	U-700	Basal	N/A	No peak	196 h
Icodec + semaglutide	Icodec U-700	Basal + prandial	N/A	No peak	196 h
	2 mg/mL semaglutide				
Insulin efsitora alfa	35 units/mg	Basal	N/A	No peak	408 h
ORMD-0801	8 mg	Basal	NP	NP	NP
Exubera	1 mg	Prandial	10–20 min	2 h	6 h
	3 mg				
Technosphere insulin	4-U	Prandial	12 min	35–55 min	1.5–4.5 h
	8-U				
	12-U				
URLi	U-100	Prandial	15–17 min	57 min	4.6–7.3 h
	U-200				

BIL basal insulin peglispro, *NP* not published, *NPH* neutral protamine Hagedorn, *RHI* regular human insulin, *URLi* ultrarapid lispro

persistence with insulin therapy, which lead to poor glycemic management and suboptimal treatment outcomes [31]. Innovative treatment strategies for improving insulin adherence and persistence include less frequent dosing [28], non-injectable administration [32], the simplification of complex regimens [33], and the use of insulin pen technologies [34]. Since the latter two approaches have been reviewed by other authors [35, 36], this article will summarize clinically significant developments in the less frequent dosing of insulin and the non-injectable administration of insulin based on phase 3 randomized controlled trials (RCTs) retrieved from PubMed and ClinicalTrials.gov between January 1, 2023 and July 31, 2023.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

LESS FREQUENT DOSING OF INSULIN: SUMMARY OF PHASE 3 CLINICAL TRIALS

Once-Daily Dosing of Basal Insulin

Patients with diabetes who do not achieve glycemic targets with once-daily or twice-daily dosing of a first-generation basal insulin may benefit from once-daily dosing of a second-generation basal insulin [37]. However, unlike endogenous insulin secretion, conventional basal insulins do not reproduce the physiological hepatic-to-peripheral insulin gradient (threefold higher insulin levels in the liver compared to skeletal muscle and adipose tissue) [38, 39].

Eli Lilly and Company developed basal insulin peglispro (BIL), the first hepato-preferential insulin analogue formulated for once-daily dosing [40, 41]. This development was motivated by the need for a basal insulin with

the capacity to provide direct suppression of hepatic glucose metabolism without peripheral over-insulinization, lower blood glucose levels for ≥ 24 h, minimize weight gain, and reduce day-to-day glycemic variability.

Basal Insulin Peglispro (LY2605541)

The IMAGINE clinical development program is a series of eight phase 3 clinical trials [42–49]. The primary objective of the six active-controlled, treat-to-target phase 3 RCTs is to evaluate change in glycated hemoglobin (HbA1c) from baseline to either week 26 or week 52 by comparing once-daily dosing of BIL to once-daily dosing of neutral protamine Hagedorn (NPH) in adult participants with insulin-naïve T2DM (IMAGINE 6) or once-daily dosing of glargine in three different populations: adult participants with insulin-naïve T2DM (IMAGINE 2); adult participants with insulin-treated T1DM (IMAGINE 1 and IMAGINE 3); and adult participants with insulin-treated T2DM (IMAGINE 4 and IMAGINE 5). Across all six clinical trials, BIL provided non-inferior and statistically superior reductions in HbA1c compared to glargine and NPH.

IMAGINE 7, a phase 3, randomized, crossover trial comparing 8-h to 40-h variable-time dosing to 24-h fixed-time dosing of BIL showed that variable-time dosing provided a reduction in baseline HbA1c that was non-inferior to fixed-time dosing after 12 weeks of treatment in adult participants with T1DM who were previously treated with insulin. Lastly, IMAGINE 8, a phase 3, randomized, crossover trial evaluating the incidence of hypoglycemia 84 h after administering a double dose, demonstrated that double dosing of BIL was associated with a significantly lower risk of clinically significant hypoglycemia (blood glucose ≤ 3.0 mmol/L or symptoms of severe hypoglycemia) compared to double dosing of glargine in adult participants with T2DM who were previously treated with insulin.

Despite these positive findings, the IMAGINE clinical development program was ultimately terminated because participants treated with BIL developed elevated levels of alanine aminotransferase and serum triglycerides as well as increased liver fat content [41, 50].

Table 3 summarizes the IMAGINE clinical development program evaluating once-daily dosing of basal insulin.

Once-Weekly Dosing of Basal Insulin

Extensive research has been conducted in an attempt to develop a basal insulin with an extended half-life, prolonged glucose-lowering activity, and potential for improving treatment adherence [28]. As a consequence, several insulin preparations have been formulated for once-weekly dosing. Novo Nordisk developed an ultra-long-acting basal insulin analogue (icodec) and a fixed-ratio combination of a basal insulin and GLP-1RA (icodec + semaglutide). Eli Lilly and Company developed an ultra-long-acting, single-chain insulin variant fused to the fragment crystallizable region of an immunoglobulin G2 (insulin efsitora alfa).

Icodec (NN1436)

The ONWARDS clinical development program is a series of six active-controlled, treat-to-target, phase 3a RCTs [51–56]. The primary objective of the program is to evaluate change in HbA1c from baseline to the end of the treatment period by comparing once-weekly dosing of icodec to once-daily dosing of conventional basal insulin (glargine or degludec) in three diverse populations: adult participants with T2DM who are insulin-naïve (ONWARDS 1, 3, and 5); adult participants with T2DM who were previously treated with insulin (ONWARDS 2 and ONWARDS 4); and adult participants with T1DM who were previously treated with insulin (ONWARDS 6).

Published results demonstrate that icodec provided reductions in baseline HbA1c that were non-inferior (ONWARDS 1–4) and statistically superior (ONWARDS 1–3) to degludec U-100 and glargine U-100. Results from ONWARDS 5 and ONWARDS 6 are not yet published, but they are expected to provide key insights that will inform various clinically relevant aspects of once-weekly dosing of icodec,

Table 3 Summary of phase 3 randomized controlled trials evaluating once-daily dosing of basal insulin

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
Basal insulin peglispro					
IMAGINE 1 Non-inferiority, OL [42]	T1DM on insulin; HbA1c < 12.0% N = 455	BIL + lispro (n = 295) Mean baseline HbA1c: 7.75 ± 0.06%	Glargine + lispro (n = 160) Mean baseline HbA1c: 7.85 ± 0.09%	78	Change in HbA1c from baseline to week 26: • BIL: − 0.69 ± 0.04% • Glargine: − 0.33 ± 0.06% • Treatment difference: − 0.37% (95% CI − 0.50 to − 0.23); $P < 0.001$ Non-inferiority margin: 0.4%
IMAGINE 2 Non-inferiority, DB [43]	Insulin-naïve T2DM on ≥ 2 OADs; HbA1c 7.0–11.0% N = 1538	BIL + OADs (n = 1003) Mean baseline HbA1c: 8.5%	Glargine + OADs (n = 535) Mean baseline HbA1c: 8.5%	78 (cohort 1) 52 (cohort 2)	Change in HbA1c from baseline to week 52: • BIL: − 1.6% • Glargine: − 1.3% • Treatment difference: − 0.29% (95% CI − 0.40 to − 0.19); $P < 0.001$ Non-inferiority margin: 0.4%
IMAGINE 3 Non-inferiority, DB [44]	T1DM on basal-bolus insulin; HbA1c < 12.0% N = 1114	BIL + lispro (n = 664) Mean baseline HbA1c: 7.88 ± 0.04%	Glargine + lispro (n = 450) Mean baseline HbA1c: 7.84 ± 0.05%	52	Change in HbA1c from baseline to week 52: • BIL: − 0.46 ± 0.03% • Glargine: − 0.24 ± 0.04% • Treatment difference: − 0.22% (95% CI − 0.32 to − 0.12); $P < 0.001$ Non-inferiority margin: 0.4%

Table 3 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
IMAGINE 4 Non-inferiority, DB [45]	T2DM on ≥ 1 daily insulin injection; HbA1c ≥ 7.0% to < 12.0% *N* = 1369	BIL + lispro (*n* = 691) Mean baseline HbA1c: 8.38 ± 0.04%	Glargine + lispro (*n* = 678) Mean baseline HbA1c: 8.47 ± 0.04%	26	Change in HbA1c from baseline to week 26: • BIL: − 1.66 ± 0.04% • Glargine: − 1.45 ± 0.04% • Treatment difference: − 0.21% (95% CI − 0.31 to − 0.11); *P* < 0.001 Non-inferiority margin: 0.4%
IMAGINE 5 Non-inferiority, OL [46]	T2DM on basal insulin (glargine, detemir, or NPH) ± ≤ 3 OADs; HbA1c < 9.0% *N* = 466	BIL ± OADs (*n* = 307) Mean baseline HbA1c: 7.43 ± 0.05%	Glargine ± OADs (*n* = 159) Mean baseline HbA1c: 7.41 ± 0.06%	52	Change in HbA1c from baseline to week 26: • BIL: − 0.82 ± 0.04% • Glargine: − 0.29 ± 0.06% • Treatment difference: − 0.52% (95% CI − 0.67 to − 0.38); *P* < 0.001 Non-inferiority margin: 0.4%
IMAGINE 6 Non-inferiority, OL [47]	Insulin-naïve T2DM on ≥ 2 OADs; HbA1c 7.0–11.0% *N* = 641	BIL (AM) + OADs (*n* = 213) BIL (PM) + aspart (*n* = 215) Mean baseline HbA1c (AM and PM): 8.5 ± 0.05%	NPH (PM) + OADs (*n* = 213) Mean baseline HbA1c: 8.5 ± 0.07%	26	Change in HbA1c from baseline to week 26: • BIL (AM and PM): − 1.7% • Glargine: − 1.4% • Treatment difference: − 0.37% (95% CI − 0.50 to − 0.23); *P* < 0.001 Non-inferiority margin: 0.4%

Table 3 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
IMAGINE 7 Non-inferiority, OL, CO, three periods [48]	T1DM on insulin; HbA1c < 9.0% *N* = 182	BIL variable-time dosing (8 ± 2 h to 40 ± 2 h intervals) (*n* = 180) Mean baseline HbA1c: 7.50 ± 0.81%	BIL fixed-time dosing (every evening) (*n* = 177) Mean baseline HbA1c: 7.50 ± 0.81%	36	Change in HbA1c from baseline to week 12: • BIL variable-time dosing: − 0.57% • BIL fixed-time dosing: − 0.63% • Treatment difference: 0.06% (95% CI − 0.01 to 0.13); *P* = 0.095 Non-inferiority margin: 0.4%
IMAGINE 8 Superiority, DB, CO, two periods [49]	T2DM on basal insulin; HbA1c ≤ 9.0% *N* = 68	BIL double dose (*n* = 34) Mean baseline HbA1c: 7.4%	Glargine double dose (*n* = 34) Mean baseline HbA1c: 7.1%	16	Incidence of clinically significant hypoglycemia 84 h after double dosing: • BIL double dose: 6.6% (9 events) • Glargine double dose: 35.5% (52 events) • Treatment difference: OR 0.13 (95% CI − 0.04 to 0.39); *P* < 0.001

AM pre-morning meal, *BIL* basal insulin peglispro, *CI* confidence interval, *CO* crossover, *DB* double-blind, *HbA1c* glycated hemoglobin, *NPH* neutral protamine Hagedorn, *OL* open-label, *OR* odds ratio, *PM* bedtime, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

including dose titration in adult participants with T2DM and administration of basal-bolus insulin therapy in adult participants with T1DM.

Icodec + Semaglutide (NN1535, IcoSema)

The ongoing COMBINE clinical development program comprises three active-controlled, open-label, phase 3 RCTs [57–59]. The primary objective of the program is to evaluate change in HbA1c from baseline to the end of the treatment period in adult participants with T2DM who were previously treated with either basal insulin or GLP-1RA. These phase 3 trials are comparing once-weekly dosing of fixed-ratio combination icodec + semaglutide to once-weekly dosing of icodec (COMBINE 1), once-weekly dosing of semaglutide (COMBINE 2), and once-daily dosing of glargine (COMBINE 3).

Insulin Efsitora Alfa (LY3209590, Basal Insulin Fc)

The ongoing Once Weekly Insulin Therapy (QWINT) clinical development program consists of five active-controlled, open-label, phase 3 RCTs [60–64] comparing once-weekly dosing of insulin efsitora alfa to once-daily dosing of basal insulin (degludec or glargine). The primary objective of the program is to evaluate change in HbA1c from baseline to the end of the treatment period in three different populations: adult participants with insulin-naïve T2DM (QWINT-1 and QWINT-2); adult participants with insulin-treated T2DM (QWINT-3 and QWINT-4); and adult participants with insulin-treated T1DM (QWINT-5).

Table 4 summarizes the ONWARDS, COMBINE, and QWINT clinical development programs evaluating once-weekly dosing of basal insulin.

CLINICAL SIGNIFICANCE OF LESS FREQUENT DOSING OF INSULIN

Glycemic management with conventional insulin therapy is typically suboptimal, necessitating treatment intensification with either multiple daily injection (MDI) of insulin or continuous subcutaneous insulin infusion (CSII) [65, 66]. The need for daily subcutaneous injections is reduced with CSII because the site of infusion must be changed every 48–72 h [67, 68]. However, adherence and persistence rates of insulin therapy are still lower than for other antidiabetic medications [69]. Although several negative predictive factors have been identified [70], the inverse relationship between frequency of insulin injections and treatment adherence and persistence [71] has not been effectively tackled by MDI or CSII.

Less frequent dosing of insulin has major clinical implications because it may help patients living with DM achieve desired outcomes by overcoming the known barriers to optimal use of insulin therapy [31, 72]. Once-weekly dosing of GLP-1RAs is associated with higher rates of treatment adherence and persistence compared to once-daily dosing [73]. By reducing the burden of injections, it is likely that once-weekly dosing of insulin will lead to similar improvements in adherence and persistence [74].

There are very few studies evaluating adherence to and persistence with less frequent dosing of insulin therapy [75]. A recently published cross-sectional study found that a reduced number of injections was the most common patient-reported factor that may improve treatment adherence [76]. More research into once-weekly dosing of insulin is needed to provide robust evidence of the impact of less frequent dosing on adherence to and persistence with insulin therapy [77].

Basal Insulin Peglispro, Icodec, Icodec + Semaglutide, and Insulin Efsitora Alfa

One hepato-preferential insulin preparation, two ultra-long-acting insulin preparations, and one fixed-ratio combination have been studied in phase 3 RCTs. Figure 1 summarizes clinically significant characteristics of these innovative insulins.

The IMAGINE Trials

BIL was designed to pharmacologically replicate the physiological hepatic-to-peripheral insulin gradient. Unfortunately, the IMAGINE clinical development program was discontinued because transaminases, serum triglyceride levels, and liver fat content were elevated in insulin-treated but not insulin-naïve adult participants with T2DM who were treated with BIL.

Insulin signaling in the liver is known to induce hepatic de novo lipogenesis by activating transcription factors and enzymes involved in fatty acid biosynthesis [78, 79]. Whether the liver changes that necessitated the termination of the IMAGINE program were adaptive changes to treatment with BIL or evidence of PEGylation-induced hepatotoxicity remains to be determined [38, 41, 80]. The potential utility of lipogenesis inhibitors [81] or glucagon receptor inhibitors [82] for counteracting the negative effects of hepatic insulin signaling is being

Table 4 Summary of phase 3 randomized controlled trials evaluating once-weekly dosing of basal insulin

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
Icodec					
ONWARDS 1 Non-inferiority, OL, two phase [51]	Insulin-naïve T2DM; HbA1c 7.0–11.0% N = 984	Icodec + non-insulin GLDs (n = 492) Mean baseline HbA1c: 8.50%	Glargine U-100 + non-insulin GLDs (n = 492) Mean baseline HbA1c: 8.44%	78	Change in HbA1c from baseline to week 52: • Icodec: − 1.55% • Glargine: − 1.35% • Treatment difference: − 0.19% (95% CI − 0.36 to − 0.03); $P < 0.001$ Non-inferiority margin: 0.3% Statistical superiority: $P = 0.02$
ONWARDS 2 Non-inferiority, OL [52]	T2DM on basal insulin; HbA1c 7.0–10.0% N = 526	Icodec + non-insulin GLDs (n = 262) Mean baseline HbA1c: 8.17%	Degludec U-100 + non-insulin GLDs (n = 263) Mean baseline HbA1c: 8.10%	26	Change in HbA1c from baseline to week 26: • Icodec: − 0.93% • Degludec: − 0.71% • Treatment difference: − 0.22% (95% CI − 0.37 to − 0.08); $P < 0.0001$ Non-inferiority margin: 0.3% Statistical superiority: $P = 0.0028$

Table 4 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
ONWARDS 3 Non-inferiority, DB [53]	Insulin-naïve T2DM; HbA1c 7.0–11.0% $N = 588$	Icodec + QD placebo ($n = 294$) Mean baseline HbA1c: 8.6%	Degludec U-100 + QW placebo ($n = 294$) Mean baseline HbA1c: 8.5%	26	Change in HbA1c from baseline to week 26: • Icodec: − 1.6% • Degludec: − 1.4% • Treatment difference: − 0.2% (95% CI − 0.3 to − 0.1); $P < 0.001$ Non-inferiority margin: 0.3% Statistical superiority: $P = 0.002$
ONWARDS 4 Non-inferiority, OL [54]	T2DM on basal-bolus insulin; HbA1c 7.0–10.0% $N = 582$	Icodec + aspart ($n = 291$) Mean baseline HbA1c: 8.29%	Glargine U-100 + aspart ($n = 291$) Mean baseline HbA1c: 8.31%	26	Change in HbA1c from baseline to week 26: • Icodec: − 1.16% • Glargine: − 1.18% • Treatment difference: 0.02% (95% CI − 0.11 to 0.15); $P < 0.0001$ Non-inferiority margin: 0.3%
ONWARDS 5 Non-inferiority, OL Status: completed; results NP [55]	Insulin-naïve T2DM; HbA1c > 7.0% $N = 1085$	Icodec with DoseGuide titration application	Basal insulin (degludec or glargine U-100 or glargine U-300)	52	Change in HbA1c from baseline

Table 4 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
ONWARDS 6 Non-inferiority, OL, two phase Status: completed; results NP [56]	T1DM on basal-bolus insulin; HbA1c < 10.0% *N* = 583	Icodec + aspart	Degludec U-100 + aspart	52	Change in HbA1c from baseline
Icodec + semaglutide					
COMBINE 1 OL Status: ongoing [57]	T2DM on basal insulin; HbA1c 7.0–10.0% *N* = 1290	Icodec + semaglutide	Icodec	52	Change in HbA1c from baseline
COMBINE 2 OL Status: ongoing [58]	Insulin-naïve T2DM on GLP-1RA; HbA1c 7.0–10.0% *N* = 680	Icodec + semaglutide	Semaglutide	52	Change in HbA1c from baseline
COMBINE 3 OL Status: ongoing [59]	T2DM on basal insulin; HbA1c 7.0–10.0% *N* = 680	Icodec + semaglutide	Glargine + aspart	52	Change in HbA1c from baseline
Insulin efsitora alfa					
QWINT-1 Non-inferiority, OL Status: ongoing [60]	Insulin-naïve T2DM; HbA1c 7.0–10.0% *N* = 670	Insulin efsitora alfa	Glargine	52	Change in HbA1c from baseline

Table 4 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
QWINT-2 OL Status: ongoing [61]	Insulin-naïve T2DM; HbA1c 7.0–10.0% *N* = 912	Insulin efsitora alfa	Degludec	52	Change in HbA1c from baseline
QWINT-3 OL Status: ongoing [62]	T2DM on basal insulin; HbA1c 6.5–10.0% *N* = 986	Insulin efsitora alfa	Degludec	78	Change in HbA1c from baseline
QWINT-4 OL Status: ongoing [63]	T2DM on MDI insulin; HbA1c 7.0–10.0% *N* = 670	Insulin efsitora alfa + lispro	Glargine U-100 + lispro U-100	26	Change in HbA1c from baseline
QWINT-5 OL Status: ongoing [64]	T1DM on basal-bolus insulin; HbA1c 7.0–10.0% *N* = 692	Insulin efsitora alfa	Degludec	52	Change in HbA1c from baseline

CI confidence interval, *DB* double-blind, *GLDs* glucose-lowering drugs, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated hemoglobin, *MDI* multiple daily injection, *NP* not published, *OL* open-label, *QD* once-daily, *QW* once-weekly, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

actively investigated. Overall, research into how PEGylation affects the liver and studies of novel therapies for counteracting the unwanted effects of hepatic insulin signaling should be prioritized in order to help develop other hepato-preferential insulins in the future.

The ONWARDS and QWINT Trials

By significantly reducing the burden of injection, once-weekly basal insulin has potential to improve adherence to and persistence with insulin therapy among patients living with DM. However, there is concern that icodec and insulin efsitora alfa may be associated with excessive day-to-day glycemic variability. The increasing use of continuous glucose monitoring (CGM) in research and clinical practice has enabled dynamic fluctuations in blood glucose levels to be studied more conveniently. Time in range (TIR), which is defined as the percentage of time that blood glucose is between 3.9 and 10.0 mmol/L [83, 84], is a clinically relevant indicator of glycemic management that is inversely correlated with HbA1c [85]. For adults with T1DM or T2DM, the recommended TIR is > 70%, meaning that blood glucose levels

should remain within range for more than 16 h 48 min over a 24-h period [86].

Treatment with icodec resulted in a significantly higher TIR compared to glargine in ONWARDS 1 (71.9% [17 h 15 min] versus 66.9% [16 h 3 min] during weeks 48–52; $P < 0.001$ and 70.2% [16 h 51 min] versus 64.8% [15 h 33 min] during weeks 74–78; $P < 0.001$), a similar TIR compared to glargine in ONWARDS 4 (66.9% [16 h 3 min] versus 66.4% [15 h 56 min] during weeks 22–26; $P = 0.84$), and a slightly higher TIR compared to degludec in ONWARDS 2 (63.1% [15 h 9 min] versus 59.5% [14 h 17 min] during weeks 22–26; $P = 0.15$). CGM data for adult populations with T1DM (ONWARDS 6 and QWINT-5) and adult populations with T2DM (QWINT-2, QWINT-3, and QWINT-4) will provide additional clinically significant information on the quality of glycemic management resulting from less frequent dosing of insulin.

Insulin efsitora alfa protracts insulin action by binding to the fetal neonatal receptor, whereas icodec reversibly binds to human serum albumin [87]. It is unclear whether these different mechanisms of protraction will lead to clinically significant differences in efficacy and safety. A head-to-head trial comparing insulin efsitora alfa and icodec may be needed in order to resolve this uncertainty.

The COMBINE Trials

Intensification of basal insulin with once-weekly dosing of icodec + semaglutide will be a clinically significant treatment option for adult patients with T2DM because it has the potential to significantly reduce injection burden, provide complementary basal and prandial glycemic management with a limited risk of hypoglycemia, reduce body weight, and manage cardiovascular risk factors [88]. Consequently, results from the COMBINE program are eagerly awaited due to the frequent association between obesity and T2DM [89] and the urgent need for safe and effective medications that manage the cardiometabolic complications of DM.

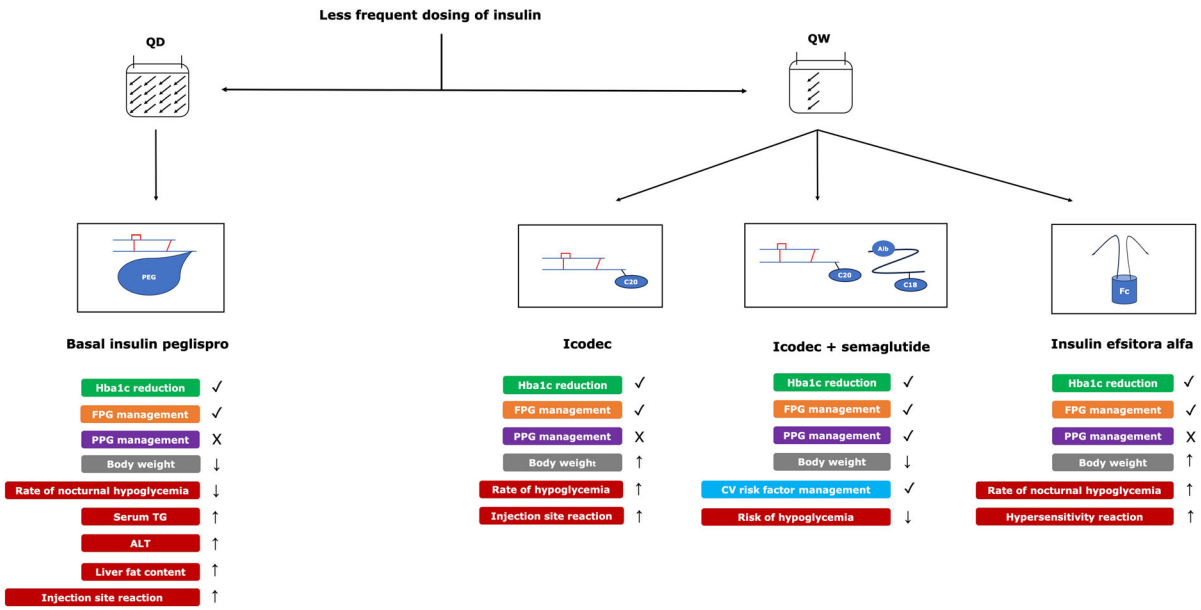

Fig. 1 Schematic of clinically significant characteristics of insulins formulated for less frequent dosing. *Aib* 2-aminoisobutyric acid, *ALT* alanine aminotransferase, *C18* octadecanedioic acid, *C20* icosanedioic acid, *CV* cardiovascular, *Fc* fragment crystallizable, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *PEG* polyethylene glycol, *PPG* post-prandial glucose, *QD* once-daily, *QW* once-weekly, *TG* triglyceride

Table 5 Summary of phase 3 randomized controlled trials evaluating the non-injectable administration of insulin

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
Exubera					
NCT00136916 Non-inferiority, OL [92]	T2DM on insulin; HbA1c 5.5–11.0%; $FEV_1 > 70\%$ of predicted; $DL_{CO} < 120\%$ or $> 70\%$ of predicted $N = 635$	EXU + intermediate- or long-acting insulin ($n = 316$) Mean baseline FEV_1: 2.91 ± 0.68 L Mean baseline DL_{CO}: 24.17 ± 5.58 mL min^{-1} $mmHg^{-1}$	RHI or short-acting insulin + intermediate- or long-acting insulin ($n = 311$) Mean baseline FEV_1: 2.93 ± 0.68 L Mean baseline DL_{CO}: 23.99 ± 5.72 mL min^{-1} $mmHg^{-1}$	104	Annual rate of change in FEV_1 from baseline: • EXU: − 0.069 ± 0.006 L/year • RHI or short-acting insulin: − 0.061 ± 0.006 L/year • Treatment difference: − 0.007 L/year (90% CI − 0.021 to 0.006) Annual rate of change in DL_{CO} from baseline: • EXU: − 0.343 ± 0.067 mL·min^{-1} $mmHg^{-1}$ $year^{-1}$ • RHI or short-acting insulin: − 0.385 ± 0.063 mL min^{-1} $mmHg^{-1}$ $year^{-1}$ • Treatment difference: 0.042 mL min^{-1}·$mmHg^{-1}$ $year^{-1}$ (90% CI − 0.109 to 0.193)
NCT00137046 Non-inferiority, OL [93]	T1DM on insulin; HbA1c 5.5–11.0%; $FEV_1 > 70\%$ of predicted; $DL_{CO} < 120\%$ or $> 70\%$ of predicted $N = 582$	EXU + intermediate- or long-acting insulin ($n = 290$) Mean baseline FEV_1: 3.50 ± 0.76 L Mean baseline DL_{CO}: 28.09 ± 6.22 mL min^{-1} $mmHg^{-1}$	Prandial insulin (RHI, lispro, or aspart) + intermediate- or long-acting insulin ($n = 290$) Mean baseline FEV_1: 3.47 ± 0.77 L Mean baseline DL_{CO}: 27.20 ± 6.41 mL min^{-1} $mmHg^{-1}$	104	Annual rate of change in FEV_1 from baseline: • EXU: −0.051 ± 0.005 L/year) • Prandial insulin: − 0.034 ± 0.005 L/year • Treatment difference: − 0.017 ± 0.007 L/year (90% CI − 0.28 to − 0.005) Annual rate of change in DL_{CO} from baseline: • EXU: − 0.437 ± 0.073 mL min^{-1} $mmHg^{-1}$ $year^{-1}$ • Prandial insulin: − 0.287 ± 0.065 mL min^{-1} $mmHg^{-1}$ $year^{-1}$ • Treatment difference: − 0.150 ± 0.098 mL min^{-1} $mmHg^{-1}$ $year^{-1}$ (90% CI − 0.310 to 0.011)

Table 5 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
Superiority, OL [94]	Insulin-naïve T2DM; HbA1c 8.0–12.0% *N* = 427	EXU + sulfonylurea (*n* = 222) Mean baseline HbA1c: 10.51 ± 0.71% (> 9.5% arm)	Metformin 1 g + sulfonylurea (*n* = 201) Mean baseline HbA1c: 10.62 ± 0.87% (> 9.5% arm)	24	Change in HbA1c > 9.5% arm from baseline: • EXU: − 2.17% • Metformin: − 1.79% • Treatment difference: − 0.38% (95% CI − 0.63 to − 0.14); *P* = 0.002 Superiority margin: *P* = 0.025
Non-inferiority, OL [95]	T1DM on MDI insulin; HbA1c 6.0–11.0% *N* = 335	EXU + Ultralente (*n* = 170) Mean baseline HbA1c: 8.1 ± 1.0%	RHI + NPH (*n* = 164) Mean baseline HbA1c: 8.1 ± 1.0%	24	Change in HbA1c from baseline: • EXU: − 0.2% • RHI: − 0.4% • Treatment difference: 0.16% (95% CI − 0.01 to 0.32); *P* value NR Non-inferiority margin: upper limit of 95% CI < 0.5%
Non-inferiority, OL [96]	T1DM on MDI insulin; HbA1c 6.0–11.0% *N* = 328	EXU + NPH (*n* = 162) Mean baseline HbA1c: 8.0 ± 1.0%	RHI + NPH (*n* = 165) Mean baseline HbA1c: 7.9 ± 1.0%	24	Change in HbA1c from baseline: • EXU: − 0.3% • RHI: − 0.1% • Treatment difference: − 0.16% (95% CI − 0.34 to 0.01); *P* value NR Non-inferiority margin: upper limit of 95% CI < 0.5%

Table 5 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
Superiority, OL [97]	Insulin-naïve T2DM; HbA1c ≥ 8.0 to < 11.0% *N* = 309	EXU (*n* = 104) Mean baseline HbA1c: 9.3% EXU + 2 OADs (*n* = 103) Mean baseline HbA1c: 9.2%	2 OADs (*n* = 99) Mean baseline HbA1c: 9.3%	12	Change in HbA1c from baseline: • EXU: − 1.4% • EXU + 2 OADs: − 1.9% • 2 OADs: − 0.2% Treatment group difference: • EXU + 2 OADs: − 1.67% (95% CI − 1.90 to − 1.44); *P* < 0.001 • EXU: − 1.18% (95% CI − 1.41 to − 0.95); *P* < 0.001
Non-inferiority, OL [98]	T2DM on MDI insulin; HbA1c 6.0–11.0% *N* = 299	EXU + Ultralente (*n* = 149) Mean baseline HbA1c: 8.1%	RHI + NPH (*n* = 149) Mean baseline HbA1c: 8.2%	24	Change in HbA1c from baseline: • EXU: − 0.7% • RHI: − 0.6% • Treatment difference: − 0.07% (95% CI − 0.32 to 0.17); *P* value NR Non-inferiority margin: upper limit of 95% CI < 0.5%
Technosphere insulin					
Non-inferiority, OL [99]	T1DM or T2DM on usual care (OADs ± insulin); HbA1c ≥ 6.6 and ≤ 12.0%; FEV_1 and DL_{CO} ≥ 70% of predicted *N* = 2053	TI-MedTone (*n* = 730) Mean baseline FEV_1: 3.213 L	Usual care (OADs ± insulin) (*n* = 824) Mean baseline FEV_1: 3.299 L	104	Change in FEV_1 from baseline to month 24: • Treatment difference: 0.037 L (95% CI 0.014–0.060); *P* value NR Non-inferiority margin: upper limit of 95% CI < 100 mL (50 mL/year)

Table 5 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
NCT00309244 Non-inferiority, OL [100]	T2DM on MDI insulin; HbA1c > 7.0 to ≤ 11.0% *N* = 677	TI-MedTone + glargine (*n* = 323) Mean baseline HbA1c: 8.7%	Biaspart (*n* = 331) Mean baseline HbA1c: 8.7%	52	Change in HbA1c from baseline: • TI-MedTone: − 0.68% • Biaspart: − 0.76% • Treatment difference: 0.07% (95% CI − 0.13 to 0.27); *P* value NR Non-inferiority margin: 0.4%
Affinity 1 Non-inferiority, OL [101]	T1DM on basal-bolus insulin; HbA1c 7.5–10.0% *N* = 518	TI-Gen2 + basal insulin (*n* = 174) Mean baseline HbA1c: 7.94%	Aspart + basal insulin (*n* = 170) Mean baseline HbA1c: 7.92%	24	Change in HbA1c from baseline: • TI-Gen2: − 0.21% • Aspart: − 0.40% • Treatment difference: 0.19% (95% CI 0.02 to 0.36); *P* value NR Non-inferiority margin: 0.4%
Affinity 2 Superiority, DB [102]	Insulin-naïve T2DM on OADs; HbA1c 7.5–10.0% *N* = 353	TI-Gen2 + OADs (metformin alone or ≥ 2 oral agents) (*n* = 177) Mean baseline HbA1c: 8.26%	TP-Gen2 + OADs (metformin alone or ≥ 2 oral agents) (*n* = 176) Mean baseline HbA1c: 8.35%	24	Change in HbA1c from baseline: • TI-Gen2: − 0.82% • TP-Gen2: − 0.42% • Treatment difference: − 0.40% (95% CI − 0.57 to − 0.23); $P < 0.0001$ Superiority margin: 0.5%
NCT00539890 Equivalence, OL [103]	T2DM on insulin; HbA1c 7.0–11.5% *N* = 309	TI-MedTone + glargine (*n* = 151) Mean baseline HbA1c: 8.9%	Aspart + glargine (*n* = 158) Mean baseline HbA1c: 9.0%	24	Change in HbA1c from baseline: • TI-MedTone: − 1.05% • Aspart: − 1.31% • Treatment difference: 0.26%; *P* = 0.06; 95% CI NR Equivalence margin: 95% CI − 0.4% to 0.4%

Table 5 continued

Clinical trial	Population	Intervention group	Comparison group	Treatment period (weeks)	Primary endpoint
NCT00700622 Non-inferiority, OL [104]	T1DM on insulin; HbA1c > 7.0 to ≤ 9.0% *N* = 130	TI-MedTone + glargine (*n* = 65) Mean baseline HbA1c: 7.8%	Lispro + glargine (*n* = 65) Mean baseline HbA1c: 7.6%	16	Change in HbA1c from baseline: • TI-MedTone: − 0.1% • Lispro: no change • Treatment difference: − 0.07%; *P* value NR Non-inferiority margin: 0.4%
INHALE-1 Non-inferiority, OL Status: ongoing [105]	T1DM or T2DM on insulin; HbA1c ≥ 7.0 to ≤ 11.0% *N* = 264	TI-Gen2 + basal insulin (degludec, detemir, or glargine)	RAIA (lispro, aspart, or glulisine)	52	Change in HbA1c from baseline
ORMD-0801					
ORA-D-013–1 Superiority, DB Status: terminated [106]	Insulin-naïve T2DM; HbA1c ≥ 7.5 to ≤ 11.0% *N* = 710	ORMD-0801 (QD) ORMD-0801 (BID)	Placebo (QD) Placebo (BID)	52	Change in HbA1c from baseline
ORA-D-013–2 Superiority, DB Status: terminated [107]	Insulin-naïve T2DM; HbA1c ≥ 7.5 to ≤ 11.0% *N* = 450	ORMD-0801	Placebo	52	Change in HbA1c from baseline

BID twice-daily, *CI* confidence interval, *DB* double-blind, DL_{CO} carbon monoxide diffusing capacity, *EXU* exubera, FEV_1 forced expiratory volume in 1 s, *HbA1c* glycated hemoglobin, *MDI* multiple daily injection, *NPH* neutral protamine Hagedorn, *NR* not reported, *OADs* oral antidiabetic drugs, *OL* open-label, *QD* once-daily, *QW* once-weekly, *RAIA* rapid-acting insulin analogue, *RHI* regular human insulin, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *TI* Technosphere insulin, *TP* Technosphere placebo

NON-INJECTABLE ADMINISTRATION OF INSULIN: SUMMARY OF PHASE 3 CLINICAL TRIALS

Insulin therapy is primarily administered via subcutaneous injection. However, missed and mistimed dosing of subcutaneous insulin occurs frequently among people living with DM [90], contributing to the suboptimal use of insulin therapy and poor treatment outcomes. Consequently, the suitability of non-injectable administration of insulin has been intensely investigated [91].

Two prandial insulins—Exubera (developed jointly by Nektar Therapeutics, Pfizer, and Sanofi-Aventis) and Technosphere insulin (developed by MannKind Corporation)—have been formulated for inhaled administration. Additionally, Oramed Pharmaceuticals developed a basal insulin called ORMD-0801, which has been formulated for oral administration.

Exubera

In two phase 3 RCTs evaluating long-term pulmonary safety in adult participants with insulin-treated T1DM [92] or insulin-treated T2DM [93], Exubera caused non-progressive and reversible declines in baseline forced expiratory volume in 1 s (FEV_1) and baseline carbon monoxide diffusing capacity that were slightly greater in magnitude but clinically non-meaningful compared to regular human insulin (RHI), lispro, and aspart.

The efficacy of Exubera has been compared to oral antidiabetic drugs (OADs) or RHI in five phase 3 RCTs [94–98] with the primary objective of evaluating change in HbA1c from baseline to the end of the treatment period in insulin-naïve or insulin-treated adult participants with T1DM or T2DM.

In participants with insulin-naïve T2DM, Exubera provided a reduction in baseline HbA1c that was superior to both metformin monotherapy and dual oral therapy consisting of an insulin secretagogue (sulfonylurea or repaglinide) + an insulin sensitizer (thiazolidinedione or metformin). Additionally, Exubera provided a non-inferior reduction in baseline HbA1c compared to RHI in participants with T1DM or T2DM who were previously treated with insulin.

Technosphere Insulin

In a phase 3 clinical trial evaluating long-term pulmonary safety in adult participants with T1DM or T2DM, Technosphere insulin caused a small and non-progressive decline in baseline FEV_1 compared to the usual antidiabetic treatment (OADs alone or OADs + insulin) [99].

The efficacy of Technosphere insulin has been evaluated in five phase 3 RCTs [100–104] that had the primary objective of evaluating the change in HbA1c from baseline to the end of the treatment period in adult participants with insulin-treated T1DM, insulin-treated T2DM, or insulin-naïve T2DM.

Inhaled administration of Technosphere insulin demonstrated consistently positive results across the phase 3 clinical trials: a non-inferior reduction in baseline HbA1c compared to biaspart in participants with insulin-treated T2DM; a non-inferior reduction in baseline HbA1c compared to aspart or lispro in participants with insulin-treated T1DM; and a superior reduction in baseline HbA1c compared to OADs in insulin-naïve participants with T2DM. Lastly, in participants with insulin-treated T2DM, Technosphere insulin provided a reduction in baseline HbA1c that was not equivalent to aspart.

INHALE-1 [105] is an ongoing open-label, active-controlled, phase 3 RCT that is comparing Technosphere insulin to rapid-acting insulin analogues (lispro, aspart, or glulisine) with the primary objective of evaluating the change in HbA1c from baseline to the end of the treatment period in participants ≤ 18 years of age with T1DM or T2DM who were previously treated with insulin. This non-inferiority clinical trial is expected to provide high-level evidence that will support the use of inhaled insulin in children and adolescents living with DM.

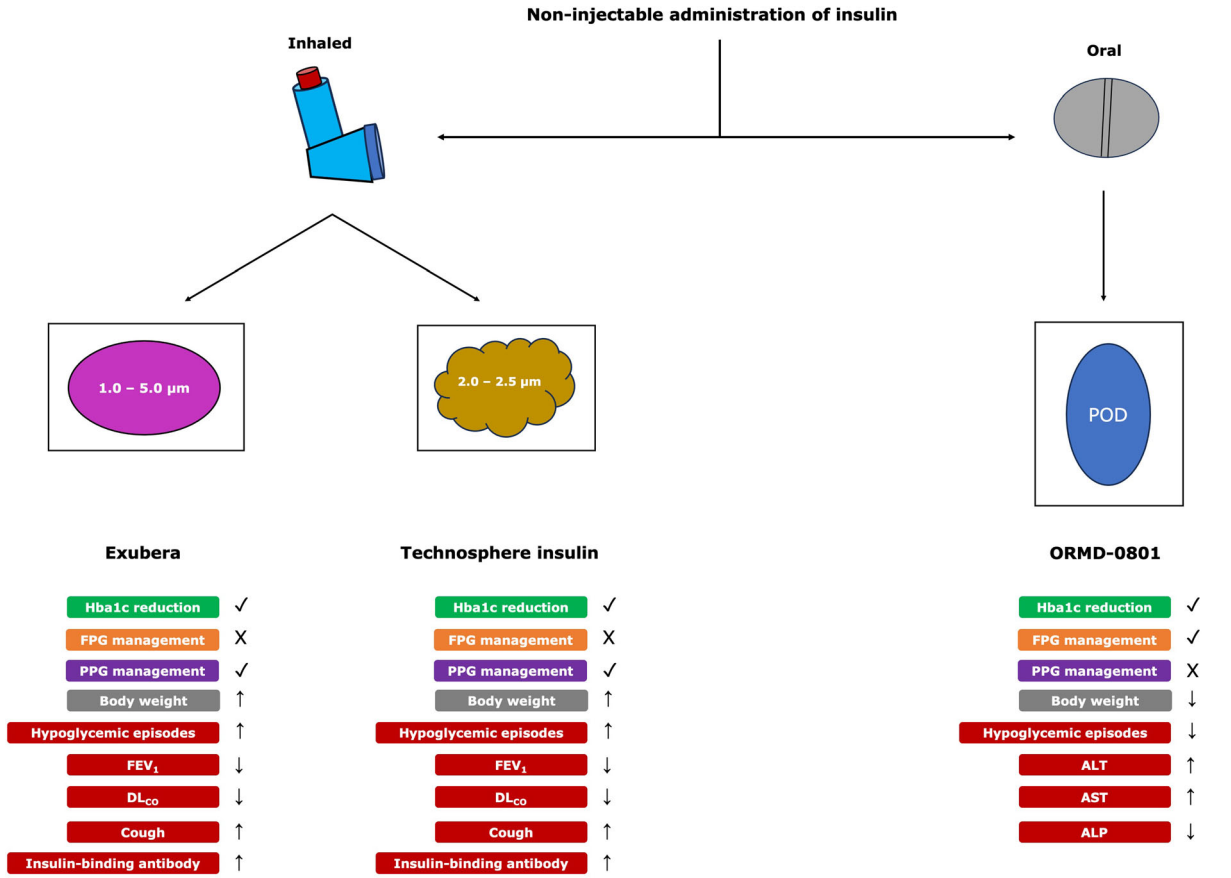

Fig. 2 Schematic of clinically significant characteristics of insulins formulated for non-injectable administration. *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, DL_{CO} carbon monoxide diffusing capacity, FEV_1 forced expiratory volume in 1 s, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *POD* protein oral delivery, *PPG* post-prandial glucose

ORMD-0801

Two placebo-controlled, phase 3 RCTs [106, 107] evaluating the change in HbA1c from baseline to the end of the treatment period in insulin-naïve adult participants with T2DM were terminated early following the completion of only 26 weeks of treatment with ORMD-0801. As a consequence, the clinical need for a safe and efficacious oral insulin preparation remains unmet.

Table 5 summarizes the phase 3 RCTs evaluating the non-injectable administration of insulin.

CLINICAL SIGNIFICANCE OF NON-INJECTABLE ADMINISTRATION OF INSULIN

The non-injectable administration of insulin has been investigated since the 1920s, when alcoholic solutions containing insulin were administered orally [108]. However, this approach was abandoned due to limited efficacy compared to the subcutaneous administration of insulin. Pulmonary administration of insulin was proposed as an alternative to subcutaneous administration due to the large surface area, high permeability, and extensive vascularization of the deep lung [109]. However, pulmonary administration is challenging due to diffusional deposition of the medication in the

mucus layer and mucociliary advection/clearance [110]. The innovative formulation of insulin into a dry powder consisting of very small particles enabled insulin to be successfully delivered to the alveoli, thereby surmounting the barriers to the pulmonary administration of peptide medications [111, 112].

Exubera, Technosphere Insulin, and ORMD-0801

Two inhaled insulin preparations and one oral insulin preparation have been studied in phase 3 RCTs. Figure 2 summarizes clinically significant characteristics of these innovative insulins.

The Exubera and Technosphere Insulin Clinical Trials

Due to positive evidence of pulmonary safety and efficacy, Exubera became the first inhaled insulin to be approved in 2006 for use in adult patients with DM in the United States (US) and Europe [113]. However, the withdrawal of Exubera from the market in the US (2007) and Europe (2008) due to poor sales [113, 114] created an opportunity for the development of other inhaled insulins for patients preferring a non-injectable treatment option. Technosphere insulin was subsequently developed and approved in 2014 [115] following positive results from phase 3 RCTs, and is currently the only inhaled insulin preparation available in the US for management of post-prandial hyperglycemia in adult patients living with DM.

Intensification of antidiabetic treatment in the pediatric population seems to be the next frontier for inhaled insulin. Since the INHALE-1 trial is expected to provide a new therapeutic option for managing post-prandial hyperglycemia in children and adolescents with DM, findings from this RCT are eagerly awaited.

The impact of non-injectable administration on adherence to and persistence with insulin therapy has been previously studied. Some authors have suggested that inhaled administration of insulin may improve treatment adherence [116, 117]. In several empirical studies, inhaled administration of insulin was associated with higher treatment satisfaction than subcutaneous administration among participants with DM [118–122]. Furthermore, adolescent and adult participants with T1DM who were treated with inhaled insulin self-reported lower barriers to treatment adherence [123]. Since real-world evidence (RWE) has been shown to play a critical role in assessing treatment adherence [124], there is an urgent need for RWE that corroborates the positive findings from empirical research on inhaled administration of insulin.

The ORMD-0801 Clinical Trials

The early termination of the phase 3 RCTs evaluating ORMD-0801 is disappointing. Consequently, the clinical significance of oral insulin remains unclear due to a lack of robust clinical evidence. To overcome this limitation, research into the chemical, formulation, and physical barriers to the oral administration of insulin [125] should continue to be prioritized in order to ensure that other therapeutic insulins designed for oral administration reach advanced stages of clinical development.

CONCLUSIONS

Less frequent dosing of insulin has been evaluated by numerous phase 3 clinical trials and has yielded mixed results. In the IMAGINE trials, once-daily dosing of basal insulin peglispro provided glycemic management that was non-inferior to glargine and NPH. However, the development of this hepato-preferential insulin was discontinued due to transaminitis, elevated serum triglyceride levels, and increased liver fat content. In the completed ONWARDS trials, once-weekly dosing of icodec provided non-inferior and statistically superior glycemic management compared to glargine and degludec. Based on these positive results, icodec is likely to be the world's first-in-class ultra-long-acting basal insulin approved for the medical management of diabetes mellitus. The ongoing COMBINE and QWINT trials are expected to provide substantive evidence of the efficacy and safety of icodec + semaglutide and insulin efsitora alfa, respectively.

Phase 3 clinical trials evaluating the non-injectable administration of insulin have culminated in Technosphere insulin being the only inhaled antidiabetic medication currently available to people living with diabetes. The need for an oral insulin remains unmet because the two clinical trials evaluating ORMD-0801 have been terminated early. We therefore look forward to continuous innovation in insulin therapy to overcome existing and emerging treatment challenges.

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Declarations

Conflict of Interest. Ken Nkonge, Dennis Nkonge, and Teresa Nkonge declare that they have no competing interests.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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